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Protocols for Monitoring of Multiple Pregnancies: A Literature Review

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Abstract

Introduction

The incidence of multiple pregnancies has increased over the past decades, mainly due to the use of assisted reproduction methods and increased maternal age at childbirth. Indicatively in the United States, the birth rate of multiple pregnancies has increased dramatically since 1980, reaching a peak in 2014, with a slight decrease since then, reaching 33 per 1000 births in 2019. From 1980 to 2009, the twin birth rate rose 76%, with little fluctuation until 2019, when it was 32.1 per 1,000 births. The triplet and higher order multiple birth rate increased more than 400% from 1980 to 1998. In 2019, it stood at 0.87 per 1,000 births, a 55% decrease from the peak in 1998, due to fewer embryos being transferred during IVF and an increase in fetal reduction procedures.

In terms of the mechanisms of generation and risk factors of multiple pregnancies, there are differences between monozygotic and dizygotic twins. In monozygotic twins, depending on the period when the spontaneous division of the incipient developing embryo occurs, different combinations of amnionicity and chorionicity arise. Their creation is due to random non-hereditary factors. Their prevalence is relatively stable and is not affected by patient-specific factors, except for pregnancies resulting from IVF techniques, which appear to increase the risk of zygote cleavage. In contrast, dizygotic twins result from the independent fertilization of two ova during one ovulatory cycle. Their prevalence varies between populations. Risk factors for dizygotic twin pregnancies include black race, advanced maternal age, increased maternal weight and height, multiparity, family history of multiple pregnancies, high levels of follicle-stimulating hormone (FSH), and infertility treatment with techniques of multiple ovulation in combination with multiple embryo transfer.

Objectives-Methods: *The aim of this paper is to review the issues and complications associated with twin and triplet pregnancies and to present an evidence-based approach to the management and monitoring of these pregnancies according to chorionicity and amnionicity.*

A literature review was performed including studies up to June 2022. The following electronic databases were searched to identify articles for the systematic review: MEDLINE, PubMed-NCBI, Cochrane Library, Cochrane Central Register of Controlled Trials, EMBASE and Scopus. In addition, guidelines relevant to the topic of the work were searched in the following: ACOG, NICE, ISUOG, and HSOG.

Results: *This paper first analyzed both the initial prenatal assessment and prenatal care in the second and third trimesters for singleton pregnancies and then reviewed twin and triplet pregnancies. In regard to multiple pregnancies, the way of diagnosis, determination of the gestational age and the chorionicity and amnionicity, and labeling of the fetuses was initially presented. Subsequently, a distinction was made between maternal, including preeclampsia and gestational diabetes mellitus, perinatal, and fetal complications of multiple pregnancies. In the latter, a further division was made into complications that characterize all multiple pregnancies (preterm birth, growth restriction and discordance, congenital anomalies), complications that occur exclusively in monochorionic multiple pregnancies [twin-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS), twin reversed arterial perfusion (TRAP), and selective fetal growth restriction (sFGR)], and complications which concern only monoamniotic multiple pregnancies (intertwin cord entanglement, conjoined twins). At the same time, reference was made to the management of the above complications. Then, special mention was made of how to deal with single fetal demise in twin and triplet pregnancies, and of the cases of multifetal pregnancy reduction and selective termination. Consequently, an attempt was made to record and present prenatal care in twin and triplet pregnancies as completely as possible. In more detail, the issue of education and promotion of pregnant women's health was initially touched upon.*

Afterwards, screening of multiple pregnancies for fetal chromosomal and congenital anomalies, fetal growth restriction and discordance, preterm birth, and placental abnormalities was studied. Then, the ultrasound monitoring algorithms of twin and triplet pregnancies were described according to chorionicity and amnionicity. Finally, issues related to the birth of twins and triplets were listed, such as planning the timing and route of delivery.

In terms of ultrasound monitoring of twin pregnancies, women with an uncomplicated dichorionic twin pregnancy should have a first-trimester ultrasound examination, a second-trimester anomaly scan (including measurement of cervical length) and scans every 4 to 6 weeks thereafter. Uncomplicated monochorionic diamniotic twins should have a first-trimester ultrasound scan and then every 2 weeks after 16 weeks for early detection of TTTS, TAPS or sFGR. In addition to anatomy scan at 18 to 22 weeks of gestation, fetal echocardiography is performed at the same weeks for monochorionic but not dichorionic twins. Regarding monochorionic monoamniotic twins, there is insufficient evidence to suggest a different frequency of fetal growth monitoring compared to monochorionic diamniotic twins.

For antenatal fetal surveillance, NST and amniotic fluid volume determination or biophysical profile are performed weekly starting at 32 weeks in dichorionic twins and at 28 weeks in monochorionic diamniotic twins. Monochorionic monoamniotic twins are monitored more closely. It is common practice to hospitalize patients with monoamniotic twin pregnancies at the beginning of the third trimester (26 to 28 weeks) in order to intensively monitor fetal heart rates.

For uncomplicated dichorionic twin pregnancies, planned delivery is recommended from 37+0 to 38+6 weeks of gestation. Delivery of monochorionic diamniotic twins is recommended at 34+0 to 37+6 weeks. In contrast, for monochorionic monoamniotic pregnancies, delivery is planned between 32+0 and 34+0 weeks of gestation. Both chorionicity and amnionicity and fetal presentations at the onset of labor influence the choice of route of delivery in twin pregnancies.

Regarding ultrasound monitoring in triplet pregnancies, an ultrasound scan is performed in the first or early second trimester to ascertain chorionicity and amnionicity. Starting at 20 weeks, the ultrasound examination for triplet trichorionic triamniotic pregnancies is generally performed every three to four weeks to monitor the development of the fetuses. Because of the common chorionic sac, for monochorionic triamniotic and dichorionic triamniotic triplets, an ultrasound protocol similar to that commonly used to monitor monochorionic twin pregnancies is followed. In case of shared amniotic sac (monochorionic monoamniotic or dichorionic diamniotic triplets), experts recommend admitting these patients to the hospital at 26 weeks of gestation, to facilitate intensive monitoring of fetal heart rates. Ultrasound follow-up for these conditions is the same as for triplets with a common chorionic sac.

The timing of delivery of triplets is based on the type of amnionicity, regardless of lung maturity. Monoamniotic and diamniotic triplets are born between 32+0 and 32+6 weeks. For an uncomplicated trichorionic triamniotic or dichorionic triamniotic triplet pregnancy, planned delivery at 35 weeks of gestation is recommended. Regarding the monochorionic triamniotic triplet pregnancy, the time of delivery depends on the individual clinical scenario and the individual assessment of the physician. In all triplet pregnancies, cesarean delivery is recommended.

Conclusions-Discussion: *Routine prenatal care of women with multiple pregnancies differs from routine prenatal care in singleton pregnancies in various aspects, such as recommendations for weight gain and micronutrient intake, routine prophylactic administration of low-dose aspirin for the prevention of preeclampsia in multiple pregnancies, choice of appropriate method for screening for chromosomal abnormalities, and frequency and goal of ultrasound monitoring. Although ultrasound measurement of cervical length is a common screening test to predict preterm delivery in singleton and twin pregnancies, short cervical length is not a sensitive test in triplets and its measurement is not recommended.*

In contrast to singleton and twin pregnancies, there is no evidence of benefit from intervention to prevent preterm birth in women with triplets and short cervical length. Also, women with triplet pregnancies should undergo focused anatomic survey to screen for neural tube defects in the second trimester, since alpha-fetoprotein (AFP) screening has not been validated in triplets. Additionally, in triplet pregnancies, no serum marker or cell free fetal DNA (cffDNA) test for aneuploidy has been validated. Conversely, increased nuchal translucency has been validated as a screening test for trisomy 21 and trisomy 18, but not for trisomy 13.

Compared to singleton pregnancies, follow-up of twin and triplet pregnancies involves more frequent ultrasound examinations, which have an earlier onset and increased frequency, in case of fetuses with a common chorionic or amniotic sac, with the aim of early recognition of possible TTTS syndrome, TAPS sequence, and selective fetal growth restriction (sFGR). Chorionicity and amnionicity determine also the timing of delivery. While cesarean delivery is recommended in all triplet pregnancies, chorionicity, amnionicity and presentations of both twins at the onset of labor influence the choice of delivery route in twin pregnancies.

Keywords

prenatal care, ultrasound, twin pregnancy, triplet pregnancy, multiple pregnancy, maternal complications, perinatal morbidity, fetal complications, monochorionic twins, twin-twin transfusion syndrome, twin anemia polycythemia sequence, selective fetal growth restriction, twin reversed arterial perfusion, monochorionic monoamniotic twins, conjoined twins, fetal demise, multifetal pregnancy reduction, selective termination, screening, follow-up of multiple pregnancies, timing of delivery, route of delivery.

Abbreviations

AA: arterioarterial

AAA: artery-to-artery anastomosis

AC: abdominal circumference

ACOG: American College of Obstetricians and Gynecologists

AFP: alpha-fetoprotein

AFV: amniotic fluid volume

AGA: appropriate for gestational age

AREDF: absent or reversed end-diastolic flow

AV: arteriovenous

BMI: body mass index

BPD: borderline personality disorder

CBC: complete blood count

CDC: Centers for Disease Control and Prevention

cfDNA: cell free DNA

cffDNA: cell free fetal DNA

CHOP: Children's Hospital of Philadelphia

CI: confidence interval

cm: centimeter

CRL: crown-rump length

CVPS: cardiovascular profile score

CVS: chorionic villous sampling

DC: dichorionic

DCDA: dichorionic diamniotic

DCTA: dichorionic triamniotic

DVP: deepest vertical pocket

ECV: external cephalic version

EDD: estimated due date

EFW: estimated fetal weight

FGR: fetal growth restriction

FHR: fetal heart rate

FIGO: International Federation of Gynecology and Obstetrics

FISH: fluorescence in situ hybridization

FL: femur length

FMF: Fetal Medicine Foundation

GBS: group B streptococcus

GTT: glucose tolerance test

HAV: hepatitis A virus

HBV: hepatitis B virus

HC: head circumference

HELLP: hemolysis, elevated liver enzymes and low platelets

HIV: human immunodeficiency virus

HSOG: Hellenic Society of Obstetrics and Gynecology

HUAM: home uterine activity monitoring

IGRAs: interferon-gamma release assays

IOM: Institute of Medicine

IP: intraperitoneal

IV: intravenous

IVF: in vitro fertilization

ISUOG: International Society of Ultrasound in Obstetrics and Gynecology

IUT: intrauterine transfusion

LBW: low birthweight

LMP: last menstrual period

MCTA: monochorionic triamniotic

MA: maternal age

MCDA: monochorionic diamniotic

MCMA: monochorionic monoamniotic

MCV: mean corpuscular volume

MoM: multiples of median

MPI: myocardial performance index

MSAFP: maternal serum alpha-fetoprotein

mg: milligram

NAAT: nucleic acid amplification testing

NICE: National Institute for Health and Care Excellence

NIPT: noninvasive prenatal testing

NT: nuchal translucency

NTDs: neural tube defects

SMFM: Society for Maternal-Fetal Medicine

sFlt-1: soluble fms-like tyrosine kinase 1

VEGF: vascular endothelial growth factor

VLBW: very low birthweight

VV: venovenous

OR: odds ratio

MPR: multifetal pregnancy reduction

PAPP-A: pregnancy associated plasma protein-A

PGT-A: preimplantation genetic testing for aneuploidy

PlGF: placental growth factor

PPROM: preterm prelabor rupture of membranes

PROM: prelabor rupture of membranes

RAAS: renin-angiotensin-aldosterone system

RFA: radiofrequency ablation

RR: relative risk

sFGR: selective fetal growth restriction

SMFM: Society for Maternal-Fetal Medicine

sPTB: spontaneous preterm birth

ST: selective termination

TA: transabdominal

TAPS: twin anemia-polycythemia sequence

TC: transcervical

TCTA: trichorionic triamniotic triplet

TOLAC: trial of labor after a prior cesarean

TTTS: twin-twin transfusion syndrome

TRAP: twin reversed arterial perfusion

TSTs: tuberculin skin tests

UA: umbilical artery

uE3: unconjugated estriol

USPSTF: United States Preventive Services Task Force

UV: umbilical vein

WHO: World Health Organization

β-HCG: beta-human chorionic gonadotropin

Introduction

Definition of multiple pregnancy

A multiple pregnancy is defined as a pregnancy in which more than one embryo has implanted and is developing within the endometrial cavity. If the embryos are two, then it is characterized as a twin pregnancy, if it is three as a triplet, if it is four as a quadruplet, etc. However, in case one of the embryos involved implants outside the endometrial cavity, it is a heterotopic pregnancy, which constitutes an object of study of ectopic pregnancies. (Loutradis D. et al., 2018)

Mechanisms of multiple pregnancies

Zygosity refers to the genetic origin of embryos. More specifically, multiple pregnancy can occur in the following ways:

- From independent fertilization and implantation of more than one fertilized egg (dizygotic**, trizygotic pregnancy,** etc.), due to the rare phenomenon of multiple ovulation, while it is more frequent when it originates iatrogenically through induction of ovulation with stimulation of the ovaries, and multiple embryo transfer during in vitro fertilization.
- From spontaneous splitting of an incipient developing embryo into individual parts (monozygotic **pregnancy)**.
- From the extremely rare case of simultaneous occurrence of the two aforementioned phenomena (**mixed pregnancy)**, especially during in vitro fertilization, due to micromanipulations in the zona pellucida of the embryos and embryo transfer of more than one embryo (Loutradis D. *et al.*, 2018) .

Chorionicity indicates the number of chorions and the composition of the placenta. Amnionicity refers to the number of **amniotic** cavities.

Dizygotic twin pregnancy

Dizygotic twins are not true twins in the strict sense, because they result from the fertilization of two eggs during one ovulatory cycle. Essentially, embryos are genetically like any other pair of siblings, so according to the law of probability they can be of the same or different sexes.

Dizygotic twin pregnancies are always dichorionic and diamniotic because each blastocyst creates its own chorionic and amniotic sac. The placentas are separate and recognizable from each other. However, many times they come together and present as one organ, with two chorionic layers separating them (Cunningham, 2018) .

Monozygotic twin pregnancy

On the other hand, monozygotic or identical twins, although they have essentially inherited the same genetic code, are usually not completely identical. That is, the division of a fertilized zygote does not necessarily result in an equal distribution of the protoplasmic material. Monozygotic twins may be discordant for genetic mutations, due to a postzygotic mutation, or they may have the same genetic disease but with marked variability in expression. Inactivation of an X chromosome in female fetuses can cause differential expression of X-linked traits or diseases. Furthermore, the phenomenon of monozygotic pregnancy is in a sense a teratogenic event and monozygotic twins have a higher incidence of often discordant malformations (Glinianaia *et al.,* 2011) . For example, in a study of 926 monozygotic twins, the prevalence of congenital heart defects was 12 times the general population rate, but 68% of affected infants had a normal sibling (Pettit *et al.,* 2013) . For any of these reasons, same-sex dizygotic twins may look more identical at birth than monozygotic twins, who are the same sex by genetics anyway. In rare cases, however, the karyotype or phenotype of a monozygotic twin pregnancy may be different due to somatic mutations or chromosomal aberrations. Most recorded cases describe postzygotic loss of the Y chromosome in one of 2 46,XY fetuses resulting in a phenotypically female fetus with Turner syndrome (45,X) and a male fetus (Cunningham, 2018) . A rare case of a 47, XXY zygote that has undergone postzygotic loss of the X chromosome in some cells and loss of the Y chromosome in other cells has also been reported. The phenotype of the resulting twins was one male and one female, both of whom had genetic mosaicism 46,XX/46,XY (Zech *et al.,* 2008) .

In monozygotic twins, depending on the period when the separation will occur, different combinations of amnionicity and chorionicity arise. So, if separation occurs:

A. during the first 3 days (stage between 8 cells and blastocyst) monozygotic dichorionic diamniotic twins result. At this point, in which the differentiation of the trophoblast has not yet taken place, two choria and two amniotic sacs are observed. Two separate placentas or a single fused placenta may result.
B. during the time period of the first 4-8 days (early blastocyst stage) monochorionic diamniotic twins arise. The division results in the formation of a blastocyst with two separate embryoblasts (inner cell masses). Each embryo will form its own amnion within a common dermis and placenta.
C. during the first 9-12 days monochorionic monoamniotic twins are born. The differentiation of the chorion and the amnion is already complete. Division results in 2 embryos with a common placenta, a chorion and an amniotic cavity.
D. after day 13, monochorionic and monoamniotic twins are incompletely separated and share blood circulation and are classified as conjoined. Depending on the point of fusion, conjoined twins are divided into omphalopagus, thoracopagus, cephalopagus, and ischiopagus in order of frequency (Cunningham, 2018) .

Alternative mechanisms

Recently, there has been an alternative hypothesis, according to which the monozygotic pregnancy arises by fission at the postzygotic stage of the two cells. In this case, due to an alteration of the zygote-blastomere transition, the first zygotic division, instead of producing two blastomeres, gives rise to twin zygotes. In addition, monochorionicity and monoamnionicity do not depend on the cleavage of the embryos, but on the fusion of the membranes. (Herranz, 2015) . However, the data are not reliable to support either the traditional or the newly proposed model (Denker, 2015) .

It has long been accepted that monochorionicity unequivocally indicates monozygosity. Rarely, however, monochorionic twins may actually be dizygotic (Hackmon *et al.*, 2009) . The mechanisms for this are theoretical, but in a review of 14 cases, almost all were conceived after ART procedures (Ekelund *et al.*, 2008) .

Superfetation

In this case, there is an interval equal to or longer than one menstrual cycle between fertilizations. Ovulation and fertilization are required during an established pregnancy, which is theoretically possible, until the uterine cavity is obliterated by the fusion of the decidua capsularis with the genuine decidua parietalis. Although known to occur in mares, it is not known to occur spontaneously in humans. A case has been reported after ovarian hyperstimulation and intrauterine insemination in the presence of an undiagnosed tubal pregnancy (Lantieri *et al.*, 2010) . Most authorities believe that the putative human cases of this phenomenon arise from markedly unequal development of twin fetuses of the same gestational age (Cunningham, 2018) .

Superfecundation

This condition refers to the fertilization of two eggs within the same menstrual cycle but not during the same intercourse, nor necessarily by sperm from the same man. In one case of this phenomenon the mother gave birth to a black newborn with blood type A and a white newborn with blood type O. The blood type of the mother and her husband was O (Harris, 1982) . More recent cases have been reported in paternity proceedings (Girela *et al.*, 1997) . Considering that this phenomenon can also occur during IVF, women should be advised to avoid intercourse after embryo transfer (McNamara *et al.*, 2016) .

Triplet pregnancy

A triplet pregnancy may have the following combinations of chorionicity and amnionicity in descending order of frequency:

- Trichorionic triamniotic triplets
- Dichorionic diamniotic triplets
- Dichorionic triamniotic triplets
- Monochorionic triamniotic triplets
- Monochorionic monoamniotic triplets

3.Epidemiology of multiple pregnancies

In 1980, the rate of multiple pregnancies in the U.S. amounted to 19.3 per 1000 births. Due to the use of assisted reproductive methods and the increased age of the mother at childbearing, the rate increased

dramatically in the following decades, reaching the highest value in 2014 at 35.1 per 1000 births, with a slight decrease since then, rising to 33/1000 in 2019.

The frequency of spontaneous multiple pregnancies can be derived by the following calculation:

- Twin pregnancy 1: 80
- Triplet pregnancy 1: 80^{2} =1 : 6 . 400
- Quadruple pregnancy 1: 80^{3} =1: 512,000 (Nathan *et al.,* 2012)

Specifically, in the U.S., twin pregnancies account for approximately 3% of all pregnancies and 97% of multiple pregnancies. From 1980 to 2009, the rate of twin pregnancies increased 76% (from 18.9 to 33.2 per 1,000 births), was generally stable from 2009 to 2012, and then increased for 2013 and 2014 (33, 9). In 2019 it was 32.1 per 1,000 births, down 2% from the 2018 rate of 32.6 and 5% from the 2014 high (Martin *et al.,* 2021).

Dizygotic twins are more common than monozygotic twins, accounting for approximately 70% and 30% of twins respectively (in the absence of assisted reproductive technology). The prevalence of dizygotic twins varies between populations. In contrast, the prevalence of monozygotic twins, whose generation is due to random non-hereditary factors, is relatively constant worldwide at 3 to 5 per 1000 births, and is not affected by patient-specific factors, except for pregnancies from in vitro fertilization (IVF) (Cunningham, 2018) . The distribution of the percentage of monozygotic twins according to chorionicity and amnionicity is:

- Diamniotic dichorionic twins: 25- 30 % of monozygotic twins
- Diamniotic monochorionic twins: 70-75 % of monozygotic twins
- Monoamniotic monochorionic twins: 1-2 % of monozygotic twins
- Conjoined twins: very rare (Gabbe, Niebyl and Simpson, 2017)

The rate of triplet and higher order multiple pregnancies increased in the US. more than 400% from 1980 (0.37 per 1000 births) to 1998 (1.93). In 2019 it was 0.87 per 1,000 births, a 6% decrease from 2017 (0.93) and a 55% drop from the 1998 peak, due to fewer embryos being transferred during IVF and an increase in fetal reduction techniques (Martin *et al.,* 2021) .

Sex rates in multiple pregnancies

In humans, as the number of embryos per pregnancy increases, the percentage of male embryos decreases. It was found that the proportion of male fetuses in 31 million singleton births in the U.S. was 51.6%. For twins it was 50.9%, for triplets 49.5% and for quadruplets 46.5% (Strandskov HH, Edelen EW, and Siemens GJ, 1946) . Swedish data of 135 years reveal that the number of males per 100 female newborns was 106 among singleton pregnancies, 103 among twins and 99 among triplets (Fellman and Eriksson, 2010) . Females are even more dominant in twins from the late stages of segregation. For example, 68% of Siamese twin bullfighters are female. Two explanations were given. First, starting in the womb and continuing throughout the life cycle, mortality rates are lower in women. Second, female zygotes have a greater tendency to divide (Mutchinick *et al.,* 2011) .

4.Predisposing factors of multiple pregnancies

Mother race

The nationality of the mother is a determining factor in dizygotic twin pregnancies, as there are significant variations in their prevalence worldwide. Spontaneous conception of dizygotic twins accounts for 1.3 per 1000 births in Japan, 8 per 1000 births in the United States and Europe, and 50 per 1000 births in Nigeria (Practice Committee of American Society for Reproductive Medicine, 2012). Most cases are recorded in the black race (16/1000 pregnancies) and the fewest in Asians (3/1000 pregnancies) (Loutradis D. *et al.*, 2018) . In an analysis of more than 8 million births in the U.S. between 2004 and 2008, the twin rate was 3.5% among black women and 3% among white women. Hispanic, Asian, and Native American women had comparatively lower rates than white women (Abel and Kruger, 2012) . These marked differences in frequency may be a consequence of racial variations in FSH levels (Nylander, 1971) . The nationality of the father does not seem to be a predisposing factor (Loutradis D. *et al.*, 2018) .

Maternal Race

About a third of the increase in multiple births in recent decades can be attributed to increasing maternal age at conception. The frequency of dizygotic twins increases two- to threefold from age 15 to age 35 (Adashi and Gutman, 2018) . Hence, there is a paradox of declining fertility but increasing twin rates as maternal age advances (Beemsterboer *et al.*, 2006) . This may be related to increases in FSH concentration with age (Bulmer, 1970) . Another explanation for the dramatic increase in the rate of twins with advanced maternal age may be the higher use of assisted reproduction in older women (Ananth and Chauhan, 2012)

. Paternal age has also been linked to the incidence of twin pregnancy, but its effect is noticeably small (Abel and Kruger, 2012) . Although twin gestation is associated with greater risks for most adverse perinatal outcomes, advanced maternal age has not been found to be an additional risk factor for fetal and infant death. Therefore, women aged 30-39 can be informed that their age is not a significant additional risk factor for adverse obstetric outcomes in the context of twin pregnancy (McLennan *et al.,* 2017) .

Parity

An increase in the number of births independently increases the frequency of dizygotic twins in all populations studied. In a 30-year study, a gradually increasing positive correlation was observed between multiparity and twin pregnancy. However, it has been pointed out that the greater use of assisted reproduction techniques may have partly contributed to this (Antsaklis, Malamas and Sindos, 2013) . In a two-year study from Nigeria, where these techniques are not usually available, the effect of polygamy compared to singleton birth was calculated. An eight-fold increase in multiple pregnancy rates was found when the number of births was 4 or less and a 20-fold increase when it was 5 or more (Olusanya and Solanke, 2012) .

Heredity

The mother's family history, as a determinant of twinning, trumps the father's. A study of 4000 family trees showed that women who were dizygotic themselves gave birth to twins at a rate of 1 in 58 births. Women who were not twins, but whose husbands were the result of a dizygotic twin pregnancy, gave birth to twins at a rate of 1 in 116 pregnancies. (White and Wyshak, 1964) . Following genome-wide linkage analyzes in 525 families of mothers of dizygotic twins, four putative linkage peaks were identified. The highest peak was on the long arm of chromosome 6, while the other peaks were on chromosomes 7, 9, and 16 (Painter *et al.,* 2010) . However, the contribution of these variants to the overall incidence of twin pregnancy is probably small (Hoekstra *et al.,* 2008) .

Maternal Weight and Height

Women who are obese (body mass index [BMI] ≥ 30 kg/m2) and tall (≥ 165 cm) are at greater risk for a dizygotic twin pregnancy than women who are underweight (BMI < 20 kg/m2) and have short stature (< 157.5 cm), not taking fertility drugs. (Reddy, Branum and Klebanoff, 2005) .

Diet

Diet may be an important factor affecting the rate of dizygotic twins in certain geographic areas, among certain races, and in individuals with particular body habits (Steinman, 2006) . According to some studies, taking folic acid supplements increases the rate of twin pregnancies. However, there were several limitations in these studies, which could have affected the results and made the association statistically non-significant (Muggli and Halliday, 2007) .

Follicle-stimulating hormone (FSH)

The common factor linking race, age, weight and fertility to multiple pregnancy may be follicle-stimulating hormone FSH levels (Benirschke and Kim, 1973) . This theory is supported by the fact that higher fertility and a higher rate of dizygotic twin pregnancy have been reported in women who conceive within 1 month of discontinuing oral contraceptives, but not in subsequent months (Rothman , 1977) . This may be due to the sudden release of FSH from the pituitary gland in larger amounts than usual during the first menstrual cycle after stopping hormonal contraception. Indeed, the paradox of decreasing fertility but increasing twin pregnancy rate with advanced maternal age may be explained by an excessive release of FSH from the pituitary in response to reduced negative feedback from impending ovarian failure (Beemsterboer *et al.*, 2006) .

Infertility Treatment

Ovulation induction with FSH plus human chorionic gonadotropin (hCG) or clomiphene citrate strongly enhances the possibility of multiple simultaneous ovulations. Using this practice, twin and higher order multiple pregnancy rates of up to 28.6% and 9.3%, respectively, have been reported (McClamrock, Jones and Adashi, 2012) . Two multicenter studies (Assessment of Multiple Gestations from Ovarian Stimulation [AMIGOS] and Pregnancy in Polycystic Ovary Syndrome II [PPCOSII]) were designed to provide guidelines for achieving maximum pregnancy rates while minimizing multiple pregnancy rates (Legro *et al.*, 2014; Diamond *et al.*, 2015) .

Dizygotic twins are more common in IVF pregnancies than in natural conception pregnancies (≥95% vs. 70%), as some women undergo double embryo transfer as part of IVF. In general, the greater the number of embryos transferred, the greater the risk of twins and other multiple pregnancies. In an embryo transfer of 4 embryos, the risk for twin, triplet and quadruple pregnancy amounts to 15%, 3% and 1% respectively. In 2014, assisted reproduction contributed to 1.6% of all births in the U.S. and in 18.3% of all newborns

in multiple pregnancies (Sunderam *et al.,* 2017) . The American Society for Reproductive Medicine (Pract Committee of the American Society for Reproductive Medicine and Practice Committee of the Society for Assisted Reproductive Technology, 2017) recently revised guidelines on the number of embryos to be transferred during IVF according to age. This effort aims to reduce the incidence of higher order multiple pregnancies. Based on these new recommendations, women under the age of 35 are encouraged to have an embryo transfer. These practices have substantially reduced the rates of multiple pregnancies. This is also shown by the fact that the rate of triplet or higher order multiple pregnancies has decreased every year since 2009 (Martin *et al.,* 2021) .

However, IVF also appears to increase the risk of zygote cleavage, thus increasing the chance of monozygotic twins. In fact, it is the only risk factor for monozygotic twinning (Aston, Peterson and Carrell, 2008) . The incidence of monochorionicity in IVF is 3.2%, while the usual incidence worldwide is 0.4%. This can be attributed either to invasive manipulations in the zona pellucida during the process of microfertilization (ICSI - Intracytoplasmic sperm injection), or in slow postzygotic movement of the embryo in the fallopian tube (Loutradis D. *et al.,* 2018) .

Other factors

The photoperiod of conception affects the frequency. There is an increase in dizygotic twin pregnancies during the summer solstice, due to greater exposure to sunlight resulting in an increase in FSH and LH levels. This fact is confirmed by the accompanying decrease in dizygotic twin pregnancies during the winter season.

In areas contaminated by polychlorinated hydrocarbons, there is an increased frequency of dizygotic twins, possibly due to their similar action to estrogens (Loutradis D. *et al.,* 2018).

Purpose of the Study

The three main components of prenatal care are risk assessment, maternal and fetal health education and promotion, and therapeutic intervention. High-quality prenatal care can prevent or lead to early recognition and treatment of maternal and fetal complications. The goal of prenatal care is the birth of a healthy child with minimal risk to the mother. After the initial prenatal visit, prenatal care involves ongoing assessment of the health status of both mother and fetus, counseling on issues that arise before and after delivery, and anticipating problems by intervening, if possible, for prevention or minimization of morbidity.

Many aspects of prenatal care and counseling for women with twin pregnancies are the same as for singleton pregnancies. However, twin pregnancy is associated with higher rates of almost every possible complication of singleton pregnancy, with the exceptions of gestational age and macrosomia. Most pregnancy complications (e.g., gestational hypertension, gestational diabetes) are treated similarly in twin and singleton pregnancies because both fetuses are affected by the condition. However, for some conditions, one fetus is affected but the other is unaffected or less severely affected. Therefore, the risks and benefits of any intervention in these cases differ for each fetus. The most serious risk is preterm birth, which accounts for most of the increased perinatal mortality, neonatal morbidity, and long-term morbidity in twins. Higher rates of intrauterine growth restriction and congenital anomalies also contribute to adverse outcome in twin births. Determining amnionicity and chorionicity is critical because monochorionic twins share a common fetoplacental circulation, which puts them at risk for serious complications unique to these pregnancies, such as twin-twin transfusion syndrome (TTTS) twin anemia-polycythemia sequence (TAPS), twin reversed arterial perfusion sequence (TRAP) and selective fetal growth restriction (sFGR). Monoamniotic twins are also at risk from entanglement of the umbilical cords, but also from being conjoined. Because these complications increase the risk for neurologic morbidity and perinatal mortality in monochorionic twins compared with dichorionic twins, monochorionic and monoamniotic twin pregnancies are monitored with different protocols than dichorionic twin pregnancies.

Ideally, multiple pregnancies should be prevented by better use of assisted reproductive technology, such as better management of ovulation induction and embryo transfer. In the absence or failure of preventive interventions or in the event of spontaneous conception, procedures have been developed to reduce the total number of fetuses in multiple pregnancies in order to improve the outcome of the mother and the surviving fetuses. Multifetal pregnancy reduction (MPR) refers to a procedure in which the total number of fetuses in a multiple pregnancy is reduced by terminating one or more fetuses, chosen mostly at random, but taking into account technical factors. In contrast, selective termination (ST) also involves reducing the number of fetuses, but the ST procedure is directed at one or more specific fetuses in a multiple pregnancy due to a known or suspected fetal abnormality, including a chromosomal, structural, genetic or growth abnormality, which has been identified by ultrasound examination or by definitive fetal diagnostic testing after amniocentesis or chorionic villus sampling.

On the other hand, triplets are associated with significantly increased risks of maternal and neonatal morbidity, as well as perinatal morbidity and mortality compared with twin and singleton pregnancies.

In the second half of pregnancy, these pregnancies are at increased risk for preterm delivery, preeclampsia, or fetal growth discordance compared to singleton pregnancies.

Thus, the aim of this paper is to review the issues and complications associated with twin and triplet pregnancies and to present an evidence-based approach to the management and monitoring of these pregnancies according to chorionicity and amnionicity.

Methods

A literature review was performed including studies up to June 2022. The following electronic databases were searched to identify articles for the systematic review: MEDLINE, PubMed – NCBI, Cochrane Library, Cochrane Central Register of Controlled Trials, EMBASE and Scopus. In addition, we searched for guidelines relevant to the topic of the work in the following: ACOG, NICE, ISUOG, and HSOG. The research was also supported by contemporary written sources.

Terms entered into the search databases were: "prenatal care", "ultrasound", "twin pregnancy", "triplet pregnancy", "multiple pregnancy", "maternal complications", "perinatal morbidity", "fetal complications", " monochorionic twins", "twin-twin transfusion syndrome", "twin anemia-polycythemia sequence", "selective fetal growth restriction", "twin reversed arterial perfusion", "monochorionic monoamniotic twins", "conjoined twins", "fetal demise", "multifetal pregnancy reduction", "selective termination", "screening", "follow-up of multiple pregnancies", "time of delivery", "route of delivery".

The literature on the subject is extensive. Systematic reviews and meta-analyses, studies at preclinical and clinical level, as well as guidelines of international organizations were selected for data collection.

Thus, the present paper first analyzed both the initial prenatal assessment and prenatal care in the second and third trimesters for singleton pregnancies and then reviewed twin and triplet pregnancies. In particular, with regard to multiple pregnancies, the way in which the diagnosis is made, the determination of the gestational age and the chorionicity and amnionicity as well as the labeling of the fetuses was initially presented. Subsequently, a distinction was made between maternal, perinatal and fetal complications of multiple pregnancies, including preeclampsia and gestational diabetes mellitus. In the latter, a further division was made into complications that characterize all multiple pregnancies (premature delivery, intrauterine growth restriction and discordance, fetal malformations), complications that occur exclusively in monochorionic multiple pregnancies [twin-twin transfusion syndrome (TTTS)), twin anemia-polycythemia sequence (TAPS), twin reversed arterial perfusion (TRAP), and selective fetal growth restriction (sFGR)], and complications which concern only monoamniotic multiple pregnancies

(entanglement of the umbilical cords, conjoined twins). At the same time, reference was made to the management of the above complications. Then, special mention was made of how to deal with intrauterine death in twin and triplet pregnancies, as well as in cases of multiple pregnancy reduction and selective fetal termination. Then, an attempt was made to record and present prenatal care in twin and triplet pregnancies as completely as possible. In more detail, the issue of education and promotion of pregnant women's health was initially touched upon. Then, population-based screening of multiple pregnancies for fetal chromosomal and structural abnormalities, fetal growth restriction and discordance, risk of preterm birth, and placental abnormalities was studied. Then, the ultrasound monitoring algorithms of twin and triplet pregnancies according to chorionicity and amnionicity were described. Finally, issues related to the birth of twins and triplets were listed, such as planning the time and manner of delivery.

Results

1.Diagnosis and monitoring of singleton pregnancy

1.1. Objectives of prenatal care

The main purpose of prenatal care is to help ensure the birth of a healthy newborn while minimizing risk to the mother. The following elements contribute to the realization of this goal:

- Early, accurate estimation of gestational age
- Identifying pregnancies at high risk for complications
- Anticipate problems, with intervention (if possible) to prevent or minimize morbidity
- Continuous assessment of maternal and fetal health status
- Health promotion, education, support and shared decision-making with the pregnant woman

1.2. Time to start prenatal care.

Prenatal care begins in the first trimester, ideally up to 10 weeks gestation, as some prenatal screening tests can be done at this gestational age. Its early initiation is also useful for determining gestational age, taking key measurements (e.g., weight [body mass index], blood pressure, laboratory evaluation of pregnant women with chronic conditions), and providing early support and intervention, in cases where it is required (HSOG Directive No. 60, 2021) .

1.3. Prenatal care during the initial visit of the pregnant woman with a singleton pregnancy

Appropriate information from the history, clinical examination, and laboratory tests can help identify pregnant women at increased risk for medical complications, pregnancy complications, or fetal abnormalities. Early recognition of these pregnancies enables the physician to discuss these issues and their management with the woman and, in some cases, offer interventions to prevent or minimize the risk of an adverse outcome. The population to which this section refers is healthy pregnant women with a singleton pregnancy with a smooth progression and no complications.

1.3.1. History

At the first prenatal visit, it is recommended that a detailed psychosocial, medical, obstetric and family history be taken.

The main items that should be included in the history are:

- **Personal, psychosocial and demographic data,** including religious beliefs about blood transfusion.
- **Personal medical history,** including allergies, medication and vaccinations, history of infections, and evidence of hereditary conditions and substance use.
- **Previous surgical history,** including bariatric surgery.
- **Family history.** Findings that may indicate an inherited disorder affecting the fetus include known or suspected genetic disease, multiple miscarriages, multiple malformations, recurrence of the same or similar disorders, intellectual disability, and autism spectrum disorder.
- **Previous obstetric history.** If the woman has risk factors for ectopic pregnancy, early identification of the implantation site is important. An adverse outcome in a previous pregnancy increases the risk of an adverse outcome in a subsequent pregnancy.
- **History of current pregnancy,** including the woman's desire for pregnancy.
- **Travel** to areas endemic for tuberculosis, malaria, Zika virus.
- **Exposure to potentially toxic environmental factors,** such as the following:
    - Air pollutants, including cigarette smoke
    - Antineoplastic drugs
    - Radiation
    - Heavy metals (mercury, lead, cadmium)

- Chemicals (e.g., ethylene oxide, formaldehyde, flame retardants, solvents, pesticides, endocrine disrupting chemicals [e.g., bisphenol A]) (Dyer *et al.*, 2018) .

1.3.2. Clinical examination

The clinical examination should include maternal blood pressure, weight, and height. If baseline blood pressure is elevated (120 to 129 mmHg systolic and <80 mmHg diastolic) or hypertensive (≥130 mmHg systolic or ≥80 mmHg diastolic), the physician should attempt to obtain prepregnancy blood pressure measurements to establish whether the woman has chronic hypertension. This information is important for the correct diagnosis (chronic hypertension vs. preeclampsia) if the pressure rises in the second half of pregnancy. Finding your body mass index helps guide appropriate weight gain during pregnancy (Bello *et al.*, 2018) .

A complete clinical examination is performed, with particular attention to the size and shape of the uterus and evaluation of the appendages. When the size of the uterus on physical examination differs from that predicted by the last menstrual period (LMP) diary, ultrasound screening is indicated, especially transvaginal screening in early pregnancy. Causes of a discordance between the actual size of the uterus and that predicted by TER include fibroids, posterior tilt of the uterus, multiple pregnancy, and incorrect TER date.

When fetal heart activity is present, the fetal heart can usually be heard from the 12th week of gestation using a portable Doppler ultrasound device transabdominally. With a transvaginal ultrasound, the heartbeat of the fetus can be recognized as early as 5.5-6 weeks.

Examination of the pregnant antepartum pelvis by clinical pyelometry is not sufficiently reliable regarding gestational age, nor can it accurately predict the likelihood of preterm labor or dystocia due to cephalopelvic disproportion.

It is not mandatory to examine the breast during the prenatal check-up (HSOG Directive No. 60, 2021) .

1.3.3. Calculation of probable due date (EDD)

EDD is defined as that date, which corresponds to an average pregnancy of approximately 280 days, or otherwise complete 40 weeks from the first day of the last period, in women with a stable menstrual cycle of 28 days. The EDD otherwise corresponds to 9 and 1/3 calendar months. A quick calculation of PTT can be done using Naegele 's rule, adding 7 days to the first day of LMP and subtracting 3 months.

Accurate calculation of gestational age is very important both for testing and for treating conditions such as fetal growth restriction, macrosomia, preterm labor, and prolongation of gestation (American College of Obstetricians and Gynecologists, 2017) .

1.3.4. Ultrasound examination

1.3.4.a. Viability ultrasound (6th - 10th week)

The purpose of the examination is initially the diagnosis of intrauterine pregnancy and the exclusion of ectopic pregnancy, the localization of fetal heartbeats and the diagnosis of singleton or multiple pregnancy (AIUM - ACR - ACOG - SMFM - SRU, 2018) .

In terms of estimating gestational age, first-trimester ultrasound is particularly important when menses are irregular, TER is unknown or uncertain, in women conceiving while taking oral contraceptive pills, and when uterine size does not match the gestational age based on TER. To determine the gestational age, the cephalocaudal length of the fetus is measured (CRL - Crown Rump Length). As a result, the American College of Obstetricians and Gynecologists recommends the following:

- A first-trimester ultrasound is the most accurate method for determining or reconfirming gestational age.
- In conceptions achieved by assisted reproductive technology, the age of the embryo and the date of embryo transfer are taken into account.
- If available, the gestational age based on TER is compared with the age from the first-trimester ultrasound, and the estimated date of delivery is recorded and discussed with the woman.
- The obstetrician's best estimate of gestational age at delivery is recorded on the birth certificate.

More generally, throughout pregnancy, the gestational age should be re-determined based on ultrasound findings, when the gestational age based on LMP and based on ultrasound differs by specific limits (American College of Obstetricians and Gynecologists, 2017):

- ≤ 13 6/7 weeks
  - ≤8 6/7 weeks: more than 5 days
  - 9 0/7 weeks to 13 6/7 weeks: more than 7 days
- 14 0/7 weeks to 15 6/7 weeks: more than 7 days
- 16 0/7 weeks to 21 6/7 weeks: more than 10 days

- 22 0/7 weeks to 27 6/7 weeks: more than 14 days
- 28 0/7 weeks and beyond: more than 21 days.

With transvaginal ultrasound, it is possible to detect an endometrial sac from 5 weeks of gestation, a leucine sac from 5.5 weeks, a fetal pole and fetal heartbeats from 6 weeks. Findings indicative of pregnancy failure are the following:

- CRL ≥ 7 mm and absent cardiac function
- Mean gestational sac diameter (MSD) ≥ 25 mm and absent fetal pole.
- Absence of a fetus with a heartbeat ≥ 2 weeks after examination showing a gestational sac without a lytical sac
- Absence of a fetus with a heartbeat ≥ 11 days after examination showing a gestational sac with a lactic sac (Doubilet *et al.*, 2013)

The investigation of vaginal bleeding, pelvic pain, possible trophoblastic disease of pregnancy, pelvic masses or uterine abnormalities is also an indication for an ultrasound check of early pregnancy (AIUM - ACR - ACOG - SMFM - SRU, 2018) .

1.3.4.b. Ultrasound of nuchal translucency (11 $^{+0}$ -13 $^{+6}$ week)

With this first-trimester ultrasound examination, the gross anatomy of the fetus is checked, so anatomical abnormalities can be detected in time. However, the detection of fetal abnormalities in the first trimester is limited by the small size of the fetus and still developing fetal development. In a systematic review of 30 studies from 1991 to 2014, the sensitivity of first-trimester ultrasound for detecting fetal abnormalities in low-risk or unselected populations was 32% (95% CI 22–43%), and in high-risk populations 61 % (95% CI 38-82%). When only significant abnormalities were considered, the sensitivity in low-risk or unselected populations was 46%. Although there was considerable heterogeneity among these studies and ultrasound equipment and expertise improved over the 23-year study period, the findings confirm both the potential benefits and limitations of first-trimester fetal anatomy monitoring. Most women will need screening in the second trimester to have a more reliable assessment of fetal anatomy (Karim *et al.*, 2017)
.

In addition, ultrasound indicators are checked to detect chromosomal abnormalities, such as trisomy 21 (Down syndrome), 18 or 13. The most important indicator is nuchal translucency (NT), the ultrasound

appearance of the subcutaneous fluid collection behind the fetus's neck. To measure it, the CRL must be from 45 to 84 mm. Causes of increased NT include aneuploidy, congenital infections and genetic syndromes, especially heart disease. The combination of maternal age and NT and the measurement of 2 hormones in the mother's serum (PAPP - A and free - β - hCG) can reach detection rates for Down syndrome of around 90% with 3% false positive results. Also taking into account the presence or absence of a nasal bone, and blood flow through the tricuspid valve of the fetal heart and the ductus venosus, the detection rate rises to 95% with approximately 3% false positive results (Nicolaides , 2011) . If the NT is 3 mm or more, the risk of aneuploidy is unlikely to be normalized using markers from biochemical testing. Because of this, if the NT measurement is at least 3 mm or exceeds the 99th percentile, the woman should be counseled and offered targeted ultrasound screening with fetal echocardiography. In addition, she should be offered cfDNA testing and prenatal diagnosis (American College of Obstetricians and Gynecologists, 2020) .

1.3.5. Consulting

Women should understand the difference between a screening test and a diagnostic test. This is particularly important in population genetic testing, in which couples need to understand what is and is not being tested, the interpretation of positive and negative results, the possibility of false positive and negative results, and possible invasive or non-invasive testing. Prenatal counseling for parents should not be prescriptive.

Fetal aneuploidies and malformations

All pregnant women should be offered prenatal genetic testing (serum testing with or without cervical smear or non -invasive testing with examination of free fetal DNA in maternal plasma [cell free fetal DNA - cffDNA]) and they should have the option of having a diagnostic interventional procedure instead of screening (regardless of the mother's age.

Diagnostic testing involves performing genetic studies on samples (e.g., chorionic villi or amnion cells), obtained through the invasive procedure of chorionic villus sampling or amniocentesis, to identify fetuses with aneuploidy.

Screening tests identify fetuses at high risk for aneuploidy and fall into two broad categories:

- Evaluation of free fetal DNA in maternal plasma (cffDNA) to screen for trisomy 21, 18, 13 and aneuploidies of the sex chromosomes is an increasingly popular option. It is emphasized that the method is not diagnostic, and any positive result should be verified by studying the karyotype of the fetus in genetic material obtained from an invasive examination.
- Assessment of maternal serum levels of specific biochemical markers associated with trisomy 21 and trisomy 18, with or without assessment of specific ultrasound markers, is the other option. This approach may lead to detection of fetal conditions beyond the primary targets.

Either approach is acceptable as long as the woman receives appropriate genetic counseling to make an informed choice. The cost to the pregnant woman can vary significantly depending on the approach and is another factor to consider.

Increasingly, first-trimester fetal anatomy screening is performed before, in conjunction with, or after first-trimester aneuploidy screening. The type and sequence of tests depends on the woman's preference, which is often influenced by insurance coverage. For example, of pregnant women who choose genetic screening instead of testing, many will have an ultrasound at 10 to 13 weeks to confirm gestational age and fetal heart activity, assess the number of fetuses, check for markers of aneuploidy, such as nuchal translucency, and assess early fetal anatomy, which is best assessed in the latter part of this interval (12 to 13 weeks). Blood is often drawn for cffDNA testing at this visit, especially if the parents do not feel sufficiently reassured by the result of the first-trimester ultrasound.

However, women with increased nuchal translucency or multiple minor sonographic markers of aneuploidy may choose diagnostic testing rather than screening based on sonographic findings. If the ultrasound is normal, the woman returns at 18 to 20 weeks for a detailed anatomy check.

For women who choose diagnostic testing instead of screening, chorionic villus sampling (CVS) may be performed at the 10- to 13-week ultrasound scan. For the few women who prefer amniocentesis to chorionic villus sampling, an ultrasound at 10 to 13 weeks is recommended to assess for evidence of earlier genetic testing (e.g., increased nuchal translucency,) and if no evidence is found, to reassure the woman, that it is reasonable to wait until 15-16 weeks for amniocentesis (American College of Obstetricians and Gynecologists, 2020) .

Genome-wide screening for copy number variants

cffDNA testing to include panels of microdeletions and microduplications and genome-wide assessment of large chromosomal imbalances has not been established. The American College of Medical Genetics and Genomics, European and American Societies for Human Genetics, Society for Maternal-Fetal Medicine (SMFM) and International Society for Prenatal Diagnosis recommend to do not is offered extensive cffDNA test as part of usual genetic control (Di Renzo, Bartha and Bilardo, 2019) . Women who wish to maximize information about the genetic status of their fetus should undergo amniocentesis or chorionic villus sampling with a microarray. The ability to detect a microdeletion or microduplication by microarray is 30 to 50 times greater than by cffDNA screening (Advani *et al.*, 2017) .

cffDNA testing was made because it is not possible to provide reliable estimates of detection rates, false positive rates, or positive predictive values, given the small number of cases detected, variable penetrance, uncertainty in underlying prevalence, difficulty in follow - up, and the lack of clinical validation based on real samples. The American College of Medical Genetics and Genomics though states that patients should be informed about cff DNA testing for certain copy number variations (CNVs), such as deletions of 22q11.2 (DiGeorge syndrome), 1p36 and 15q11.2- 13 (Angelman or Prader-Willi syndrome), recommends against cff DNA testing for genome-wide screening for CNVs (Gregg *et al.*, 2016) .

Carrier testing for genetically inherited diseases

In the United States, population-based genetic carrier testing for cystic fibrosis and spinal muscular atrophy is routinely offered, and red blood cell markers are also used for carrier testing for hemoglobinopathies (' Committee Opinion No. _ 690: Carrier Screening in the Age of Genomic Medicine ', 2017) . For other inherited disorders, doctors may choose to take a national or nationwide approach. Alternatively, they can offer all patients an expanded population carrier screening panel.

If the patient is found to be a carrier of a particular condition, her partner should be screened to determine the risk of an affected child. Referral to a genetic counselor is helpful to discuss the specific disorder, risk, options for prenatal diagnosis, and the woman's reproductive choices. One study found that the most common missed indications for referral to a genetic counselor were a personal or family history of congenital anomalies, intellectual disability, autism, and a positive carrier control test for a genetic disease (McClatchey *et al.*, 2018) .

Hemoglobinopathy (α- or β-thalassemia, hemoglobin S, C, D or E).

A simple screening test, which should be performed in all pregnant women as part of the general blood count, is the assessment of red blood cell markers: a mean red blood cell volume (MCV) of less than 80 femtoliters (fL) in the absence of iron deficiency indicates patients with increased risk for alpha or beta thalassemia.

All pregnant women should undergo an electrophoresis test from the first visit and upon pathological results, the diagnosis should be supplemented with molecular testing to detect mutations and deficiencies of the α- and β-type hemoglobin genes.

However, CBC and MCV may not detect carriers of hemoglobin S, C, or E. Analysis of maternal hemoglobin can be performed by either high-performance liquid chromatography (HPLC) or isoelectric focusing (IEF) to identify these noncarriers. normal hemoglobins. To check for sickle cell anemia, women should undergo a sickle-cell test. Hemoglobin S and C mutations are more common in people of African descent, including North Africa and the Caribbean, Central and South America, Greece, southern Italy, Turkey, Arab countries, and India. Hemoglobin E is common in people of Southeast Asian descent (Ryan *et al.*, 2010) .

Cystic fibrosis

Testing for cystic fibrosis gene mutations can be offered as an option to all pregnant women early in pregnancy at the first visit without this being a mandatory practice. Over 1900 different mutations of the CF gene have been identified. It is the most common single-gene disorder in non-Hispanic Whites of Northern European descent, with a carrier frequency of 1 in 24 to 1 in 25 and a birth prevalence of 1 in 2500 births.

Other diseases

Depending on the couple's history, directed genetic testing can be done to diagnose diseases such as fragile X syndrome, phenylketonuria, Tay-Sachs disease, Canavan disease, familial dysautonomia, mucolipidosis IV, Niemann Pick type A disease, Fanconi group C anemia, Bloom, Gaucher disease, familial hyperinsulinism, glycogen storage disease type I, Joubert syndrome (' Committee Opinion No. _ 691: Carrier Screening for Genetic Conditions ', 2017) .

1.3.6. Laboratory Tests

1.3.6.a. Laboratory tests to confirm pregnancy

In the absence of diagnostic findings of pregnancy (i.e., ultrasound image of the gestational sac/fetus or auscultation of the fetal heartbeat with a hand-held Doppler), pregnancy should be confirmed by detection of the β-subunit of human chorionic gonadotropin (β-hCG) in the blood or urine of the pregnant woman. The syncytiotrophoblast produces hCG in amounts that increase exponentially during the first trimester after implantation. A major function of hCG is to prevent degeneration of the corpus luteum, which is the main site of progesterone formation during the first 6 weeks of pregnancy.

With a sensitive test, the hormone can be detected in the mother's serum or urine 8 to 9 days after ovulation. The doubling time of serum hCG concentration is 1.4 to 2.1 days (29-53 hours). Serum levels vary widely and increase from the day of implantation rapidly to day 41 of gestation, then more slowly reaching peak levels at 60 to 70 days (10 weeks). Thereafter, the concentration slowly declines until a plateau is reached at approximately 16 weeks of gestation (Lenton, Neal and Sulaiman, 1982) .

Several investigators have described β- hCG levels above which failure to visualize an intrauterine pregnancy suggests that the pregnancy is either retrograde or ectopic. Some institutions set the cutoff at ≥1500 mIU / mL, while others use ≥2000 mIU / mL. However, an even higher threshold (>3510 mIU / mL) has been proposed, according to which a gestational sac was observed in 99% of intrauterine pregnancies with a viable fetus (Connolly *et al.,* 2013) .

If the initial β- hCG level exceeds the specified limit and there is no evidence of intrauterine pregnancy by transvaginal ultrasound, then there is a concern of an ectopic pregnancy. The diagnosis is limited in most cases to intrauterine pregnancy failure, recent recurrent pregnancy or ectopic pregnancy. Early multiple pregnancy also remains a possibility. Without clear evidence of ectopic pregnancy, sequential assessment of β- hCG levels is reasonable and its value checked 48 hours later. This prevents unnecessary administration of methotrexate for ectopic pregnancy and avoids harming an early normal multiple pregnancy.

The concentration of β- hCG increases in a normally developing pregnancy by a minimum of 53% in 48 hours with a minimum 24-hour increase of 24% (Barnhart *et al.,* 2004) . However, an even more conservative minimum increase of 35% in 48 hours has been found (Seeber *et al.,* 2006) . With multiple pregnancies, there is the same expected rate of increase as with singleton pregnancies (Chung *et al.,* 2006) . Despite these guidelines, one third of women with an ectopic pregnancy will have a 53% increase at 48

hours. No single pattern characterizes ectopic pregnancy, and approximately half of ectopic pregnancies will have decreased β-hCG levels, while the other half will have increasing levels (Silva *et al.*, 2006) .

1.3.6.b. Laboratory tests to monitor pregnancy

The following describes prenatal screening tests, which are performed during the first prenatal visit according to the guidelines of the American Society of Obstetricians and Gynecologists (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017) .

Blood group, Rhesus, antibody test and indirect Coombs

The purpose of the test is to detect antibodies in the Rh-negative mother that can cause hemolytic disease of the newborn.

Rhesus testing of the partner is recommended in RhD negative women.

All RhD negative pregnant women should have an antibody test (indirect Coombs test) at the first visit. If the test is negative, it can be repeated at 28 weeks.

RhD negative pregnant women without alloantibodies should receive 300 μg of anti- D immunoglobulin at 28 weeks of pregnancy and whenever there is a risk of feto-uterine bleeding, such as retrograde pregnancy, ectopic pregnancy, termination of pregnancy, fetal reduction in multiple pregnancy, chorionic villus sampling, amniocentesis, intrauterine fetal death, injury to the woman's abdomen, bleeding of any cause before delivery, and after delivery within 72 hours.

Test the RhD genotype of the fetus by examining free fetal DNA (cffDNA) in the mother's blood, so that in RhD negative pregnant women 1) or the unnecessary monitoring for anemia in RhD negative pregnant women with alloantibodies 2) or the unnecessary administration of anti- D immunoglobulin in pregnant women without alloantibodies. In the latter case, the American College of Obstetricians and Gynecologists (2017) does not recommend routine cfDNA testing in RhD- negative pregnancies until it becomes cost-effective (ACOG, 2017) .

General blood (hematocrit, hemoglobin, mean red blood cell volume, ferritin)

Anemia is defined by hemoglobin values <11 g/dL (hematocrit <33%) in the first and third trimesters and <10.5 g/dL (approximate hematocrit <32%) in the second trimester. Severe anemia during pregnancy is defined as hemoglobin <7 g / dL and requires medical intervention. Very severe anemia is defined as

hemoglobin <4 g / dL and is a medical emergency because of the risk of congestive heart failure in the pregnant woman.

A mean MCV of <80 fL in the absence of iron deficiency suggests thalassemia and further testing with hemoglobin electrophoresis is indicated. If the pregnant woman is found to be a carrier for hemoglobinopathy, corresponding testing of the partner is recommended.

Anemia in pregnancy is usually associated with iron deficiency. Increasingly, pregnant women are being screened for iron deficiency with ferritin levels, even when they are not anemic. This is based on the concern that by routinely testing only pregnant women with anemia or low mean red cell volume (MCV) a significant number of iron-deficient women may be missed and denied a simple treatment (oral or intravenous iron replacement)., which is potentially beneficial to both mother and fetus without being harmful (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, 2021a) .

Screening for cervical cancer

Pregnancy is not a contraindication for screening for cervical cancer with a Pap test. However, for pregnant women the management of a pathological result is different.

Rubella immunity test

IgG and IgM serology for rubella immunity is performed at the first prenatal visit, unless the woman is known to be immune from previous serology. If immunity to rubella is established as a result of infection or immunization, retesting is not necessary.

If there is no immunity, the woman should avoid exposure to people with rubella and get vaccinated after delivery. The rubella vaccine is a live vaccine and is therefore contraindicated during pregnancy.

Chickenpox immunity test

Immunity to varicella should be determined at the first prenatal visit. Pregnant women without evidence of immunity to varicella should be advised to avoid exposure to persons with varicella, may be candidates for passive immunization during pregnancy if exposed to the virus, and should receive varicella vaccination after childbirth. The varicella vaccine is a live vaccine and is therefore contraindicated during pregnancy (Marin *et al.*, 2007) .

General urine test

Screening for proteinuria, such as with a urine dipstick, is useful as a basis for comparison with tests later in pregnancy in managing possible nephrotic syndrome or diagnosing preeclampsia.

Urine culture

It is recommended in addition to general urinalysis and urine culture because asymptomatic bacteriuria, left untreated, places the pregnant woman at high risk of developing pyelonephritis and at moderately increased risk of preterm delivery.

Treatment of a positive culture depends on local guidelines. However, some physicians recommend treating B streptococcal bacteruria (GBS) at colony counts $<10^5$ CFU/mL. The presence of GBS bacteriuria in any number of colonies is an indication for intrapartum GBS prophylaxis to prevent early neonatal infection.

Up to 30% of pregnant women fail to clear asymptomatic bacteriuria after a short course of treatment (Patterson and Andriole, 1997) . Thus, a repeat culture, which can be done one week after treatment is completed, is generally recommended as a trial of treatment. However, there are insufficient data on the utility of repeat testing after an initial episode of asymptomatic bacteriuria, and it is not known whether retreatment of recurrent or persistent bacteriuria improves outcomes.

Human Immunodeficiency Virus (HIV)

Medical organizations generally support universal HIV testing of pregnant women early in each pregnancy. Advantages of universal testing include:

- Appropriate medical treatment can be initiated.
- Patients can receive advice on preventing transmission or identifying infected partners.
- Perinatal transmission can be significantly reduced with appropriate intervention (e.g., antiretroviral therapy before and during delivery, caesarean section, avoidance of breastfeeding).
- An informed decision can be made to continue the pregnancy ('ACOG Committee Opinion No. 752: Prenatal and Perinatal Human Immunodeficiency Virus Testing', 2018) .

Hepatitis B

All pregnant women are tested for hepatitis B surface antigen (HBsAg), regardless of previous vaccination status, because screening for hepatitis B virus (HBV) infection is not usually performed before

vaccination. Those who carry HBsAg can transmit HBV to the fetus, usually at birth. Passive and active immunization of the newborn within 12 hours of birth can reduce the risk of HBV transmission by >95%. HBsAg-negative pregnant women at high risk for HBV infection (e.g., injection drug user, sexual partner or household contact with chronic HBV) should be screened for hepatitis B surface antibody (anti-HBs) and hepatitis B nuclear antibody (anti-HBc). Those without evidence of previous HBV infection or exposure (negative for anti-HBs and anti-HBc) should be vaccinated with an appropriate vaccine.

Hepatitis C

Hepatitis C virus (HCV) testing is recommended for all pregnant women at the first prenatal visit. The rationale is that HCV infection is increasing in women of reproductive age, risk-based screening is not performed consistently, risk-based screening alone fails to detect a significant minority of infected individuals, and documentation of infection may influence pregnancy management (e.g., avoiding taking chorionic villi and using an internal fetal heart rate monitoring lead). In addition, knowledge of HCV during pregnancy facilitates appropriate treatment of the mother after delivery and improves follow-up of the infant.

Initial screening or diagnostic testing for chronic HCV typically begins with an antibody test by immunoassay.

- If the antibody test is negative, then chronic HCV infection is unlikely, and testing can be stopped.
- A positive HCV antibody test should be followed by an HCV RNA test. The absence of detectable HCV RNA using a sensitive assay essentially confirms the absence of chronic HCV infection. False-negative tests for RNA are uncommon. In this case a positive antibody test is generally a false positive or reflects a previous, cleared infection.
- A positive HCV RNA result is indicative of HCV infection.

In 2020, the Centers for Disease Control and Prevention revised previous guidance based on risk factors and recommended universal HCV screening during every pregnancy except where HCV prevalence is <0.1 % (Schillie *et al.,* 2020) .

Syphilis

Serological testing for the diagnosis of syphilis must be performed and can be done with either a nontreponemal (RPR or VDRL) or treponemal test (FTA - Abs or TP - PA), depending on the preference

of the laboratory performing the test. Confirmatory testing is necessary because of the potential for false-positive results with these tests. The diagnostic approach is the same as in non-pregnant individuals.

Chlamydia

Chlamydia prevalence is highly related to age and sexual behavior. The Centers for Disease Control and Prevention (CDC) recommends screening of all pregnant women <25 years of age and those ≥25 years of age with risk factors for sexually transmitted infections.

Nucleic acid amplification tests (NAATs) have high sensitivity and excellent specificity for the detection of Chlamydia trachomatis and are superior to vaginal fluid culture. During prenatal care, the preferred approach is to test a sample taken from an endocervical or vaginal smear, although urine testing appears to be equally sensitive. Some NAATs have been approved by the US Food and Drug Administration (FDA) for use in liquid-based cytology specimens.

Patients with positive test results should be treated. In pregnancy, they are then tested for cure three to four weeks after treatment and retested three to four months later (Workowski *et al.*, 2021) .

1.3.6.c. Selective screening

Thyroid function test (TSH, free T 4, anti - TPO)

Both hyperthyroidism and hypothyroidism during pregnancy can have adverse effects on the mother and fetus.

Pregnant women with signs or symptoms of thyroid disease should have their thyroid-stimulating hormone (TSH) level measured. TSH should be interpreted using trimester-specific reference ranges for pregnant women when available. If TSH is abnormal, free or total T4 should be measured.

- The diagnosis of clinical hyperthyroidism during pregnancy is primarily based on a suppressed (<0.1 mU / L) or undetectable (<0.01 mU / L) serum TSH value and a measurement of free T4 and/or free T3 (or total T4 and/or total T3) that exceeds the normal range for pregnancy.
- The diagnosis of clinical primary hypothyroidism during pregnancy is based on a TSH above the population-specific and trimester upper limit of normal, or above 4 mU/L when local reference ranges are not available, in combination with a decreased concn. free T4.
- The diagnosis of subclinical hypothyroidism during pregnancy is based on an elevated trimester-specific serum TSH concentration and a normal free T4 concentration.

Screening for subclinical hypothyroidism is controversial. The companies [e.g. ACOG ('Thyroid Disease in Pregnancy: ACOG Practice Bulletin, Number 223', 2020),the Endocrine Company (De Groot *et al.*, 2012) , the American Thyroid Association (Alexander *et al.*, 2017)] recommend targeted and not universal screening in pregnancy, screening under specific conditions (personal or family history of thyroid disease, type 1 diabetes mellitus or clinical suspicion of thyroid disease, taking medications related to thyroid dysfunction). However, a targeted approach will miss up to 1/3 of pregnant women with subclinical hypothyroidism (Vaidya *et al.*, 2007) . For this reason and the concern that not treating these patients may be associated with adverse pregnancy outcomes, some experts have advocated universal screening for thyroid dysfunction during pregnancy or in patients planning to become pregnant (Brent, 2007).

Control of type 2 diabetes and gestational diabetes

Both the American Diabetes Association (ADA) and ACOG recommend screening (fasting glucose) early in pregnancy for undiagnosed type 2 diabetes in patients with risk factors ('ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus', 2018; American Diabetes Association, 2021) . If pregnant women with diabetes (type 2 or gestational) are identified and either make lifestyle changes (diet, exercise) or receive treatment, then rates of maternal and fetal morbidity, particularly macrosomia, preeclampsia and shoulder dystocia. In contrast, a USPSTF guideline concluded that the available evidence was insufficient to assess the balance of benefits and harms of screening asymptomatic pregnant women for impaired glucose tolerance before 24 weeks' gestation. (US Preventive Services Task Force, Davidson, Barry, Mangione, Cabana, Caughey, Davis, Donahue, Doubeni, Kubik, Li, Ogedegbe, Pbert, Silverstein, Stevermer, et al., *2021)* .

Pregnant women have an increased risk of undiagnosed type 2 diabetes when they have a BMI ≥25 kg / m 2 (or ≥23 kg / m 2 in Asian American women) plus one or more of the following characteristics:

- Gestational diabetes in a previous pregnancy
- HbA 1c ≥5.7% (39 mmol / mol), impaired glucose tolerance or impaired fasting glucose in previous examination
- First degree relative with diabetes
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American)
- History of cardiovascular disease
- Hypertension (≥140/90 mmHg) or being treated for hypertension

- HDL cholesterol level <35 mg / dL (0.90 mmol / L) and/or triglyceride level >250 mg / dL (2.82 mmol / L)
- Polycystic ovary syndrome
- Physical inactivity
- Other clinical condition associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

For women at increased risk of diabetes, a diagnosis of preexisting clinical diabetes may be made at the initial prenatal visit if:

- Fasting sugar ≥126 mg / dL (7.0 mmol / L) or
- HbA 1 C ≥6.5% (48 mmol / mol) or
- Random blood sugar ≥200 mg / dL (11.1 mmol / L) and classic symptoms of hyperglycemia

If the fasting sugar is 92-126 mg / dl, it is gestational diabetes (American Diabetes Association, 2021)

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Screening for preeclampsia

➢ **Risk factors for preeclampsia**

Pregnant women should be evaluated early in pregnancy for risk factors for preeclampsia. By quantifying the risk of preeclampsia arising from various individual clinical and demographic risk factors, the physician is better equipped to assess a woman's risk of preeclampsia and whether she is a candidate for increased pregnancy surveillance and/or prophylactic measures such as low dose of aspirin. In the United States, the US Preventive Services Task Force criteria for patients at high risk of developing preeclampsia are commonly used to quantify risk and select candidates for aspirin. So, the incidence of preeclampsia is estimated to be at least 8% for pregnant women with any of these high-risk factors:

- Previous pregnancy with preeclampsia, especially with early onset and adverse outcome
- Diabetes mellitus type 1 or 2
- Chronic hypertension
- Multiple pregnancy
- Nephropathy
- Autoimmune disease with possible vascular complications (antiphospholipid syndrome, systemic lupus erythematosus)

Moderate risk factors include the following:

- Interest rate
- Obesity (body mass index >30 kg/m2).
- Family history of preeclampsia in mother or sister
- Age ≥35 years
- Sociodemographic characteristics (black race, lower income level [recognizing that they are not biological factors])
- Personal risk factors (e.g., previous pregnancy with low birth weight or small-for-gestational-age infant, previous adverse pregnancy outcome [e.g., stillbirth], interval >10 years between pregnancies).
- In vitro arrest

The USPSTF and ACOG also recommend low-dose aspirin for patients with a single moderate-risk factor. This thinking was motivated by concerns about disparities in outcomes for people with less access to medical care and about potentially reducing the racial disparity in the prevalence of preeclampsia in disadvantaged groups.

Although nulliparous women are the group comprising the largest proportion of preeclampsia cases, nulliparity alone is not an indication for prophylaxis. A meta-analysis of trials limited to low-risk women found no benefit (Man *et al.*, 2021) and large trials limited to unselected nulliparous women also found little or no benefit from prophylactic low-dose aspirin therapy (Subtil *et al.*, 2003) .

In the UK, the National Institute for Health and Care Excellence (NICE) developed a similar list (NICE, 2019) :

High risk factors are:

- Hypertensive disease in previous pregnancy
- Chronic hypertension
- Type 1 or type 2 diabetes
- Chronic kidney disease
- Autoimmune diseases, especially systemic lupus erythematosus and antiphospholipid syndrome
- Moderate risk factors are:
- First pregnancy

- Mother's age >40 years
- Time interval between two pregnancies >10 years
- Body Mass Index (BMI) >35 kg/m2
- Multiple pregnancy
- Family history of preeclampsia

Women at increased risk of preeclampsia are those with 1 feature of the above high-risk factors or at least 2 features of the moderate risk factors for preeclampsia according to the NICE list.

During the pandemic, SARS-CoV-2 infection in pregnancy was also associated with an increased risk of preeclampsia (Conde - Agudelo and Romero, 2022) .

In a meta-analysis of cohort studies including ≥1000 patients that assessed the risk of preeclampsia in relation to common clinical risk factors assessed at ≤16 weeks' gestation (92 studies, >25 million pregnancies), the highest rate of preeclampsia occurred in patients with antiphospholipid syndrome (pooled rate 17.3%, pooled relative risk [HR] 2.8), and the highest relative risk of preeclampsia occurred in patients with a prior history of the disease (pooled rate 12%, pooled HR 8.4) (Bartsch *et al.*, 2016) . Other significant risk factors included chronic hypertension (group rate 16%, pooled SD 5.1), pre-existing diabetes (group rate 11.0%, pooled SD 3.7), pre-pregnancy BMI >30 kg/ m2 (group rate 7.1%, pooled HR 2), multiple pregnancy (group rate 6.4%, pooled HR 2.9) and the use of assisted reproductive technology (group rate 6.2%, pooled HR 1.8).

Because historical risk factors predict only about 30% of patients who will develop preeclampsia (Leslie, Thilaganathan and Papageorghiou, 2011) , the use of laboratory and imaging tests in conjunction with these factors to estimate a patient's risk of developing preeclampsia is an active area of research.

However, current risk prediction models have low positive predictive value, potentially worrying a large number of pregnant women about a disorder they will not develop and exposing them to tests and interventions that will not benefit them (' Gestational Hypertension and Preeclampsia : ACOG Practice Bulletin, Number 222', 2020) . One reason for the low predictive value may be insufficient consideration of risk-mitigating factors, such as a previous normotensive pregnancy. Another reason may include not distinguishing between early- and late-onset preeclampsia, which have different risk profiles and recurrence rates.

- **Doppler of uterine vessels**

Meta-analyses show that Doppler of the uterine arteries both in the first trimester (Velauthar *et al.*, 2014) and in the second trimester (Kleinrouweler *et al.*, 2013) can predict pregnant women at increased risk of preeclampsia (Yu *et al.*, 2005) . However, several experts recommend that this test not be performed in early pregnancy. The rate of false positive results is quite high, leading to excessive anxiety for pregnant women and high healthcare costs (Myatt *et al.*, 2012) .

Resistance to flow in the uterine arteries usually decreases as pregnancy progresses. Increased resistance for gestational age is an early radiographic feature of preeclampsia and likely reflects high resistance due to defective differentiation of the trophoblast, which leads to defective penetration of the myometrial spiral arteries. Thus, these vessels fail to convert into low-resistance vessels and form the broad tortuous vascular network of the normal placenta.

Doppler waveform analysis techniques have emerged to predict preeclampsia, as well as other disorders associated with placental disruption (e.g., fetal growth restriction, pregnancy loss): 1) presence or absence diastolic notch (unilateral, bilateral) of the uterine arcuate vessels and 2) flow waveform ratios (e.g., high resistance or pulsatility index, systolic/diastolic ratio) (Papageorghiou, Yu and Nicolaides, 2004) .

The use of uterine artery Doppler to predict preeclampsia was best shown in a systematic review of 74 studies involving nearly 80,000 participants. These studies involved 15 uterine artery Doppler markers and patients at low or high risk of developing preeclampsia. Uterine artery Doppler ultrasound was more accurate in predicting preeclampsia when performed in the second trimester than in the first trimester. In patients at high risk of developing preeclampsia, the overall risk of preeclampsia was best predicted by an increase in pulsatility index during the second trimester accompanied by uterine artery notching (sensitivity 19%, specificity 99%, odds ratio for a positive result [+OR] 21, odds ratio for a negative result [-OR] 0.82), and the risk of severe preeclampsia was best predicted by an increased resistance index during the second trimester (sensitivity 80%, specificity 78%, +OR 3.7, -OR 0, 26) (Cnossen, Morris, *et al.*, 2008).

Doppler studies of uterine artery flow velocity to predict preeclampsia are difficult to compare because investigators have used different techniques, definitions of abnormal flow velocity waveform, populations, gestational age at examination, and criteria for diagnosing preeclampsia. Typically, uterine artery Doppler findings are not interpreted alone, but rather in conjunction with other clinical/demographic risk factors, serum biomarkers, and other ultrasound measurements, such as 3D placental volumes. There

is also growing evidence for the assessment of uterine blood flow with MRI and other more sophisticated technologies.

- **Biomarkers**

Data from humans and animal models suggest that aberrant expression of angiogenic regulators is important in the pathogenesis of the diffuse endothelial damage and increased capillary permeability that are the pathophysiological hallmarks of preeclampsia. Angiogenic factors of interest include vascular endothelial growth factor endothelial growth factor - VEGF) and placental growth factor growth factor - PlGF), as well as two anti-angiogenic proteins, soluble endoglin (soluble endoglin -sEng) and the truncated form of the full-length VEGF receptor type-1 (Flt -1), known as soluble form of fms-like tyrosine kinase 1 (soluble fms - like tyrosine kinase 1-sFlt-1).

Ischemic trophoblast, a characteristic finding in preeclampsia, increases the production of antiangiogenic proteins (sEng, sFlt1) and decreases the production of angiogenic proteins (VEGF, PlGF). Changes in absolute levels of VEGF, PlGF, sFlt-1 (Lam, Lim and Karumanchi, 2005) and sEng (Robinson and Johnson, 2007) in maternal blood and urine precede the onset of clinical preeclampsia by several weeks to months, correlate with the severity of the disease, while these proteins normalize after delivery.

However, blood and urine levels of these factors have not been shown to be clinically useful in predicting preeclampsia far from disease onset.

- **Other laboratory tests**

Screening of maternal serum markers is an important component of screening programs for Down syndrome. Increasing evidence suggests that unexplained abnormal concentrations of pregnancy-associated plasma protein A [PAPP-A] (Poon and Nicolaides, 2014) , as well as abnormalities in the levels of free fetal DNA and micro - RNA, in the first and second trimester are also predictive of adverse pregnancy outcomes, including preeclampsia (Contro, Bernabini and Farina, 2017; Qin *et al.,* 2021) . These associations are not strong enough to warrant changes in routine prenatal care, but biomarkers have been used in risk prediction models.

- **Predictive models**

As described above, specific maternal characteristics, Doppler ultrasound findings, and blood biomarkers are associated with an increased risk of preeclampsia. Traditionally, each risk factor has been treated as a

separate screening test, and a greater number of risk factors are considered to carry a higher risk of developing preeclampsia.

Many researchers have used these variables in logistic regression analysis to create a tool to predict an individual woman's risk of developing preeclampsia while still early in pregnancy, such as the Preeclampsia Risk Calculator from the Fetal Medicine Foundation (https:// fetalmedicine.org/research/assess/preeclampsia). In validation studies, the detection rate of the combined first-trimester screening algorithms from FMF London and Fetal Medicine Barcelona for predicting early preeclampsia ranged from 75 to 92% with a false-positive rate of 10% (Mosimann *et al.,* 2020) . Ideally, women identified as high risk would be encouraged to address any modifiable risk factors, be educated about the signs and symptoms of preeclampsia, and therefore notify their physician as soon as clinical manifestations appear, and more frequent office visits are recommended. Some doctors also start these women on low-dose aspirin.

The utility of prescribing aspirin based on risk determined by these tools rather than demographic or historical risk factors has not been extensively studied. Although the positive screening test rate may be lower and the odds ratio for a positive result may be higher than with traditional risk factor-based models (Guy *et al.,* 2021) , these tools still have relatively low odds ratios for a positive outcome, causing many patients to become anxious and receive unnecessary treatment. They usually require determination of mean arterial pressure, Doppler ultrasonography at 11 to 13 weeks for uterine artery pulsatility index, and additional laboratory tests (e.g., serum PAPP-A and serum placental growth factor PlGF). Furthermore, methodological shortcomings are common, which limits their reliability and validity. For example, a systematic review evaluated 24 studies of 38 prognostic models that included uterine artery Doppler as one of the independent variables (Brunelli and Prefumo, 2015) . The median number of study participants was 697, the median number of preeclampsia events per model was 37, and the median number of risk predictors was 5. Almost a quarter of the models had fewer than 10 events per preeclampsia predictor, and nearly 95% had fewer than of 10 events per predictor of early preeclampsia. Only one model adequately described treatment and handling of missing data, and only three models reported model validation.

- **Prevention of pre-eclampsia**

Most risk factors for preeclampsia are not modifiable, but avoidance of pre-pregnancy obesity, excessive gestational weight gain, and multiple pregnancy in the setting of infertility treatment are notable exceptions.

Obese patients can reduce their risk of preeclampsia by losing weight before pregnancy. Bariatric surgery may be an option for people with severe obesity.

Patients with or without obesity can reduce their risk of preeclampsia by not exceeding the Institute of Medicine's recommendations for gestational weight gain (Haugen *et al.*, 2014) .

Aspirin (81 to 150 mg daily) is the only drug for which there is evidence of benefit in reducing the risk of preeclampsia when given prophylactically throughout the second and third trimesters in high-risk patients. For patients at low risk of developing preeclampsia, the available evidence does not support the use of aspirin to prevent preeclampsia, but a modest (about 10%) reduction in the risk of preeclampsia and its consequences (growth restriction, preterm delivery) is possible for patients with moderate to high risk of developing the disease. The recommendations of some major expert groups regarding aspirin administration are summarized as follows:

- The American College of Chest Physicians guidelines for the management of venous thromboembolism and thrombophilia during pregnancy recommend low-dose aspirin for women considered to be at risk for preeclampsia. They noted that the relative effect of antiplatelet therapy appears to be similar in women at low and high risk for preeclampsia, but low-risk women have a significantly lower absolute benefit (Bates *et al.*, 2012) .
- The American Heart Association and the American Stroke Association recommend low-dose aspirin for women with chronic primary or secondary hypertension or previous pregnancy-related hypertension to prevent stroke associated with preeclampsia (Bushnell *et al.*, 2014) .
- The USPSTF recommends the use of low-dose aspirin 81 mg/day in women at high risk for preeclampsia to reduce the risk of preeclampsia, preterm delivery, and fetal growth restriction. They acknowledged that there are no validated methods (biomarkers, clinical diagnostic tests, medical history) to identify women at high risk for preeclampsia but offered a realistic approach to identify a population of patients with an absolute risk for preeclampsia of at least 8%: Women with ≥1 high risk factors risk should take low-dose aspirin. For women with multiple moderate risk factors, the benefit of aspirin therapy is less clear, so physicians should use clinical judgment and discuss with women the benefits and harms of using low-dose aspirin. Aspirin should be started between 12 and 28 weeks of gestation (US Preventive Services Task Force, Davidson, Barry, Mangione, Cabana, Caughey, Davis, Donahue, Doubeni, Kubik, Li, Ogedegbe, Pbert, Silverstein, Simon, et *al*, 2021) .

- ACOG and Society for Maternal - Fetal Medicine recommend low-dose aspirin (81 mg/day) in women at high risk of preeclampsia and state that it should be started between 12 weeks and 28 weeks of gestation (preferably before 16 weeks) and continued daily until birth. They report that low-dose aspirin should be considered for women with more than one of several moderate risk factors for preeclampsia. They recommend that it not be used exclusively to indicate previous unexplained stillbirth, fetal growth restriction, or spontaneous preterm labor in the absence of risk factors for preeclampsia (ACOG, 2021) .
- The NICE guideline for the management of hypertensive disorders in pregnancy advises the use of low-dose aspirin 75 mg/day for women with at least one high-risk factor for pre-eclampsia or at least two moderate-risk factors for pre-eclampsia (Visintin *et al.*, 2010) .
- The World Health Organization WHO recommends the use of low-dose aspirin 75 mg/day for high-risk women (history of preeclampsia, diabetes, chronic hypertension, renal or autoimmune disease, or multiple pregnancy) (World Health Organization, 2011) .
- The Society of Obstetricians and Gynecologists of Canada recommends low-dose aspirin 75 to 162 mg/day for women at high risk of preeclampsia. They define as increased risk those with prior preeclampsia, associated preexisting medical conditions (e.g., hypertension, kidney disease, diabetes, antiphospholipid syndrome), multiple pregnancy, or two or more lower risk factors (Magee *et al.*, 2014) .
- The International Federation of Gynecology and Obstetrics recommends low-dose aspirin for women identified as high risk (Poon *et al.*, 2019) . The recommended dose is approximately 150 mg starting at 11 to 14 $^{+6}$ weeks and taken every night until the 36th ^{week} of pregnancy, delivery or diagnosis of pre-eclampsia.

For patients undergoing infertility treatment with IVF or ovulation induction alone, several techniques can be used to reduce the chances of multiple pregnancy.

Many factors other than prophylactic aspirin have been studied to reduce the risk of preeclampsia (e.g., calcium, vitamin E and C, antioxidants, omega-3 fatty acids, heparin), but the data do not show significant or consistent evidence of benefit in all the populations.

Infection

Symptomatic patients should be screened for suspected infection. The following discussion applies to the selection of asymptomatic women for screening.

- **Toxoplasmosis**

Whether all pregnant women should undergo IgG and IgM serology testing for toxoplasmosis is controversial. National companies in the United States (' Practice bulletin no . 151: Cytomegalovirus, parvovirus B 19, varicella zoster, and toxoplasmosis in pregnancy ', 2015) and the United Kingdom (Gilbert and Peckham, 2002) and some parts of Europe recommend against universal routine screening for toxoplasmosis in pregnancy because the prevalence of the disease and the incidence of maternal infection are very low and screening is expensive. Other parts of Europe have taken a different approach. Screening is performed monthly, bimonthly or quarterly during pregnancy as part of routine prenatal care (Gilbert, Gras, and European Multicentre Study on Congenital Toxoplasmosis, 2003; Wallon *et al.*, 2013) . In 2020, a group of experts from the French College of Obstetricians and Gynecologists reviewed the evidence and recommended the continuation of monthly screening (Picone *et al.*, 2020) .

The most common way the mother becomes infected is either through environmental exposure to contaminated animal waste (cats), or through eating undercooked or processed contaminated meat, or unwashed fruits and vegetables.

- **CMV**

The ACOG companies ('Practice bulletin no. 151: Cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy', 2015) and SMFM (Society for Maternal-Fetal Medicine (SMFM), Hughes and Gyamfi-Bannerman, 2016) recommend to do not it is done The terminological control routine for cytomegalovirus (CMV).

Pregnancy screening for CMV is indicated:

- In the differential diagnosis of infectious mononucleosis-like diseases.
- If a fetal abnormality suggestive of congenital CMV infection is detected on ultrasound.
- If the pregnant woman requests the examination.

- **Hepatitis A**

In the United States, hepatitis A vaccination during pregnancy is recommended for women at high risk of infection, such as those with:

- Progr ammatized international vinegar a _
- Illicit drug use (injecting or not)

- Occupational risk of infection (e.g., daycare, residential facility, military personnel)
- Close contact with an adopted person from a foreign country or with homeless people
- Concern about a serious outcome from hepatitis A virus (HAV) infection (e.g., personal history of chronic liver disease or HIV).

Prevaccination testing to determine preexisting immunity to HAV is generally not warranted, but is reasonable for individuals with a high probability of prior exposure to HAV (Nelson *et al.*, 2020) .

➢ **Measles**

In areas of ongoing measles outbreaks with prolonged close-knit community transmission, serological testing for measles immunoglobulin G (IgG) in pregnant women without documented immunity to measles is reasonable. Any of the standard serological tests for measles-specific IgG can be used for laboratory documentation.

For patients not at high risk of measles exposure, evidence of immunity includes documentation of age-appropriate completion of measles-mumps-rubella (MMR) vaccination (at least one dose of live measles-containing vaccine), laboratory evidence of immunity, or laboratory confirmation of measles. For patients at high risk of measles exposure (e.g., health care workers, postsecondary students, international travelers), the immunity data is similar except that at least two doses of live measles-containing vaccine are required. However, if laboratory evidence of immunity is available, this is sufficient documentation of immunity, regardless of the number of vaccine doses previously administered.

Pregnant women without documented evidence of immunity should be vaccinated after delivery, as MMR is a live vaccine (McLean *et al.*, 2013) .

➢ **Gonorrhea**

All pregnant women aged <25 years and pregnant women aged ≥25 years at increased risk of gonorrhea should be screened for Neisseria gonorrhoeae at the first prenatal visit. Physicians should consult local public health authorities for information about groups most vulnerable to acquiring gonorrhea based on local disease prevalence.

NAAT (Nucleic acid amplification testing) is the preferred test for the microbiological diagnosis of N. gonorrhoeae due to its greater accuracy. A swab is used to collect a vaginal or cervical sample for testing. Pregnant patients who are positive are treated immediately and retested in three months (Workowski *et al.*, 2021) .

- **Tuberculosis**

Asymptomatic women are screened for latent TB infection during pregnancy when one of the following significant risk factors for progression to active disease is present that would warrant early treatment:

- Suspicion of recent tuberculosis infection based on epidemiological report
- HIV infection or profound immunosuppressive therapy
- Tools for diagnosing latent TB include tuberculin skin tests (TSTs) and interferon-gamma release assays (IGRAs). The latter are preferred in patients with a history of vaccination with BCG (Bacillus Calmette - Guerin) and for people from groups that historically have low performance rates for reading the skin test ('Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society', 2000) .

- **Bacterial vaginitis**

The companies ACOG (Committee on Practice Bulletins—Obstetrics, The American College of Obstetricians and Gynecologists, 2012) , USPSTF (US Preventive Services Task Force *et al.*, 2020) and CDC (Workowski *et al.*, 2021) they suggest to do not it is done regular control and treatment of all of pregnant with asymptomatic bacterial vaginitis for her prevention of premature childbirth and of consequences of .

Whether pregnant women with a history of previous preterm birth should be screened for bacterial vaginosis and treated (if positive) to reduce the risk of recurrent preterm birth is controversial.

- **Trichomonas**

Although screening for Trichomonas vaginalis is not recommended as a routine component of prenatal care for asymptomatic HIV- negative women, those with HIV infection and aged ≤35 years residing in a correctional facility should be screened for trichomonas at the first prenatal visit and treated if infected. Trichomonas in people with HIV is associated with an increased risk of vertical and horizontal transmission of HIV. The examination should be repeated three months after treatment (Workowski *et al.*, 2021) .

- **Herpes simplex virus**

For pregnant women with no history of previous herpes simplex virus (HSV) infection, serologic testing has been suggested to accurately identify two groups of individuals:

- Those who are truly HSV negative, so they can take precautions to avoid infection.
- HSV positive may therefore be offered suppressive antiviral therapy, carefully examined for lesions at the onset of labor, and offered caesarean section if indicated (e.g., lesions present)

Although accurate serological tests are available for typing and to guide counseling, universal serological testing is not recommended. Available evidence suggests that testing for HSV does not meet the usual criteria for an effective preventive strategy, as has been demonstrated for other infections such as HIV and HBV (Workowski *et al.*, 2021) .

- **Zika**

In areas where Zika is not transmitted by mosquitoes, doctors should ask all pregnant women about possible exposure:

- Staying in or traveling to an area where mosquito transmission of the Zika virus has been reported, or
- Unprotected sexual intercourse with a person who meets these criteria. Pregnant women should be tested within 12 weeks of possible exposure, regardless of symptoms.

- **COVID -19**

Testing for SARS-CoV-2 is not routinely performed in asymptomatic women in the community based on pregnancy status alone.

Screening on admission to the delivery clinic depends on symptoms, the prevalence of COVID-19 in the community, and the vaccination status of the patient (Hashim *et al.*, 2022) .

- **Chagas disease**

Chagas disease is endemic in Latin America. Therefore, the possibility of this infection should be considered in pregnant patients who have lived in this area. Infected individuals are often unaware of their infection and the potential severity of the condition (e.g., cardiovascular/digestive complications, transmission to the fetus, hydrops fetalis). Prenatal screening is carried out in some countries (Verani *et al.*, 2010) .

1.4. Prenatal control in the second and third trimester of singleton pregnancy

1.4.1. Frequency of prenatal visits

Observational data suggest that prenatal care can save lives and show an association between number of antenatal visits and/or early gestational age at initiation of care and pregnancy outcome, after controlling for confounders (eg. gestational age) (Dowswell *et al.,* 2015) . However, there are limited data on the optimal number and frequency of prenatal visits or the optimal content of these visits.

In the United States, typical visit intervals for nulliparous women with uncomplicated pregnancies are every 4 weeks through 28 weeks of gestation, every 2 weeks from 28 to 36 weeks, and weekly thereafter until delivery. Women with high-risk pregnancies are monitored more frequently, depending on the nature of the problems. According to this follow-up schedule, a woman with an uncomplicated pregnancy whose first visit is at 6 weeks of gestation and the last visit is at 41 weeks will have 16 prenatal visits (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017) .

While the standard prenatal visit schedule in the United States is commonly followed, it requires significant effort and planning on the part of the pregnant woman without clear evidence of benefit.

Apgar score <7, neonatal death, or small-for-gestational-age infants among women who had more of 10 prenatal visits and those who had 10 or fewer prenatal visits. Women in the high-visit group were 33% more likely to have an induction of labor and 50% more likely to have a caesarean section than women in the few-visit group, but the data are insufficient to infer a causal relationship (Carter *et al.,* 2016) .

For women with high-risk pregnancies based on various criteria, randomized trials comparing standard versus enhanced prenatal care (e.g., additional office visits, health education, home visits, telephone contact, psychosocial support) have not reported significant improvement in outcome with enhanced care (Klerman *et al.,* 2001) .

The National Institute for Health and Clinical Excellence (NICE) recommends a reduced frequency of visits: 10 appointments for nulliparous women and 7 appointments for the rest, and that each visit should have a specific purpose or goal. This approach takes into account the cost and time constraints of modern society and the lack of proven effectiveness of frequent prenatal visits in randomized trials (National Institute for Health and Clinical Excellence, 2021) .

The 2016 World Health Organization (WHO) Prenatal Care Guidelines recommend at least eight antenatal visits for all women, regardless of the number of deliveries. The WHO advises one visit in the first trimester, two in the second trimester and five in the third trimester (World Health Organization, 2016) .

This represents an increase of four visits from previous recommendations in response to a 2015 systematic

review that reported a 15% increase in perinatal deaths for women with low-risk pregnancies in middle- and lower-income countries who had reduced antenatal visits (typically fewer than five visits) in compared to women with more visits (Dowswell *et al.,* 2015) .

High risk pregnancy

A healthy woman with a simple pregnancy is generally considered low risk. Although there is no precise definition of a high-risk pregnancy, it generally includes women who do not meet the definition of a low-risk pregnancy due to medical or surgical conditions, past or present obstetric complications, or social or demographic factors (e.g., older or younger age of the mother, lack of social support, high number of births [≥4 to 6 births]). There is consensus that these women need additional care during pregnancy (National Institute for Health and Clinical Excellence, 2021) . The nature and frequency of additional care depends on individual factors.

Covid -19

The American College of Obstetricians and Gynecologists suggests due to the Covid -19 pandemic some modifications to traditional protocols for prenatal visits, which should be tailored to low- versus high-risk patients (e.g., multiple pregnancy, hypertension, diabetes). These include:

- Telemedicine appointment (by phone or video call) for a check-up that does not require a clinical examination, laboratory or imaging test or parenteral medication administration. For example, symptom testing and counseling and some types of screening (e.g., depression) can be done remotely.
- Reducing the number of appointments/visits:
    - Group laboratory tests on the same visit/day (e.g., aneuploidies, diabetes, infection control) when possible. For example, the physician may recommend a two-hour oral glucose tolerance test (GTT) of 75 g instead of a three-hour GTT of 100 g (in patients with positive results). Testing for free fetal DNA in maternal blood can be used (after 10 weeks) for screening for Down syndrome instead of the combined test (i.e., cervical smear and serum biochemical markers).
    - Grouping of indications for indicated ultrasound examinations to minimize their number (e.g., a single examination at 18 weeks for gestational age, fetal anatomy study, and placental abruption) when possible.

  - Revision of the time and frequency of non - stress tests and biophysical profiles, when possible.
  - Home monitoring of pregnant women's weight, blood pressure, glucose and urine protein levels.
- Limiting the number of people in visits and waiting rooms and maintaining physical distance
- Use of virtual media for meetings beyond prenatal visits (e.g., delivery room tours, childbirth classes)
- Expanded use of phone or video helplines and email for patient questions (van den Berg *et al.*, 2022)

1.4.2. Signs and symptoms that should be reported to the doctor

Pregnant women should be advised about signs and symptoms that should be reported to a doctor immediately, such as:

- Vaginal bleeding
- Discharge of fluid from the vagina
- Decreased fetal activity
- Signs and symptoms of preterm labor (e.g., low back pain, increased uterine activity compared to before, period-like cramps, diarrhea, increased pelvic pressure, clear vaginal discharge, spotting or bleeding, contractions)
- Signs and symptoms of pre-eclampsia (e.g., headache unresponsive to a single dose of paracetamol, visual changes, persistent epigastric or right hypochondrium abdominal pain)
- As with any patient, signs and symptoms suggestive of a medical or surgical disorder should be reported.

1.4.3. Evaluations on an ongoing basis

The assessments that are done on an ongoing basis at each prenatal visit are the following:

- Blood pressure measurement- The procedure for checking blood pressure is generally similar to that of non-pregnant women. Blood pressure decreases slightly in the second trimester and then increases slightly at the end in normal pregnancies. Measurement of blood pressure is essential for the diagnosis of hypertension, but no cutoff for mean arterial or systolic or diastolic blood pressure

in early pregnancy performs well in predicting future occurrence of preeclampsia or gestational hypertension (Cnossen, Vollebregt, et al ., 2008) .

- Weight measurement - Weight gain during pregnancy can affect the outcome of the pregnancy. Weight gain goals depend on the woman's baseline weight. Dietary requirements and recommendations for weight gain are higher in multiple pregnancies. Guidelines are provided separately. Continuous assessment of weight gain during pregnancy, as well as ongoing discussion about diet and exercise, can help prevent excessive weight gain during pregnancy and postpartum overweight or obesity (Institute of Medicine (US) and National Research Council (US) Committee that Reexamine IOM Pregnancy Weight Guidelines . Rasmussen KM, Yaktine AL, editors, 2009) .
- Urine dipstick for protein, although the value of this test is questionable in normotensive women (Rhode, Shapiro and Jones, 2007) .
- Assessment of fetal growth in the second and third trimesters either by measurement of fundus height or by ultrasound assessment for women with risk factors for intrauterine growth restriction.
- Documenting fetal heartbeats.
- Assessment of maternal perception of fetal activity (in the second and third trimesters).
- Evaluation of the presentation of the fetus (in the third trimester).
- Assessment of significant events from a previous visit, such as recent travel, illness, stressors, or exposure to infection (e.g., Zika virus or severe acute respiratory syndrome, coronavirus 2 [SARS - CoV -2]), etc.
- Overview of signs and symptoms of possible pregnancy problems.

These simple, non-invasive, inexpensive assessments detect up to 50% of fetuses with a growth abnormality, prevent 70% of eclampsia by early detection of pre-eclampsia (Carroli, Rooney and Villar, 2001) and identify 80% of breech presentations before delivery when external transformation can be done reducing the need for caesarean section (Leung, Pun and Wong, 1999) .

Pharmaceutical preparations of trace elements

During pregnancy, the following medications are also considered and recommended to be taken by mouth

- **Folic acid**
  - **Evidence** - The body of evidence supports the effectiveness of folic acid supplementation and nutritional supplementation in reducing the occurrence and recurrence of open neural tube lesions

(neural tube defects [NTDs]) by at least 70%. Folic acid supplementation, usually as part of a multivitamin, has also been associated with a variety of other benefits, including reducing the risk of hypertensive disorders during pregnancy and the occurrence of congenital anomalies other than NTDs.

- **Recommended Intake** - The Dietary Guidelines for Americans recommend 0.6 mg of folic acid/day for pregnant women (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2020) . In addition to a folate-rich diet, the United States Preventive Services Task Force (USPSTF) recommends a supplement containing 0.4 to 0.8 mg of folic acid one month before and for the first two to three months after conception for reducing the risk of NTDs (US Preventive Services Task Force *et al.,* 2017) . Thereafter, the recommended daily intake is 0.6 mg to meet the growth needs of the fetus and placenta. Continued folic acid supplementation after the first trimester prevents the decrease in serum folate and the increase in homocysteine concentrations that occur when supplementation is discontinued (McNulty *et al.,* 2013) . For high-risk pregnant women (history of NTDs, diabetes and use of anticonvulsants), the recommendations for folic acid are higher (4 mg /day).

➢ **Elemental Iron**

- **Evidence** - Iron is essential for the development of the fetal brain and placenta and for increasing the mother's red blood cell mass. Iron deficiency, which is the most prevalent deficiency of a nutrient worldwide (McLean *et al.,* 2009) and a leading cause of anemia, it is estimated to occur in 19% of pregnant women in the United States, ranging from 7% in the first trimester to 30% in the third trimester (Mei *et al.,* 2011) . Although systematic reviews have observed that routine iron supplementation in pregnancy consistently leads to a reduction in the incidence of iron deficiency anemia towards the end of pregnancy (eg RR 0.29, 95% CI 0.17–0.49), the clear benefits to mothers or offspring have not been consistently demonstrated with a variety of other outcomes (Cantor *et al.,* 2015) , even in pregnant women with iron deficiency anemia (Reveiz *et al.,* 2011) . However, the available evidence is generally of low quality.
- **Recommended intake** - Dietary reference values for iron in pregnancy vary worldwide (Fairweather - Tait, 2022) . The Centers for Disease Control and Prevention CDC recommends an iron intake of 27 mg/day during pregnancy (up from 18 mg/day in non-pregnant/non-lactating women) to prevent iron deficiency anemia ('Recommendations to prevent and control iron

deficiency in the United States.Centers for Disease Control and Prevention', 1998) . THE WHERE recommends daily downloading supplements of iron from the mouth with 30 to 60 mg of elemental of iron (World Health Organization, 2012) . This amount is easily covered by most prenatal vitamin formulations and is an adequate supplement for non-anemic individuals. British authorities have concluded that no additional dietary iron is required during pregnancy, provided iron stores at conception are adequate (Norwich, UK : The Stationery Office, 2011) . Of note, in the United States, the average dietary intake of iron among pregnant women is 17 mg/day from food alone and 38 mg/day from food plus supplements (Bailey *et al.,* 2019) . Importantly, 36% of pregnant women consume less than the required amount. For pregnant women with iron deficiency anemia (first- or third-trimester hemoglobin [Hb] <11 g/dL or second-trimester Hb <10.5 g/dL and low serum ferritin [<40 ng/mL]), an additional iron supplement (30 to 120 mg/day) is required until anemia is corrected (World Health Organization, 2012) . One option is 65 mg elemental iron (325 mg ferrous sulfate) every other day (Stoffel *et al.,* 2017) . Iron absorption decreases with increasing dose, so larger amounts of supplements are best split into several doses throughout the day. Intermittent iron supplementation (one to three times per week) appears to be as effective as daily supplementation in preventing anemia toward the end of pregnancy, is better tolerated, and may lead to better compliance (Pe ñ a - Rosas *et al.,* 2012) . The tolerable upper limit of 45 mg/day set by the National Academy of Medicine (formerly the Institute of Medicine [IOM]) based on gastrointestinal side effects is well below international recommendations (Institute of Medicine (US) Panel on Micronutrients, 2001) and he's got be disputed (Schümann _ _ *et al.,* 2007) . It is worth noting that iron absorption increases significantly with advanced gestational age (Delaney *et al.,* 2022) . Evidence shows, however, that this increase is smaller in overweight mothers (Stoffel *et al.,* 2022) .For people who cannot tolerate oral iron, iron can be administered safely and effectively intravenously (Wong *et al.,* 2016) .

- **Calcium**
  - **Evidence** - Low levels of calcium and vitamin D have been associated with adverse maternal and child health outcomes, but it is unclear whether low levels are the causative factor or a marker of poor maternal health. Skeletal development of the fetus requires about 30 g of calcium during pregnancy, mainly during the last trimester. This amount is a relatively small percentage of total maternal body calcium and is readily mobilized from maternal stores if necessary. Intestinal

absorption and renal retention of calcium increase progressively throughout pregnancy (Hacker, Fung and King, 2012) . For pregnant women with low basal dietary calcium intake, taking high-dose calcium supplements may reduce the risk of hypertensive disorder of pregnancy (Hofmeyr *et al.,* 2018) . Calcium supplementation does not appear to reduce this risk in healthy, nulliparous pregnant women in whom basal dietary calcium intake is adequate. Although there may be a benefit in preventing preeclampsia in high-risk populations, further study is needed, as the available information is based on small numbers of patients and heterogeneity in the study populations. Calcium supplementation does not appear to reduce the risk of spontaneous preterm delivery or low birth weight (Buppasiri *et al.,* 2015) .

- **Recommended Intake** - In the United States, the recommended daily intake of calcium is 1000 to 1300 mg/day for pregnant and lactating women, depending on age (National Institutes of Health, 2021) . Of note, the average calcium intake among pregnant women in the United States is 1090 mg/day from food and 1300 mg/day from food plus supplements. It is estimated that 21% of pregnant women consume less than 800 mg/day from food alone (Bailey *et al.,* 2019) .

➢ **Vitamin D**

- **Evidence** - In addition to its role in calcium and bone homeostasis, vitamin D potentially regulates many other cellular functions. Low vitamin D levels in the perinatal period may have short- or long-term consequences for bone, immune system, and general health, but the exact threshold for optimal vitamin D levels during pregnancy and the effects of high-dose supplementation (4000 to 5000 international units per day) on pregnancy outcomes are not well defined (Litonjua *et al.,* 2016; Cannell, 2017; Hollis and Wagner, 2017; Mustapa Kamal Basha *et al.,* 2020; Venter *et al.,* 2020) .
- **Recommended Intake** - The Dietary Guidelines for Americans recommend a daily intake of 600 international units per day during pregnancy (U.S. Department of Agriculture and U. _ S. _ Department of Health and Human Services, 2020) . Vitamin D deficiency is estimated to affect between 40 and 98% of pregnant women worldwide (van Schoor and Lips, 2011) . Most prenatal vitamins contain 400 international units of vitamin D, but some formulations contain as little as 200 or as much as 1000 to 1200 international units. The safe upper limit of vitamin D has not been well studied, but was conservatively set at 4000 international units in a 2011 guideline (Ross *et al.,* 2011) .

Nutritional requirements are higher in multiple pregnancies. Guidelines are provided separately.

1.4.4. Periodic reviews and procedures

1.4.4.a. 15-24 weeks of pregnancy

Screening for neural tube defects

For women who choose to undergo screening for neural tube defects, the α-fetal protein (AFP) maternal serum (MSAFP) and ultrasound examination are both effective methods. AFP is a fetus-specific globulin, synthesized by the fetal milk sac, gastrointestinal tract, and liver. Its function is unknown. Maternal serum population-based screening (MSAFP) is ideally performed at 16 to 18 weeks' gestation, but may be performed as early as 15 weeks or as late as 20 weeks (Driscoll, Gross, and Professional Practice Guidelines Committee, 2009) .According to ACOG guidelines, B-level ultrasound examination of fetal anatomy is generally the preferred approach ('Practice Bulletin No. 187: Neural Tube Defects', 2017) .

Population control for trisomy 21

For women who make their first prenatal appointment in the second trimester or choose to be screened for Down syndrome (trisomy 21) in the second trimester, the most common test is the quadruple test (a-fetal protein [AFP] measurement, unconjugated estriol [uE3], human chorionic gonadotropin [hCG] and inhibin A in maternal serum between 15 and 22 weeks' gestation). Testing for free fetal DNA in the mother is another option (Nicolaides, 2011) .

Screening for fetal abnormalities

For women who choose to undergo ultrasound screening for fetal structural abnormalities, the procedure is performed with the anatomical or B-level ultrasound optimally in the second trimester, between 18 and 22 weeks' gestation. (National Institute for Health and Clinical Excellence, 2021) . During this examination, the number of fetuses, cardiac function and fetal biometry are also checked, and the condition and position of the placenta and the volume of amniotic fluid are determined (AIUM - ACR - ACOG - SMFM - SRU, 2018) .

Although many congenital anomalies can be detected in the first trimester, the sensitivity is higher in the second trimester. Additional tests (chorionic villus sampling or amniocentesis) and follow-up tests will be needed to confirm the suspected diagnosis.

Meta-analyses of randomized trials evaluating the utility of routine prenatal ultrasound examination reported the following findings. Compared to selective use, routine ultrasound examination in early pregnancy (up to 24 weeks' gestation) (Whitworth, Bricker and Mullan, 2015) :

- It improved detection of multiple pregnancies (3 vs. 39% of multiple pregnancies not detected, relative risk [RR] of failing to detect multiple pregnancies 0.07, with 95% confidence interval [CI] 0.03–0.17).
- It improved detection of major fetal anomaly (15.3 vs 4.4% detected, RR 3.46, 95% CI 1.67-7.14).
- It improved the dating of pregnancy, resulting in fewer challenges for prolonged pregnancy (1.8 vs 3.1% challenge rate, RR 0.59, 95% CI 0.42-0.83).

However, perinatal death (stillbirth after study entry, death of a live-born infant up to 28 days of age) was similar for the routine and screening groups (0.7 vs. 0.8%, RR 0.89, 95% CI 0 .70-1.12).

Several factors (e.g., gestational age at examination, type of malformation, number of ultrasounds performed, operator experience, equipment quality, population characteristics) influence detection rates and were not included in the meta-analysis.

Screening for cervical insufficiency

A short cervical length (≤25 mm) on transvaginal ultrasound between 16- and 24-weeks' gestation is associated with an increased risk of preterm delivery. The length of the cervix can be measured when a pregnant woman undergoes a B-level ultrasound. There is insufficient evidence to mandate a policy of cervical length screening between 16 and 24 weeks for all pregnancies (Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella, 2012) . However, in randomized trials, interventions such as vaginal progesterone therapy have reduced the rate of subsequent preterm birth (Romero *et al.,* 2012) .

Screening for preeclampsia or intrauterine growth restriction

B -level ultrasound, the flow resistance of the uterine arteries can be assessed by Doppler measurement in order to identify pregnancies with an increased risk of pre-eclampsia or intrauterine growth restriction (intrauterine growth restriction - IUGR or fetal growth restriction - FGR).

1.4.4.b. 24-28 weeks of pregnancy

Screening for gestational diabetes

In the United States, universal screening for gestational diabetes is recommended at 24 to 28 weeks' gestation. Early screening should be considered in women with significant risk factors (e.g., gestational diabetes in a previous pregnancy, first degree congenital diabetes). Screening may be performed after 28 weeks in women who initially present for prenatal care after 28 weeks (' ACOG Practice Bulletin No. _ 190: Gestational Diabetes Mellitus ', 2018) .

If in the U.S. had a population-based screening approach based on risk factors been used, 90% of pregnant women in the United States would have at least one risk factor for impaired glucose tolerance during pregnancy (Danilenko - Dixon *et al.,* 1999) . Furthermore, screening for risk factors is a poor method for identifying patients to undergo a glucose tolerance test (GTT) because up to 20% of pregnant women diagnosed with gestational diabetes have no risk factors (Farrar *et al.,* 2017) .

A systematic review by the USPSTF concluded that there is a modest net benefit of screening for gestational diabetes at 24 weeks' gestation or later in improving maternal and fetal outcomes (Pillay *et al.,* 2021) .

Instead, NICE recommends assessing the risk of gestational diabetes based on the following risk factors:

- BMI over 30 kg/m2
- previous macrosomic neonate weighing 4.5 kg or more
- previous gestational diabetes
- family history of diabetes (first-degree relative with diabetes)
- an ethnicity with a high prevalence of diabetes.

For women with any of these risk factors, it recommends testing with a glucose tolerance curve at 24-28 weeks (National Institute for Health and Clinical Excellence, 2021) .

Administration of hyperimmune anti- D γ-globulin in RhD negative women

In Rh D negative women, antibody testing is repeated at 28 weeks of gestation and anti-D immunoglobulin is administered. Although there is good evidence that administration of immunoglobulin is cost-effective, there are no data establishing the cost-effectiveness of repeat antibody testing at this time if the initial antibody test was negative.

In RhD-positive women who had a negative antibody test early in pregnancy, retesting for antibodies in the third trimester is not cost-effective (ACOG, 2017) .

Screening for anemia

Hemoglobin or hematocrit should be checked early in the third trimester to check for anemia. Increased iron and folate requirements during pregnancy can result in anemia, which can usually be corrected before delivery with appropriate supplementation.

Anemia in late pregnancy is defined as follows:

- Second trimester – Hemoglobin level <10.5 g/dL (approximate hematocrit <32%)
- Third trimester – Hemoglobin level <11 g/dL (approximate hematocrit <33%)

These values are based on data from an iron-supplemented population (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, 2021 a)

1.4.4.c. 28-36 weeks of pregnancy

Screening for sexually transmitted infections

The Centers for Disease Control and Prevention (CDC) recommends testing for STIs (e.g., HIV, syphilis, chlamydia, gonorrhea) in the third trimester (28 to 36 weeks) in women at increased risk:

- Personal history of previous sexually transmitted infection
- Age <25 years
- New sexual partner in the last 60 days
- More than one sexual partner or sexual partner with multiple partners at the same time
- The sexual partner was diagnosed with a sexually transmitted infection
- No or inconsistent condom use outside of a mutually monogamous sexual relationship
- Sexual activity for money or drugs
- Sexual contact with sex workers
- Meeting anonymous mates from the internet
- Lower socioeconomic status or high school education or less
- Admission to a correctional institution or juvenile detention center
- Use of illegal drugs
- Residence in a community with a high prevalence of sexually transmitted infections (Workowski *et al.*, 2021) .

The value of repeat testing is supported by a retrospective study of STI test results in 1.3 million pregnant women in the United States (Blatt *et al.*, 2012) . Among women who tested positive for chlamydia or

gonorrhea at least once during pregnancy and were retested before delivery, the last prenatal test was positive in 6% (969/16,039) of women who had previously tested positive for chlamydia and in 3.8% (100/2610) of women who had previously tested positive for gonorrhea. Among women aged 16 to 24 or 25 years who tested negative at the first prenatal visit but were at increased risk of acquiring an STD, 3.4% (1746/50,959) had a subsequent positive chlamydia test and 1.1% (564/ 51,077) a subsequent positive test for gonorrhea. In some areas, repeated testing for syphilis and HIV is mandatory. HIV retesting using an opt-out approach in the third trimester (≤36 weeks' gestation) is recommended for women at increased risk of HIV infection, women living or receiving care in areas of high HIV prevalence, symptomatic women (e.g., fever, lymphadenopathy, skin rash, myalgias, arthralgias, headache, mouth ulcers, leukopenia, thrombocytopenia, elevated transaminases), incarcerated women and women who refused screening earlier in pregnancy (Workowski *et al.,* 2021) . The basis for this recommendation is that appropriate intervention during labor can significantly reduce perinatal transmission. A conventional or rapid test can be used in the third trimester.

Screening for intrauterine growth restriction

- **Definition**

  The two most common definitions of fetal growth restriction (IUGR or FGR) are an estimated fetal weight below the 10th percentile for gestational age (Battaglia and Lubchenco, 1967) and an abdominal circumference (AC) below the 10th percentile for gestational age (' Fetal Growth Restriction : ACOG Practice Bulletin, Number 227', 2021) . The use of the 10th percentile to define FGR is problematic because it does not distinguish between small fetuses that are in the lower range of normal versus small fetuses due to a pathological process that prevented them from achieving their growth potential and versus fetuses that grow higher from the 10th percentile, but have a delay in growth if their growth potential corresponded to an even higher position. However, the lower the percentile, the more likely the diagnosis of FGR is than for a normal small fetus (small for gestational age - SGA).

- **Classification**

  - Early FGR refers to diagnosis before 32 weeks of gestation, in the absence of congenital anomalies.
  - Late FGR refers to diagnosis at ≥32 weeks of gestation, in the absence of congenital anomalies.

- Symmetrical FGR comprises 20 to 30% of FGR and refers to a pattern of growth in which all fetal organs are proportionally reduced due to the overall damage of cellular hyperplasia early in gestation. Symmetrical FGR is thought to result from a pathologic process that manifests early in pregnancy.
- Asymmetric FGR comprises the remaining 70 to 80% and is characterized by a relatively greater reduction in abdominal circumference (e.g., liver volume and subcutaneous adipose tissue) than in head circumference. Asymmetric fetal growth is thought to result from the ability of the fetus to adapt to an abnormal environment in late gestation, redistributing blood flow to benefit vital organs (e.g., brain, heart, placenta) at the expense of its non-vital organs (e.g. abdominal organs, lungs, skin, kidneys) (Bahado - Singh *et al.*, 1999) .

➢ **Population control**

Ideally, prenatal detection of FGR will provide an opportunity to use interventions to reduce the morbidity and mortality associated with this problem. However, the benefit of screening for FGR has not been clearly established. There are different approaches :

- Measurement of the distance between the upper lip of the pubic symphysis to the bottom of the uterus and selective ultrasound.

  The first suspicion of FGR often occurs when this length does not agree with the expected size for the gestational week. Discordance has been defined in a number of ways. The most common criterion is the fundal height in centimeters to be at least 3 cm less than the gestational age in weeks (eg fundal height 32 cm at 36 weeks' gestation) (Beliz á n *et al.*, 1978) .

  Risk assessment for intrauterine growth restriction based on maternal, environmental, placental, and fetal risk factors is recommended. Thus :

  - For women at high risk for FGR, a developmental ultrasound is performed to estimate fetal weight and provide a detailed ultrasound assessment of the fetus, placenta, and amniotic fluid at least once or twice in the third trimester (every three to four weeks), as well as when bottom height lag is detected. The frequency of ultrasound examination within this range depends on the physician's assessment of the patient's level of risk for FGR. Information from the ultrasound examination is used to support or exclude the diagnosis of FGR.

- For women who are not at high risk for FGR, ultrasonography is performed when fundal height hypoplasia is detected, when fundal height cannot be palpated (e.g., obese patient), or fundal height is not reliable (e.g., eg fibroids, appendicular masses, multiple pregnancy) (Committee on Practice Bulletins—Obstetrics and the American Institute of Ultrasound in Medicine, 2016; McCowan, Figueras and Anderson, 2018) .

- Universal ultrasound examination

  Universal ultrasonography is an alternative screening method for FGR. There is no consensus on the timing or number of screening tests. In general, if two follow-up tests are performed after the B-level ultrasound of the fetus at 18-22 weeks, these are performed at approximately 32 and 36 weeks of gestation (Bricker, Medley and Pratt, 2015) . If a test is performed, it is performed between 32 and 36 weeks of gestation and the predictive performance is highest near 36 weeks (Ciobanu *et al.*, 2019) .

➢ **Developmental ultrasound - Doppler (24 weeks - 40 weeks)**

The purpose of this examination is to check the development of the fetus, to estimate the amount of amniotic fluid as well as the position of the placenta and it can be performed from the 24th week. FGR may be associated with abnormal Doppler waveforms in maternal vessels (uterine arteries) and fetal vessels (umbilical artery, middle cerebral artery, ductus venosus) when the etiology is placental dysfunction associated with progressive obliteration of capillary vessels. Evaluation of Doppler measurements with appropriate intervention can reduce perinatal mortality in these pregnancies. Doppler findings in FGR are discussed below:

- **Umbilical Artery-** When 30% of the placenta ceases to function, an increase in umbilical artery resistance is consistently observed leading to decreased end-diastolic flow and is a weak predictor of adverse outcome in FGR (Maggio *et al.*, 2015) . The most common Doppler indices used in clinical practice are:
  - Pulsability Index (PI = peak systolic velocity - end-diastolic velocity / mean velocity)
  - Resistance Index (RI = peak systolic velocity - end-diastolic velocity/ peak systolic velocity)
  - S/D ratio: Peak systolic velocity/end-diastolic velocity

  The pulsatility index is preferred because it gives a better estimate of waveform characteristics than the RI or S/D index (Bhide *et al.*, 2021) .

When 60 to 70% of the placenta is inactivated, umbilical artery end-diastolic flow is absent or reversed, and the fetal prognosis is poor. Reverse end-diastolic flow is associated with worse neonatal outcomes compared to the absence of end-diastolic flow (Baschat, 2010) .

- **Uterine Artery** - Resistance in the uterine arteries is normally low in early pregnancy and decreases as pregnancy progresses. Thus increased mean resistance may be indicative of insufficient trophoblast penetration and increases the likelihood of preeclampsia and FGR (Smith *et al.,* 2007) . The uterine artery contraction/dilation (S/D) ratio in normal pregnancies should be <2.7 after 26 weeks of gestation. If end-diastolic flow does not increase throughout pregnancy or if a small uterine artery notch is detected at the end of systole, the fetus is at high risk of developing FGR (Schulman *et al.,* 1986) .
- **Fetal descending aorta** - An increased pulsatility index in the fetal descending aorta is associated with both FGR and adverse outcomes, including severe FGR, necrotizing enterocolitis, nonreassuring fetal heart rate patterns, and perinatal mortality. In a group of 30 fetuses with absent end-diastolic flow in the descending aorta, abnormal waveforms were detected an average of 80 days before the onset of fetal heart rate abnormalities (Arabin *et al.,* 1988) . All neonates were growth restricted and 66% had abnormal placentas with villous fibrosis and microfibrous deposits. The sensitivity and specificity of the absence of end-diastolic flow in the descending aorta for predicting FGR with FHR abnormalities is approximately 85 and 80%, respectively (Bonatz *et al.,* 1997) . These pregnancies are also characterized by higher rates of caesarean section, right ventricular failure, and perinatal mortality.
- **Fetal Middle Cerebral Artery** - In the normally developing fetus, the brain is a region of low vascular resistance and the recipient of continuous forward flow throughout the cardiac cycle. Asymmetric FGR is likely caused by redistribution of fetal blood flow to the fetal brain at the expense of less essential areas, such as subcutaneous tissue, kidneys, and liver. Since the already low mean cerebral resistance must be further reduced to enhance cerebral blood flow, FGR may be associated with increased end-diastolic velocities and decreased pulsatility index values Index PI), in the resistance indicator (Resistance Index RI) and in the contraction/dilation relationship (S ystolic / diastolic ratio S /D) (Baschat, Gembruch and Harman, 2001) . Normalization of markers can occur when the autoregulatory response becomes dysfunctional (Simpson *et al.,* 2016) .

- **Cerebroplacental** ratio - It is the pulsatility index of the middle cerebral artery (or resistance index) divided by the pulsatility index of the umbilical artery (or resistance index). A low ratio indicates redistribution of fetal blood flow (cerebral sparing) and is predictive of adverse neonatal outcome (Conde-Agudelo *et al.,* 2018) .
- **Fetal ductus venosus** - With progressive increases in umbilical arterial resistance, fetal cardiac output may decrease, and central venous pressure may increase, resulting in decreased diastolic flow in the ductus venosus and other large veins. Vasodilation of the ductus venosus further diverts nutrient- and oxygen-rich blood toward the heart but enhances retrograde transmission of atrial pressure. The resistance index of the ductus venosus increases, eventually with loss of the a-wave. An absent or inverted ductus venosus α-wave indicates cardiovascular instability and may be a sign of impending metabolic acidosis and death (Turan *et al.,* 2011) . Because the time from detection of ductal regurgitation to fetal death or non-reassuring fetal control is variable, there is probably a transition phase between the presence of positive end-diastolic flow and the absence or reversion of end-diastolic flow (Picconi et al ., 2008) .

In fetuses with estimated weight <10th percentile and/or abdominal circumference <10th percentile, we obtain both umbilical and middle cerebral artery pulsatility index weekly. If either is abnormal (>95th percentile for umbilical artery, <10th percentile for middle cerebral), we diagnose FGR with placental insufficiency. In some cases of FGR, middle cerebral artery Doppler may be the first parameter to become abnormal, followed by the umbilical artery (Bhide *et al.,* 2021) .

If consecutive Doppler results are normal, the frequency of Doppler examination may be reduced to two-week intervals. The two-week interval is reasonable for the fetus with EFW ≥ 5th percentile, normal growth velocity, normal amniotic fluid volume, and no maternal risk factors for placental dysfunction. The Society for Maternal-Fetal Medicine recommends an umbilical artery Doppler study every one to two weeks initially and, if normal, the interval between tests can be extended to two to four week intervals (Society for Maternal - Fetal Medicine (SMFM) *et al.,* 2020) .

If umbilical artery diastolic flow is present but decreased (abnormal umbilical artery pulsatility index PI > 95th percentile), weekly Doppler is performed to look for a possible progression to absent or reversed flow.

Absent or reversed end-diastolic flow in the umbilical artery may be a sign of impending fetal cardiovascular and metabolic deterioration. If any of these abnormal patterns are detected, labor should be considered. The decision to deliver in this setting is based on gestational age as long as the daily NST

or BPP is normal. The absence of abnormal flow patterns in the ductus venosus has been used to support the decision to extend such a pregnancy and may allow the pregnancy to be extended up to two weeks. The Society for Maternal-Fetal Medicine has advised against using this routine test for clinical management (Society for Maternal - Fetal Medicine (SMFM) *et al.*, 2020) .

Although the use of venous Doppler remains largely investigational, an increasing number of maternal-fetal medicine specialists are using this tool to avoid very preterm delivery in fetuses with absent or reversed end-diastolic arterial flow in the umbilical artery and reassuring antenatal screening. fetus (resting cardiotocography [non - stress test], biophysical profile). In these pregnancies, the absence of abnormal flow patterns in the ductus venosus is used to support the decision to extend the pregnancy to 30 to 33 weeks if the NST and biophysical profile remain reassuring (Baschat , 2004) .

Determining the appropriate approach to prenatal assessment of fetal well-being

The main techniques for evaluating the fetus are the nonstress cardiotocography test (NS)], the biophysical profile (BP), the modified biophysical profile, the contraction test stress test (CST) and the number of fetal movements. Assessment of amniotic fluid volume (independent of biophysical profile and modified biophysical profile) and Doppler velocimetry of fetal and maternal vessels provide additional information on fetal status. Despite the widespread use of these techniques, there is limited evidence to demonstrate their optimal use or to demonstrate their effectiveness in improving perinatal outcomes. The goals of prenatal fetal assessment are firstly to identify fetuses at risk of intrauterine death or developing neurological complications from slowly progressive (chronic) intrauterine hypoxia, and secondly for the physician to intervene to prevent these adverse outcomes, if possible.

- **Clues**

The American College of Obstetricians and Gynecologists (ACOG) recommends antepartum fetal evaluation for pregnancies at increased risk of fetal death, which the College defined as a stillbirth rate greater than 0.8 per 1000 and associated with a relative risk for stillbirth >2.0 compared to pregnancies without the condition. This stillbirth rate was chosen because it is the false negative rate of the biophysical profile (American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, Society for Maternal-Fetal Medicine, 2021) .

The most common clinical situations in which prenatal fetal testing is usually performed are listed below:

- Diabetes- Pre-existing or gestational diabetes treated with medication. Gestational diabetes in which glucose levels are normal with nutritional therapy does not appear to be associated with an increased risk of stillbirth, so prenatal fetal screening may be omitted.
- Hypertensive disorders- Chronic or pregnancy-related hypertension
- FGR fetal growth restriction
- Twin pregnancy
- Prolongation of gestation- Screening is often initiated between 41 $^{+0}$ and 42 $^{+0}$ weeks of gestation, but may be initiated at an estimated gestational age of 39 $^{+0}$ to 40 $^{+0}$ weeks in a pregnancy in which the age is suboptimally determined (' Committee Opinion No. 688: Management of Suboptimally Dated Pregnancies ', 2017) .
- Decreased fetal activity
- Systemic lupus erythematosus
- Antiphospholipid syndrome
- Sickle cell anemia
- RhD alloimmunization
- Oligohydramnium or polyhydramnium
- Previous fetal death
- Premature rupture of membranes- Premature rupture of membranes may be associated with oligohydramnios and possibly subclinical endometrial infection. The goal of antenatal screening in this context is early recognition of intra-amniotic infection requiring delivery.

In addition, epidemiological data suggest a small increased risk of fetal death associated with a number of additional conditions, which are possible indications, including:

- Advanced maternal age
- Obesity
- Significant structural abnormalities of the fetus (Frey *et al.*, 2014)
- Abnormal values in biochemical tests of the population control for trisomy 21 (Down syndrome) in the first and second trimesters (Gagnon, Wilson, and SOCIETY OF OBSTETRICS AND GYNAECOLOGISTS OF CANADA GENETICS COMMITTEE, 2008)

- **Measurement of fetal movements**

All pregnant women should be aware of fetal movements, either subjectively or using a kick-counting method, and notify their physician if fetal movement decreases.

Objective assessment of fetal movements by the mother is based on evidence that fetal movement is reduced in response to fetal hypoxemia (Bocking, 2003) . Although there is general agreement that patients with reduced fetal motility should undergo further fetal evaluation, the available evidence does not support a clear fetal motility threshold or "alert threshold" that indicates when the risk of fetal death or injury is increased. Randomized fetal motility trials looking at assessment of fetal well-being have not found conclusive evidence for the benefit of this intervention.

- **Resting ECG (NST)**

The NST was developed as a result of the observations that firstly the presence of two or more fetal heart rate accelerations during a contraction endurance test (CST) often predicted a negative CST and secondly the absence of the accelerations was associated with adverse perinatal outcomes (Evertson *et al.*, 1979) . Accelerations, spontaneous or induced (e.g., by vibroacoustic stimulation), are a good indicator of normal fetal autonomic function and the absence of acidosis and neurologic depression. Although a meta-analysis of randomized trials found no clear evidence that NST improved perinatal outcome, the quality of the evidence was low or very low (Grivell *et al.*, 2015) .

From week 32, a NST is considered reactive or reassuring if there are two or more fetal heart rate accelerations that peak at least 15 beats / min above baseline and last at least 15 seconds from onset to return to baseline (15 x 15) in a period of 20 minutes (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, 2021b) . A reactive test provides reliable evidence of normal fetal oxygenation, regardless of the length of observation time required to demonstrate reactivity (Brown and Patrick, 1981) .

Different criteria have been proposed for **gestational age less than 32 weeks.** In this case, an NST can be defined as reactive if there are two accelerations that peak at least 10 beats above baseline and last at least 10 seconds (10 x 10) (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, 2021b) . Whether physicians choose to apply the conventional 15 x 15 criteria or adopt the 10 x 10 criteria when performing NST before 32 weeks' gestation, they should use the same approach in all patients. However, once a fetus has demonstrated the maturity to generate accelerations of

15 beats for 15 seconds, an acceleration of 10 beats for 10 seconds may not have the same ability to confirm normal fetal oxygenation, even before 32 weeks pregnancy.

The **optimal duration of NST** has not been determined. Some sources recommend that the NST be continued for at least 20 minutes, even if two qualifying accelerations have been observed before this time (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017) . However, large studies evaluating the prognostic value of NST in combination with amniotic fluid volume estimation have not included this requirement (Miller, Rabello and Paul, 1996) .

The significance of a **reactive NST with** ECP decelerations is unclear. Many observational studies have described an increased incidence of intrapartum decelerations and invasive deliveries when this combination occurs (Hoskins, Frieden et al . and Young, 1991; Glantz and D' Amico, 2001) , unless the decelerations are short (Meis *et al.,* 1986) . However, the results are usually good. The majority of ECP decelerations during NST are variable decelerations, reflecting transient episodes of cord compression. Variable, late, or prolonged decelerations observed during prenatal testing require further evaluation, which may include extensive monitoring of EGFR and uterine activity, ultrasound assessment of fetal growth and anatomy, biophysical profile, amniotic fluid volume, and/or Doppler velocimetry in the context of fetal growth restriction. Intermittent fetal heart arrhythmias may also cause decelerations and may be diagnosed by echocardiography. Management depends on the arrhythmia and patient-specific factors.

An **NST is non-reactive** if it does not meet the acceleration criteria for a reactive NST. ECP should be monitored for at least 40 minutes before the test is interpreted as non-reactive. Unresponsiveness may be a sign of fetal oxygenation interruption to the point of metabolic acidosis. The mean umbilical vein pH associated with a nonreactive NST is 7.28±0.11, which is higher than the pH associated with a low biophysical profile (BPP) score of 7.16±0.08 (Manning *et al.,* 1993) . Other possible causes of a nonreactive NST include fetal immaturity, fetal sleep, maternal smoking, fetal neurological or cardiac abnormalities, sepsis, or maternal ingestion of drugs with cardiac effects (Oncken *et al.,* 2002) . Sleep is a common and benign cause of non-reactive NST. Sleep cycles can last up to 40 minutes (Pillai and James, 1990b) . One study reported sleep cycles lasting up to 53 minutes (Suwanrath and Suntharasaj, 2010) . In a study that observed late preterm fetuses from unselected pregnancies for 100 minutes, quiet sleep occurred at least once in 30% of fetuses, but 96% of fetuses cycled between quiet sleep and active states during the observation period (Pillai and James, 1990a) .

Regarding the **evaluation of pregnancies with nonreactive NSTs,** up to 60% of nonreactive NSTs may be false positives (usually defined as nonreactive NSTs prompting labor), but delivery is not associated with findings suggestive of acute fetal oxygenation (e.g. ECP decelerations or loss of variability, meconium passage, invasive delivery for acute ECP changes, low Apgar scores or abnormal umbilical cord blood gas values) or chronic suboptimal fetal oxygenation (e.g. restriction of fetal development, oligohydramnios). A non-reactive NST usually requires further evaluation. Some options include:

- Repeat test in 30 minutes
- Perform vibrational and acoustic stimulation to induce accelerations
- Run a backup test (either CST or complete biophysical profile) (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, 2021b) .
- If possible, modification of factors that may cause nonreactive results (e.g., smoking near the test).

The main advantage of NST over CST is that it does not require an IV-line, oxytocin, or contractions. Disadvantages are that false-negative and false-positive test rates are higher than for CST (a false-negative NST is when a prenatal stillbirth occurs within a week of a reactive test; a false-positive NST is a non-reactive CT followed by a normal backup test, such as a negative CST score or high biophysical profile [BPP]) (Freeman, Anderson and Dorchester, 1982a) .

➢ NST with amniotic fluid evaluation

Ultrasound assessment of amniotic fluid volume is often performed as an adjunct to NST to improve sensitivity (i.e., reduce the rate of false-negative reactive tests). Only low-quality data support this hypothesis. A small retrospective study reported that pregnancies with reactive NSTs and low amniotic fluid index AFI (Amniotic Fluid Index) (0 to 5 cm) were at increased risk for meconium discharge and a five-minute Apgar score <7 at delivery compared with those with a normal amniotic fluid index (Rutherford *et al.,* 1987) . A study in extended pregnancies reported that reduced amniotic fluid volume and variable decelerations were associated with an increased incidence of fetal distress, even when the NST was reactive, but the performance of the combined test was similar to that of either test alone (Bochner et al ., 1987) .

➢ Contraction strength test

Contraction resistance test stress test [CST]) is based on the fetal response to a transient decrease in fetal oxygen supply during uterine contractions. If the fetus becomes hypoxemic (fetal arterial pO2 below 20

mmHg) reflex slowing of the fetal heart rate occurs, which may manifest clinically as late decelerations. The change in EKP is mediated by fetal chemoreceptors and tasenoreceptors and by parasympathetic and sympathetic fibers in the heart and cerebral vasculature (Itskovitz, Goetzman and Rudolph, 1982) .

CST is interpreted as follows:

- Positive- A positive (abnormal) test has late decelerations after ≥50% of contractions. The test is positive even if the frequency of contractions is less than three in 10 minutes.
- Negative- A negative (normal) test has no late decelerations or significant variable decelerations.
- Equivocal- An equivocal-suspicious test has intermittent late decelerations or significant variable decelerations, while an equivocal-tachysystolic test has decelerations with contractions that occur more frequently than every two minutes or last longer than 90 seconds.
- Unsatisfactory - An unsatisfactory test has fewer than three contractions in 10 minutes (and is not positive as defined above) or cannot be interpreted for other reasons (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, 2021b) .

CST is rarely performed given the wide availability of other tests (e.g. NST, biophysical profile) that do not have its main disadvantages: the need to stimulate contractions with intravenous oxytocin, the contraindication for induction of contractions in certain situations (e.g. placenta previa) and the high rate of false positives (i.e., the fetus continues to tolerate labor without heart rate changes requiring intervention). However, the false-negative rate (i.e., the rate of fetal death within one week of a negative test) is very low, thus providing reassurance of adequate fetal oxygenation after a normal test result (Freeman, Anderson and Dorchester, 1982b) .

A positive (abnormal) CST indicates transient fetal hypoxemia during uterine contractions and may be an indication for labor, depending on the clinical scenario. Further evaluation may include a biophysical profile (BPP) and, in the setting of fetal growth restriction, Doppler velocimetry. A CST with variable decelerations indicates cord compression which may be due to oligohydramnios (Hoskins, Frieden and Young, 1991) . In one study, 50% of reactive CST positives were false positives, while 100% of nonreactive CST positives were true positives. Thus, the presence of accelerations during CST may reduce the need for intervention, but additional assessment (e.g., BPP) is warranted (Braly and Freeman, 1977) .

- **Biophysical profile**

The biophysical profile (BP) combines NST with ultrasound assessment of the fetus by assigning scores to the following parameters: fetal respiratory movements, fetal movements, fetal tone and amniotic fluid volume. Thus, this test assesses markers of both acute hypoxia (NST, respiration, body movement, tone) and chronic hypoxia (AFV). The biophysical profile score has a direct linear correlation with fetal pH. The **criteria for the biophysical profile** are as follows :

- NST: 2 points if at least 2 episodes of ECP accelerations of at least 15 beats for at least 15 seconds are observed in association with fetal movements within 30 minutes
- Fetal respiratory movements: 2 points if one or more episodes of rhythmic respiratory movement lasting at least 30 seconds are observed within 30 minutes
- Fetal tone: 2 points if one or more episodes of extension of one limb of the fetus or spine with return to flexion are detected.
- Fetal movements: 2 points if 3 or more distinct trunk or limb movements are observed within 30 minutes. An episode of active continuous movement is counted as one movement (Manning, Platt and Sipos, 1980) .
- Amniotic fluid volume: 2 points if there is at least one fluid pocket that is ≥2 cm deep and ≥1 cm wide

H **interpretation of the BP result** is as follows:

- A score of 10/10, 8/8 or 8/10 without oligohydramnios is reassuring for fetal well-being as the risk of fetal death within one week is low (0.5/1000 births)
- A result of 6/10 without oligohydramnios is an equivocal result and should be repeated within 24 hours if the pregnancy is not terminated.
- A result of 0 to 4/10 indicates a high risk of fetal asphyxiation within one week (90 to 600/1000 births) if the fetus remains without delivery or therapeutic intervention is not received.
- Scores of 6/10 or 8/10 with oligohydramnios (0 points for amniotic fluid) are abnormal, as the risk of fetal asphyxia within one week is 89/1000 with expectant management. These scores should be interpreted in the context of gestational age (e.g., neonatal morbidity and mortality if the fetus is delivered) and maternal and obstetric factors (e.g., risk of fetal death associated with maternal, fetal, or obstetric disorder if the fetus is not born, if the cervix is favorable, maternal risks from continuing the pregnancy).

The minimum gestational age for initiation of testing should reflect the lower threshold at which labor intervention would be considered. We repeat normal-scored BP (10/10 or 8/10 without oligohydramnios) weekly or biweekly until delivery when the high-risk condition persists and appears stable, and more frequently when there is significant clinical deterioration (e.g., worsening pre-eclampsia, reduced fetal activity) or in selected very high-risk situations (severe fetal growth restriction with abnormal Doppler velocimetry).

The **modified biophysical profile** consists of NST as a measure of acute oxygenation and assessment of amniotic fluid volume as a measure of long-term oxygenation. It is considered abnormal if the NST is unreactive, there is no amniotic fluid pocket ≥2 cm, or both. It simplifies the examination and reduces the time required to complete the test by focusing on those elements of BP that are most predictive of outcome. Assessment of both amniotic fluid volume and NST appears to be as reliable a predictor of long-term fetal well-being as the complete biophysical profile.

The false negative rates for the biophysical profile and the corresponding modified profile are very low, but the false positives are high (a false negative is when an antenatal stillbirth occurs within a week of a high score, a false positive is when a low score is followed from normal backup test).

- **Assessment of amniotic fluid volume**

In the hypoxemic fetus, cardiac output is redirected to the brain, heart, and adrenal glands and away from less vital organs, such as the kidney. Decreased renal perfusion leads to decreased fetal urine production, which can lead to a decreased amount of amniotic fluid (oligohydramnios) over time. This is the main rationale for evaluating amniotic fluid volume as an adjunct to NST and as a routine component of the biophysical profile. ECP abnormalities may be seen, as cord compression is more likely in oligohydramnios.

Amniotic fluid volume can be assessed qualitatively or quantitatively. Maximum amniotic fluid pool and amniotic fluid index are commonly used assessment methods and are equivalent in their prediction of adverse outcome in singleton pregnancies (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, 2021b) .

- **Doppler ultrasound**

Measurement of blood flow velocities in maternal and fetal vessels provides information about uteroplacental blood flow and fetal responses to physiological challenges. Abnormal placental vascular

development, as in preeclampsia, leads to progressive hemodynamic changes in the fetoplacental circulation. Doppler indices from the umbilical artery increase when 60 to 70% of the placental vascular tree is compromised (Thompson and Trudinger, 1990) . The resistance of the fetal middle cerebral artery decreases, and the resistance of the fetal aorta increases to preferentially direct blood to the fetal brain and heart. Eventually, end-diastolic flow in the umbilical artery stops or reverses and resistance increases in the fetal venous system (ductal venosus, inferior vena cava) (Ferrazzi *et al.*, 2002) . These changes occur at variable time periods and correlate with fetal acidosis (Weiner, 1990) .

Unlike most other methods of fetal assessment, Doppler tests have been rigorously evaluated in randomized trials. The information derived from the velocity waveforms varies depending on the particular vessel being examined.

Umbilical artery Doppler is the most common Doppler technique used for fetal assessment where fetal hypoxemia is a concern. American College of Obstetricians and Gynecologists guidelines support the use of umbilical artery Doppler measurements in the management of suspected fetal growth restriction, but not for normally developing fetuses. When monitoring the growth-restricted fetus, umbilical artery Doppler should be used with standard fetal assessment (NST and/or biophysical profile) (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, 2021b) .

Middle cerebral artery peak systolic flow velocity (MCA-PSV) is the best tool for predicting fetal anemia in pregnancies at risk such as RhD alloimmunization.

The clinical utility of Doppler measurement of the fetal **venous system** is greatest in fetal situations with cardiac manifestations and/or severe placental insufficiency. These conditions include fetal growth restriction due to placental insufficiency, fetal-twin transfusion syndrome, hydrops fetalis, and fetal arrhythmia (Hofstaetter and Gudmundsson, 2010) .

Some investigators have investigated the use of **uterine artery Doppler** for fetal assessment in the third trimester in women with complicated pregnancies, but its role in these cases has not been clearly defined (Hernandez - Andrade *et al.*, 2002; Gudmundsson *et al.*, 2003) . Resistance to flow in the uterine arteries usually decreases as pregnancy progresses. Failure of adequate trophoblast invasion and remodeling of maternal spiral arteries is characterized by persistent high-pressure maternal circulation and increased resistance to uterine artery blood flow. Elevated resistance indices and/or persistent uterine artery nicks at 22 to 24 weeks' gestation indicate reduced blood flow in the maternal placental compartment and have been associated with the development of preeclampsia, fetal growth restriction, and perinatal death (Papageorghiou *et al* ., 2002) .

External cephalic version

For pregnancies with breech presentation, an external transformation is offered (external cephalic version [ECV]) at 36 weeks of gestation. Randomized trials have shown that transformation is an effective procedure for increasing the likelihood of cephalic presentation at the onset of labor and reducing the caesarean section rate (assuming that breech delivery is not desired). It has been shown to have a high degree of safety and success at this gestational age, but may be started earlier (34 to 35 weeks) to improve the success rate. Earlier conversion will likely reduce the cesarean delivery rate, but the safety of ECV performed before 36 weeks is less well established. This process is also suitable for transverse or oblique presentation.

The effectiveness of the method is supported by two systematic reviews. In a systematic review that included eight randomized trials (1308 patients) of late-gestation conversion, women who underwent ECV compared with those with iliac-prone fetuses who had not attempted ECV had a reduced risk of noncephalic presentation at birth by about 60% (relative risk [RR] 0.42, 95% CI 0.29-0.61) and reduced the risk of cesarean delivery by about 40% (RR 0.57, 95% CI 0.40 0, 82) (Hofmeyr, Kulier and West, 2015) . A second systematic review including more than 180,000 patients, but with a greater risk of bias due to the inclusion of non-randomized studies, found similar results (Devold Pay *et al.,* 2020) .

Although ECV reduces the rate of cesarean delivery compared with no delivery, the rate of cesarean delivery after successful ECV remains higher than in the general obstetric population. In a 2014 meta-analysis of observational studies of mode of birth after successful ECV, the cesarean delivery rate after successful ECV was approximately twice as high as the rate in patients with cephalic fetuses and no ECV (21 vs 11%, RR 2.19, 95% CI 1.73–2.76). The increased risk of cesarean delivery was due to both dystocia and nonreassuring fetal heart rate patterns (de Hundt *et al* ., 2014) .

1.4.4.d. 36-41 weeks of pregnancy

Screening for group B B-hemolytic streptococcus

In the United States, all pregnant women are screened at 36 $^{+0}$ to 37 $^{+6}$ weeks of gestation for group B beta-hemolytic streptococcal colonization with both lower vaginal and rectal swabs. The only women not included are those with previous GBS bacteruria in the current pregnancy or with a previous infant with invasive GBS disease, because these women should receive antibiotic prophylaxis during delivery.

Antibiotic coverage of colonized women during labor has been shown to reduce the incidence of early-onset neonatal GBS. Although a shorter duration of recommended antibiotics for labor is less effective

compared with 4 or more hours of prophylaxis, 2 hours of antibiotic exposure has been shown to reduce the number of GBS vaginal colonies and reduce the frequency of a clinical diagnosis of neonatal sepsis. Obstetric interventions, when necessary, should not be delayed solely to provide 4 hours of antibiotics before birth ('Prevention of Group B Streptococcal Early-Onset Disease in Newborns: ACOG Committee Opinion, Number 797', 2020) .

Educating women in preparation for childbirth

- Labor pain management
- Mode of delivery
- Stimulation of Labor
- Prolongation of gestation- If the cervix is partially dilated and the patient desires intervention, a digital hysteroscopy after 39 weeks may hasten the onset of labor. For women ≥41 weeks' gestation, induction of labor rather than waiting is recommended (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017) .

Educating women about postpartum issues

- Contraception after childbirth
- Postpartum care and complications
- Breastfeeding
- Selection and possible meeting with a pediatrician (Yogman *et al.*, 2018)
- Newborn safety and care

2. Diagnosis of multiple pregnancy

Twin pregnancy

Ultrasound examination is the best method to diagnose a twin pregnancy. Most pregnant women in resource-rich countries undergo one or more routine ultrasound examinations to obtain detailed information about the developing pregnancy, including the number of fetuses. Randomized trials comparing routine ultrasound with clinical-only ultrasound have shown that a significant number of twin pregnancies are not recognized until the third trimester or even delivery in women who do not undergo routine ultrasound:

- The RADIUS (Routine Antenatal Diagnostic Imaging with Ultrasound Study) study of more than 15,000 pregnancies found that when a routine second-trimester ultrasound was not performed, 38% of twin pregnancies were not diagnosed until after 26 weeks' gestation and 13% were not diagnosed until childbirth (Ewigman *et al.*, 1993) .
- The Helsinki Ultrasound Trial reported similar findings: About 25% of twin pregnancies were not diagnosed until after 21 weeks of gestation (Saari - Kemppainen *et al.*, 1990) .

In both studies, no twin pregnancies were lost when an ultrasound examination was performed between 15- and 22-weeks' gestation.

Guidelines for prenatal ultrasound screening vary worldwide. In the United States, the American College of Obstetricians and Gynecologists recommends an ultrasound examination for all pregnant women, ideally at 18 to 22 weeks' gestation in the absence of specific indications (e.g., size larger than dates, vaginal bleeding, pelvic pain) (Committee on Practice Bulletins — Obstetrics and the American Institute of Ultrasound in Medicine, 2016) .

Triplet pregnancy

The diagnosis of triplet pregnancy is based on the ultrasound examination, which is generally done initially to estimate the gestational age or the heart activity of the fetus. An increased likelihood of a triplet pregnancy may be suspected based on the use of assisted reproductive technology for conception and/or a large-for-gestational-age uterine size.

2.1. Determination of gestational age in multiple pregnancies

Twin pregnancy

Gestational age is determined by ultrasound examination, unless there is no known date of conception (e.g., in vitro fertilization [IVF] embryo transfer). If there is discordance between twins in the biometric measurements used to estimate gestational age, the general consensus is that the probable date of delivery should be based on the measurements for the older twin (Morin *et al.*, 2011; A. Khalil *et al.*, 2016) . This will minimize the risk of missing a diagnosis of growth restriction, which is common in multiple pregnancies, due to underestimation of gestational age.

Ultrasound assessment before 22 weeks' gestation provides an accurate estimate of gestational age, which is important in all pregnancies, but especially important in the management of twin pregnancies because of the higher incidence of complications. The accurate estimation of the gestational age is necessary for

the exact timing of the various preventive and diagnostic tests carried out during pregnancy, for the control of fetal growth in relation to the gestational age and for the exact timing of delivery planning.

Triplet pregnancy

In women who have become pregnant as a result of assisted reproductive technology, the first ultrasound examination of pregnancy is generally carried out at six weeks of pregnancy, when the fetal heartbeat can be detected for the first time. Online calculators are available, such as the pregnancy due date and gestational age calculator (' Pregnancy Due Date and Gestational Age Calculator ', http :// perinatology . com / calculators / Due - Date. htm) , and applications to calculate estimated due date and gestational age based on one of the following dates, as appropriate: ovulation date, egg retrieval date, insemination date, or 6-8 cell embryo transfer date (day 3) or blastocyst (day 5).

In naturally conceived triplet pregnancies, estimating the gestational age and determining the estimated date of delivery is the same as for singletons.

2.2. Determination of chorionicity-amnionicity in multiple pregnancies

Twin pregnancy

Chorionicity and amnionicity are most accurately determined by ultrasound in the first trimester after seven weeks of gestation [sensitivity ≥98% (Emery *et al.,* 2015)], but this may be before the first twin pregnancy diagnosis. Accuracy is lower but acceptable in the early second trimester [sensitivity ≥90% (Emery *et al.,* 2015)] (Lee *et al.,* 2006; Wan *et al.,* 2011; Blumenfeld *et al.,* 2014) . Ultrasound assessment of fetal membranes is more difficult and less accurate in the third trimester, particularly in case of oligohydramnios.

Chorionicity and amnionicity are determined in the following ways:

- **The identification of two separate placentas is a highly reliable indicator of dichorionic twins.** This indicator is generally only useful in early pregnancy, as separate placentas often appear fused later in pregnancy. Therefore, it is important to emphasize that a single visible placental mass is not diagnostic of a monochorionic pregnancy. Rarely, a monochorionic placenta that is bilobed or has paraplacentas gives the impression of two separate placentas (Lopriore *et al.,* 2006) .

- **The presence or absence of a membrane between the twins and its ultrasound features early in pregnancy indicate chorionicity and amnionicity.** Care should be taken when assessing the presence or absence of a common membrane early in the first trimester (approximately seven to nine weeks), when the amnion may not be readily detectable and lead to a misdiagnosis of monoamniotic twins. In this early evaluation, two placental sacs indicate diamniotic twins, and one placental sac indicates monoamniotic twins. Amnionicity should be confirmed at a later ultrasound, as discrepancies have been reported in both cases, i.e., diamniotic twins with two lectic sacs and monoamniotic twins with a single sac.

  In the case of suspected early fetal death in a monochorionic twin pregnancy, the absence of vascular flow in the dead twin should be confirmed to rule out reverse arterial flow sequence (TRAP).

  - **Monochorionic monoamniotic twins :**

    Finding umbilical cord entanglement (M- mode with two different heartbeats in adjacent cord loops) is diagnostic for monoamniotic twins, but umbilical cord entanglement is not always detected.

    Another finding is that the intertwin membrane is absent in the monochorionic monoamniotic twin pregnancy. Visualization of the membrane becomes more difficult with advanced gestational age due to crowding of the fetuses, progressive thinning of the membrane, and, in some cases, the development of oligohydramnios in one or both sacs. These factors may lead to a false diagnosis of monochorionic monoamniotic twins. On the other hand, monochorionic monoamniotic twins may be misdiagnosed as monochorionic diamniotic twins when the amnion-chorion separation is mistaken for a membrane between the twins.

    In early pregnancy (before 10 weeks), the membrane may be missed and lead to an inaccurate diagnosis of monoamniotic twins. Estimating the number of amniotic sacs is useful in these cases, as monoamniotic twins will most often have only one amniotic sac (Aisenbrey *et al.*, 1995) .

  - **Dichorionic diamniotic twins :**

    A film with the tipping point (twin peak sign) or lambda sign indicates dichorionic twins. This sign refers to a triangular presentation of tissue extending between the layers of the common membrane from a fused dichorionic placenta (Wood *et al.,* 1996) . It is best seen at 10 to 14 weeks, becomes less apparent after 20 weeks of gestation and may disappear.

An additional indication that twins are dichorionic is that the common membrane is thicker in dichorionic than monochorionic twins, as the dichorionic diamniotic membrane consists of four layers (i.e., two layers of amnion and chorion), whereas the common membrane in a monochorionic diamniotic pregnancy consists of only two amniotic layers. There is no consensus on the dividing line between thin and thick films. Limits of 1.5 to 2 mm have been suggested in the first trimester (Kurtz *et al.,* 1992; Carroll *et al.,* 2002) . The difference in membrane thickness is less apparent later in pregnancy (Townsend, Simpson and Filly, 1988; D ' Alton and Dudley, 1989) . After the first trimester, the identification of different-sex fetuses is a highly reliable means of confirming dichorionic pregnancy, which is why obstetric ultrasound guidelines include evaluation of the genitalia when twins are identified (AIUM - ACR - ACOG - SMFM - SRU, 2018) .

- **Monochorionic diamniotic twins** :

  An intertwin membrane with a T-shaped sign indicates a monochorionic placenta. This point refers to the appearance of a thin common membrane, which is formed by the 2 individual amniotic lobes without the mediation of the dermis, as it recovers with the placenta at an angle of 90°.

- The **number of chorionic and amnion membrane layers** in the common membrane can be measured, but it is technically difficult. Therefore, this method is not commonly used. It is best achieved between 16- and 24-weeks' gestation using high-resolution, high-magnification images with the membrane perpendicular to the ultrasound beam.

In a study involving more than 600 twin pregnancies from 11 to 14 weeks' gestation at a tertiary referral center, the use of T-score, lambda-score, and placental count had 100% sensitivity and 99.8% specificity for determining monochorionicity, with only one dichorionic pregnancy misassigned as monochorionic (Dias, Arcangeli, *et al.,* 2011) . A placental hematoma excluded the diagnosis of T or lambda point in the misassigned pregnancy. Other smaller studies have reported sensitivity of 90 to 100% and specificity of 97.4 to 99.5% using these markers and fetal sex. In a systematic review of the accuracy of the lambda score alone (2292 twins, nine studies), the sensitivity for predicting dichorionicity was 99% (95% CI 98–100) and the specificity was 95% (95% CI 92–97) (Maruotti *et al.,* 2016) . The pooled sensitivity of the absence of the lambda sign for predicting monochorionicity was 96% (95% CI 92–98) and the pooled specificity was 99% (95% CI 98–99).

- **Pitfalls in ultrasound diagnosis**

There are many reasons for imperfect ultrasound accuracy, and clinicians should be aware of the possibility of exceptions to the usual rules for determining chorionicity and amnionicity. For example, a monochorionic placenta may be bilateral and appear as two separate placentas (but careful imaging will reveal vascular anastomoses between the lobes and thus a risk for twin-twin transfusion syndrome TTTS), and rarely monozygotic twins have phenotypic discordance gender (Lu *et al.,* 2018) .

- **Use of non-invasive prenatal testing to determine zygosity**

It may be possible to determine zygosity with non-invasive prenatal testing (NIPT- Noninvasive prenatal testing) and this could help assess chorionicity when ultrasound findings are unclear. A small prospective blinded study to validate a single nucleotide polymorphism-based NIPT reported 100% accuracy for zygosity in samples from all 29 monozygotic and 64 dizygotic twins in which a result was reported (Norwitz *et al.,* 2019) . Two other samples did not yield any results. While amnionicity and chorionicity in monozygotic twins reflect the timing of zygotic division, dizygotic twins will be dichorionic in almost all cases. However, because cases of monochorionic dizygotic twins are rare, dizygosity on NIPT very rarely does not also determine dichorism (Peters *et al.,* 2017) .

Triplet pregnancy

Determination of chorionicity and amnionicity, ideally performed between 8- and 13-weeks' gestation, is critical for risk assessment, counseling and pregnancy management. The process and interpretation of chorioamnionicity is similar to that in twin pregnancies.

2.3. Labeling of fetuses in multiple pregnancies

Twin pregnancy

It is important to use a consistent strategy for identifying and labeling each twin at consecutive examinations in the second and third trimesters. Generally, twin A is the presenting fetus, whose sac is closest to the internal cervical os, and which would emerge first in an assumed normal delivery. Since confusion can occur when the presenting twin appears to switch positions, it is important to describe the position of the placenta and the gender of each twin. In same-sex twins, each twin can be identified by its orientation relative to the other twin: left or right for twins placed side by side, and top (fundal) or bottom (cervical) for twins placed vertically. The superior twin in laterally oriented twins may appear to change

over time, but the inferior twin in vertically oriented twins is likely to remain the presenting twin throughout gestation (Dias, Ladd, *et al.*, 2011) . It is also helpful to document the sites of placental implantation (anterior, posterior, lateral) and the locations and types of umbilical cord insertion (e.g., eccentric vs. central, normal vs. membranous).

Twins may not be born in the order expected by prenatal ultrasound especially when delivered by caesarean section.

Triplet pregnancy

It is important to use a consistent strategy to identify and label each triplet on repeat ultrasound examinations in the second and third trimesters. Each triplet can be identified by its gender and orientation in relation to the other triplets, although this can change. Documenting the sites of placental implantation (anterior, posterior, lateral) and the locations and types of umbilical cord insertion are also useful for labeling.

3. Maternal adaptation to multiple pregnancies

The various physiological burdens of pregnancy and the potential for serious maternal complications are usually greater with a multiple pregnancy than with a singleton pregnancy. This is taken into account, especially when counseling a woman whose health has been compromised and in whom a multiple pregnancy is recognized early. Similar attention is paid to the woman who is not pregnant but is considering infertility treatment.

From the first trimester, and due to higher serum β-hCG levels, women with multiple pregnancies often experience nausea and vomiting to a greater extent than women with singleton pregnancies. In multiple pregnancies, the increase in pregnant blood volume is greater and averages 50 to 60% compared to 40 to 50% in singleton pregnancies (Pritchard , 1965) . This increased hypervolemia teleologically compensates for the blood loss with vaginal delivery of twins, which is twice that of a single fetus. Although red blood cell mass also increases, the increase is proportionally less in twin pregnancies. Combined with higher requirements for iron and folate, this predisposes to anemia.

Women who have twins also have a typical pattern of blood pressure variation. MacDonald-Wallis and his colleagues (Macdonald - Wallis *et al.*, 2012) analyzed consecutive blood pressures in more than 13,000 singleton and twin pregnancies. As early as the 8th week of gestation, diastolic blood pressure in women

with twins was lower than in singletons, but generally increased to a greater extent at the end of pregnancy. A previous study showed that this increase was at least 15 mm Hg in 95% of women with twins compared with only 54% of women with singleton pregnancies (Campbell, 1986) .

Hypervolemia together with reduced vascular resistance has a dramatic effect on cardiac function. In a study of 119 women with twin pregnancies, cardiac output increased 20% over that of women with singleton pregnancies (Kametas *et al.*, 2003) . Similarly, Kuleva and colleagues (Kuleva *et al.*, 2011) using echocardiography found a greater increase in cardiac output in 20 women with uncomplicated twin pregnancies. Both studies found that the increased cardiac output was primarily due to a larger stroke volume rather than a higher heart rate. Vascular resistance was significantly lower in twin pregnancies throughout pregnancy compared to singleton pregnancies. In a study of 30 uncomplicated twin pregnancies, this same group of researchers using echocardiography later detected progressive diastolic dysfunction from the first to the third trimester. The dysfunction then normalized after delivery (Ghi *et al.*, 2015) .

The growth of the uterus in a multiple pregnancy is substantially greater than in a singleton pregnancy. The uterus and its non-fetal contents can have a volume of 10 L or more and weigh more than 20 kg. Especially in monozygotic twins, excessive amounts of amniotic fluid can accumulate quickly. In these cases, the maternal abdominal organs and lungs may be compressed and noticeably displaced by the expanding uterus. As a result, the size and weight of a large uterus may preclude more than just a sedentary life for these women.

If polyhydramnios develops, maternal renal function may be severely affected, probably as a consequence of obstructive uropathy (Quigley and Cruikshank, 1977) . In severe polyhydramnios, therapeutic amniocentesis may provide relief for the mother, may improve obstructive uropathy, and possibly reduce the risk of a preterm infant following preterm labor or premature rupture of membranes. Unfortunately, polyhydramnios is often characterized by an acute onset earlier than the expected due date and rapid reaccumulation despite amniocentesis.

4. Types of complications in multiple pregnancies: Diagnosis, monitoring and treatment

4.1. Maternal complications in multiple pregnancies

4.1.1. Preeclampsia

- **Epidemiology**

Pregnancy-related hypertensive disorders are more likely to develop in multiple pregnancy. The exact frequency attributable to a twin pregnancy is difficult to determine because in these pregnancies preterm labor is more likely to occur and before preeclampsia usually develops. Also, women with twin pregnancies are often larger and multiparous, qualities associated with higher rates of preeclampsia. In a study with 513 twin pregnancies, preeclampsia was detected in 15% of pregnant women (Fox *et al.*, 2014) . No particular zygosity confers a greater rate of hypertensive disorder in twin pregnancies (Luč ovnik *et al.*, 2016) . In a study with data from King 's Hospitals College and Medway Maritime for the time period 2006-2015 included 95459 singleton pregnancies and 2554 twin pregnancies, from which around 335 were removed due to miscarriage, termination of pregnancy, fetal defect, and inability to monitor the progress of the pregnancy. The incidence of preeclampsia was 2.3% in singleton pregnancies, 8.1% in dichorionic twins and 6% in monochorionic twins. The relative risk was 3.5 in dichorionic twin pregnancies and 2.61 in monochorionic versus singleton pregnancies. Also, in this particular study, it was found that the early onset of pre-eclampsia (24^{+0}-36^{+6} weeks) in twin pregnancies is 9 times higher than in singletons. It has also been found that the complications of pre-eclampsia, regarding both the fetus and the mother, are also more frequent in twin pregnancies. For this reason, a more systematic screening for preeclampsia is required in twin pregnancies than in singleton pregnancies (Francisco *et al.*, 2017) .

Another study compared 257 women with twins and gestational diabetes with 277 non-diabetic women who had twins. These researchers found a double risk of preeclampsia in women diagnosed with gestational diabetes (Gonz á lez Gonz á lez *et al.*, 2012) .

One study found that assisted reproductive technology pregnancies had an increased risk (relative risk [HR]: 2.1) of developing mild or severe preeclampsia, even after controlling for maternal age and number of children (Lynch *et al.*, 2002) .

The US National Center for Health Statistics analyzed 316,696 twin, 12,193 triplet, and 778 quadruplet pregnancies and concluded that the risk of pregnancy-related hypertension was significantly increased for triplets and quadruplets (11 and 12%, respectively) compared with the risk for twins (8%) (Luke and

Brown, 2008) . According to another study, the occurrence of hypertensive complications is proportional to the total number of fetuses, with singleton pregnancies in 6.5%, twins in 12.7%, and triplets in 20.0% (Day *et al.*, 2005) .

These data suggest that fetal number and placental mass are involved in the pathogenesis of preeclampsia. Women with twin pregnancies have twice the levels of the anti-angiogenic protein sFlt -1 (soluble form of fms-like tyrosine kinase 1, soluble fms - like tyrosine kinase 1) from women with singleton pregnancies. Levels appear to be associated with a larger placental mass rather than primary placental pathology (Bdolah *et al.*, 2008; Maynard *et al.*, 2008) . In one study, sFlt-1 protein and PlGF (placental growth factor) were measured in 79 women with twins referred for evaluation of preeclampsia. In the 58 women identified as having either gestational hypertension or preeclampsia, there was a progressive increase in sFlt-1 concentrations, a decrease in PlGF levels, and an increase in the sFlt-1/PlGF ratio compared with normotensive twin pregnancies. With a multiple pregnancy, hypertension not only develops more often but also tends to develop earlier and be more severe. In the analysis of angiogenic factors mentioned above, more than half of the affected women presented before 34 weeks, and the increase in the sFlt-1/PlGF ratio was more striking (Rana *et al.*, 2012) .

The severe end of the spectrum (early severe preeclampsia and HELLP syndrome [Hemolysis, Elevated Liver Enzymes, Low Platelets]) tends to occur more frequently in multiple than singleton pregnancies (Sibai *et al.*, 2000) .

Atypical manifestations of preeclampsia are also more common in multiple pregnancies, particularly triplet and higher order multiple pregnancies. A retrospective review of 21 triplet and 8 quadruplet pregnancies found that only half of the women who went into labor because of preeclampsia had elevated blood pressure before delivery. Furthermore, proteinuria was present in only 3 of the 16 women before delivery. The predominant manifestations of preeclampsia in this series were laboratory abnormalities (mainly elevated liver enzymes) and maternal symptoms. One theory for the higher incidence of atypical preeclampsia in women with triplet and higher order multiple pregnancies is that the exaggerated hemodynamic changes seen in such cases will mask the "typical" maternal manifestations of preeclampsia (Hardardottir et al., *1996)* .

- **Screening**

Uterine artery Doppler findings, and blood biomarkers are associated with an increased risk of preeclampsia.

According to a study, the test to predict the risk of preeclampsia in the first trimester in singleton pregnancies can also be adopted in the case of twin pregnancies. The best performance of population-based first-trimester screening for preeclampsia in twin pregnancy is achieved by a combination of maternal characteristics and medical history, mean blood pressure, uterine artery PI resistance index and PlGF (the triple test) and no additional contribution from PAPP- A, which also applies to first-trimester screening in singleton pregnancies. Two datasets of twin pregnancies were used for this study. The first data set came from the EVENTS study (Early vaginal progesterone for the prevention of spontaneous prEterm birth iN TwinS) (Rehal *et al.,* 2021) , which was conducted in 22 maternity hospitals in England, Spain, Bulgaria, Italy, Belgium and France between May 2017 and April 2019. All women were found to have at their routine visit at 11^{+0} to 13^{+6} weeks' gestation dichorionic or monochorionic diamniotic twin pregnancy with two live fetuses and no major fetal anomaly and were invited to participate in a population-based control study on the prediction of adverse pregnancy outcome, regardless of their decision to participate in the study progesterone or not. The second data set came from a prospective study of adverse obstetric outcomes in women who had their first routine visit at King's College Hospital in London and Medway Maritime Hospital in Gillingham, United Kingdom, between January 2006 and December 2015. In population-based control with maternal factors alone, the detection rate with 10% false-positive results was 30.6% for delivery with pre-eclampsia before 32 weeks' gestation and this increased to 86.4% in screening with the combined test. The corresponding values for delivery with preeclampsia before 37 weeks were 24.9% and 41.1%. In singleton pregnancies, the detection rate of preeclamptic delivery at less than 37 weeks' gestation in first-trimester screening with the triple test is 75% with a 10% false-positive result, while in twin pregnancies the same detection rate of 75% can be achieved with 40% false positive result (Benk ő *et al.,* 2021) .

Additionally, another study concludes using similar biomarkers to singleton pregnancies to predict preeclampsia in first and second trimester twin pregnancies (Svirsky *et al.,* 2016) . The biomarkers studied were the following: PIGF, PAPP - A, β- hCG, and AFP. In the cases with preeclampsia, PIGF was significantly reduced, while β- hCG and AFP were elevated. β- hCG was found to be a better biomarker for preeclampsia in the second trimester, while AFP was a better biomarker in the first trimester. An increase in PAPP - A was observed in twin pregnancies with preeclampsia in contrast to a decrease in PAPP - A observed in singleton pregnancies with preeclampsia. This is probably due to placental overfilling, because there is reduced blood flow and compensatory flow increases. Of course, it is worth mentioning that the value of PAPP - A is increased in twin pregnancies compared to singletons, whether

they manifest pre-eclampsia or not. In conclusion, the values of PIGF, β- hCG and AFP in the first and second trimester of pregnancy are particularly useful for predicting PE in twin pregnancies, while the PAPP - A index increases during the first trimester of twin pregnancies that will manifest preeclampsia and for for this reason it is necessary to develop a different algorithm to predict the disease in twin pregnancies with regard to this index.

- **Prevention**

Multiple pregnancy is considered a high-risk factor for preeclampsia and is therefore an indication for prophylactic administration of low-dose aspirin. The dose for multiple pregnancies is the same as for singleton pregnancies. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine support the United States Preventive Services Task Force's recommendation for low-dose aspirin (81 mg/day) to reduce the incidence of preeclampsia and related complications of preterm labor and endometriosis growth restriction in multiple pregnancies. Low-dose aspirin (81 mg/day) should be started between 12 and 28 weeks (preferably before 16 weeks) and continued daily until delivery (ACOG, 2021; American College of Obstetricians and Gynecologists' Committee on Practice Bulletins —Obstetrics, Society for Maternal-Fetal Medicine, 2021; US Preventive Services Task Force, Davidson, Barry, Mangione, Cabana, Caughey, Davis, Donahue, Doubeni, Kubik, Li, Ogedegbe, Pbert, Silverstein, Simon, et al., 2021) .

- **Management**

The diagnosis, management, and course of preeclampsia/gestational hypertension are usually not affected by multiple gestation (Krotz *et al.*, 2002) , with some exceptions.

A number of studies have reported that maternal uric acid concentration increases with fetal number in both normal and preeclamptic pregnancies, with typical values of 5.2 and 6.4 mg/dL respectively in twin pregnancies (Fischer et al ., 1995; Hsu *et al.*, 1997; Fischer, Weisberg and Hediger, 2001; Cohen *et al.*, 2002) .

In addition, case reports have described resolution of early severe preeclampsia after the death of one twin (Sarhanis and Pugh, 1992; Hagai *et al.*, 1994; Audibert *et al.*, 2003) . Thus, in such cases, close monitoring is often the appropriate method of approach.

If hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome develop, transfer to a tertiary care center may improve the outcome for the woman and the fetuses (Sibai, 2004) .

4.1.2. Gestational diabetes mellitus

Twin pregnancy

Whether gestational diabetes is more common in twin pregnancies is unclear (Henderson *et al.,* 1995; Schwartz *et al.,* 1999; Sivan *et al.,* 2002; Buhling *et al.,* 2003) . Screening, diagnosis and management are similar to singleton pregnancy. However, the effect of gestational diabetes on fetal development in twin pregnancies is unclear. Large-for-gestational-age neonates appear to be less common than singleton pregnancies complicated by gestational diabetes (Ashwal *et al.,* 2021) .

Triplet pregnancy

Since triplet pregnancies are at high risk for gestational diabetes compared to singletons (12.8 vs. 2.9% respectively according to one study) and a high proportion of these patients have polycystic ovary syndrome-related insulin resistance, screening for diabetes early in pregnancy (e.g., at the first or second prenatal visit) is recommended. If this test is negative, the test is repeated at 24 to 28 weeks of gestation (Weissman and Drugan, 2016) . Screening and diabetes management are the same as singleton pregnancies.

4.1.3. Other maternal complications during pregnancy

Multiple gestation has been found to be an independent risk factor for admission to the Intensive Care Unit (ICU) (Bouvier - Colle *et al.,* 1997) . Also, although fortunately still a very rare event, maternal death is also increased in multiple pregnancies. A relative risk of 2.9 (95% CI, 1.4 to 6.1) has been reported for maternal death in multiple pregnancies (Senat *et al.,* 1998) .

Twin pregnancy

Other maternal disorders more commonly seen in pregnant women with multiple gestations include pregnancy rash multiforme (often described as pruritic urticarial papules and plaques of pregnancy [PUPPP]), intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy, iron deficiency anemia, hyperemesis gravidarum, placental abruption, and thromboembolic disease. The increased risk of thrombosis is related, at least in part, to the increased prevalence of antepartum hospitalization and cesarean delivery among these women (Hall, Campbell and Davidson, 1979; Campbell and Templeton, 2004; Bailit, 2005) . These disorders are generally treated as in singleton pregnancies.

Triplet pregnancy

The following pregnancy complications are more common in triplet pregnancies compared to singleton pregnancies. The diagnosis and treatment for each complication is similar to that in singleton pregnancies:

- Nausea and hyperemesis gravidarum
- Placental abruption has been reported in 1.6% of triplet pregnancies versus <1% of singleton pregnancies (Wen *et al.,* 2004) .
- Thrombocytopenia occurs in up to one third of triplet pregnancies. The most common cause is preeclampsia (Al - Kouatly *et al.,* 2003) .
- Fatty liver of pregnancy has been reported in up to 7% of triplet pregnancies versus 1 in 10,000 singleton pregnancies (Malone *et al.,* 1998) .
- Intrahepatic cholestasis of pregnancy is more often observed in multiple pregnancies.
- Multiple gestation has been associated with an increased risk for placenta previa (Ananth *et al.,* 2003) , which may be related to the large placenta volume in multiple pregnancies and the increased exposure to assisted reproduction techniques (Karami, Jenabi and Fereidooni, 2018) .

4.1.4. Maternal morbidity due to childbirth

Maternal complications during labor are generally more common with twin than singleton pregnancies. In a large case-control study from France, the incidence of severe acute maternal morbidity in twin pregnancies was 6.2% (197 of 3202, 95% CI 5.3–7.1) and in singleton pregnancies 1.3% (2303 of 179,107, 95% CI 1.2-1.3), and the higher risk in twins remained after adjustment for confounders (adjusted OR 4.2, 95% CI 3.1-5.8) (Madar *et al.,* 2019) . The increased risk was similar for both antepartum, intrapartum, and postpartum complications and regardless of the underlying source of morbidity (severe bleeding, severe hypertensive complications, or other conditions).

In one analysis, caesarean section itself accounted for only 20.6% (95% CI 12.9–28.2) of the overall risk of severe intrapartum/postpartum severe acute maternal morbidity associated with twin pregnancy. However, route of delivery did not appear to be a significant risk factor for maternal morbidity in other studies. In the Twin Study Birth Study (1398 pregnancies), the rate of death or severe maternal morbidity in patients randomly assigned to planned caesarean section was similar to those who underwent planned vaginal delivery (7.3 vs. 8.5%, RR 0.86, 95% CI 0.65-1.13) (Barrett *et al.,* 2013) . A large prospective study, including more than 8000 twin pregnancies, also found that rates of severe acute maternal morbidity

were similar for patients planning vaginal delivery and those planning cesarean delivery (5.4 and 6.1%, respectively)) (Korb *et al.*, 2018) .

4.2. Perinatal, neonatal and infant morbidity and mortality in multiple pregnancies

Multiple pregnancies carry significant perinatal risks. Newborns from multiple pregnancies have higher rates of low birth weight (LBW, low birthweight), very low birth weight (VLBW, very low birthweight) and early gestational age at delivery. One in 8 twins and one in 3 triplets are born before 32 weeks of gestation compared to only 2 in 100 fetuses in singleton pregnancies (Martin *et al.*, 2021) .

In addition, infant, neonatal and post-neonatal mortality in multiple pregnancies is significantly higher than that of singleton pregnancies. According to a recent study, twins are more than 4 times, triplets 10 times, and quadruplets more than 20 times more likely to die in infancy (Martin *et al.*, 2015) .

Rates of cerebral palsy have been estimated to be 4 to 8 times higher in twins than in singleton fetuses and up to 47 times higher in triplets. Most of this increased risk is attributed to higher rates of early preterm birth and very low birth weight in multiple pregnancies. It is worth emphasizing that although the overall rates of cerebral palsy are higher in twin than in singleton pregnancies, preterm LBW twins do not have higher rates than fetuses of similar gestational weight and age in singleton pregnancies. Interestingly, however, most studies have shown higher rates of cerebral palsy for twins born after 37 weeks and weighing more than 2500 g compared to comparable singleton fetuses. This difference is mostly a reflection of the effect of monochorionicity on twin development (Gabbe, Niebyl and Simpson, 2017) .

Regarding twin pregnancies, neonatal morbidity and mortality tend to be lower in first fetuses than in second fetuses from a twin pair, regardless of mode of delivery. In a systematic review of observational studies, the overall neonatal morbidity of the first and second twin was 3.0 and 4.6%, respectively (OR 0.53, 95% CI 0.39–0.70), and the overall neonatal morbidity mortality was 0.3 and 0.6% respectively. (OR 0.55, 95% CI 0.38-0.81) (Rossi, Mullin and Chmait, 2011) . The higher risk of adverse neonatal outcome in second twins is probably associated with lower birth weight, a higher incidence of poor presentation, umbilical cord prolapse, detachment and a higher incidence of obstetric maneuvers during labor (Smith, Pell and Dobbie, 2002; Sheay, Ananth and Kinzler, 2004). These factors often lead to cesarean section of the second twin and explain, at least in part, the higher neonatal morbidity of the second twin after combined delivery (vaginal/cesarean, 19.8%) compared with vaginal delivery (9.5 %, OR 0.55, 95% CI 0.41-0.74) or cesarean delivery (9.8%, OR 0.47, 95% CI 0.43-0.53) of both twins (Rossi, Mullin and Chmait, 2011) .

In triplet pregnancies, preterm delivery and low birth weight are the most common causes of death and morbidity. In two population-based cohort studies, the overall perinatal mortality was approximately 2.5% (Kawaguchi *et al.*, 2013; Mol *et al.*, 2019) and monochorionic triplet pregnancies had a 2.6 times greater risk of perinatal death than trichorionic triplet pregnancies (OR 2.6, 95% CI 1.176-5.76) (Kawaguchi *et al.*, 2013) . The mean/median gestational age at delivery was approximately 33 weeks' gestation in both studies, and neonatal morbidity was frequent and consistent with the early gestational age of these births (Kawaguchi *et al.*, 2013; Mol *et al.*, 2019) .

4.3. Fetal complications in multiple pregnancies

4.3.1. Complications that characterize all multiple pregnancies

All multiple pregnancies have higher rates than singleton pregnancies of the following fetal complications:

- Preterm birth
- Growth restriction
- Congenital anomalies

However, the rates of " postterm " pregnancy (beyond 42 $^{+0/7}$ weeks of gestation) and macrosomia are lower than in singleton pregnancy (Chauhan *et al.*, 2010) .

4.3.1.a. Preterm birth

Twin pregnancies have a higher preterm birth rate than singleton pregnancies and a lower preterm birth rate than triplet pregnancies. The risk of preterm birth (and death) in twins is influenced by chorionicity and amnionicity(Litwinska, Syngelaki, Cimpoca, Frei, *et al.*, 2020) .

Twin pregnancy

- **General image**

The main source of perinatal morbidity and mortality in twin pregnancies is preterm birth. The high rate of preterm birth is related, in part, to medically indicated preterm delivery, especially due to complications associated with monochorionicity (e.g., twin-twin transfusion syndrome [TTTS], selective fetal growth restriction [sFGR]). Spontaneous preterm labor (sPTB) is also increased and is related, at least in part, to

increased myometrial distension leading to more frequent and greater myometrial contractility compared to singleton pregnancies (Lyall *et al.*, 2002; Turton *et al.*, 2013) .

Some reported risk factors for preterm birth that are unique to twin pregnancy include: twin fetuses that are both male (Tan *et al.*, 2004; Melamed, Yogev and Glezerman, 2009) , spontaneous reduction of a fetus (e.g. triplets reduced to twins are born at an earlier gestational age than twins that did not result from the reduction of a higher order multiple pregnancy) (Barton, Missmer and Hornstein, 2011) , and a previous spontaneous birth of singletons " early term " of pregnancy (from 37 $^{+0/7}$ to 38 $^{+6/7}$ weeks of gestation) followed by a subsequent twin pregnancy (SL 3.5) (Berveiller *et al.*, 2020) .

More generally :

- There is no convincing evidence that regular prophylactic use of tocolytic drugs (Yamasmit *et al.*, 2015) , pessary (Liem *et al.*, 2013; Nicolaides *et al.*, 2016; Berghella, Dugoff and Ludmir, 2017) , cervical cerclage (Li, Shen and Hua, 2019; Liu *et al.*, 2021) or supplemental progesterone (vaginal or intramuscular) (Dodd *et al.*, 2019; EPPPIC Group, 2021) in twin pregnancies in which the cervix is normal (i.e., not dilated or short in length) in the second trimester reduces the chances of preterm delivery (D'Antonio *et al.*, 2021) .

  Conversely, cervical cerclage is reasonable in women with a classic history of cervical insufficiency in a previous singleton pregnancy. More generally in all pregnancies, cervical cerclage (called history-indicated cerclage) is recommended at 12 to 14 weeks' gestation in women with recurrent (more than one) second-trimester spontaneous abortions preceded by painless cervical dilation. Structural weakness of the cervix can be effectively treated with structural support from the band. Anatomical, biochemical and clinical evidence from observational studies and randomized trials strongly supports this approach (Leppert *et al.*, 1987; 'Final report of the Medical Research Council/Royal College of Obstetricians and Gynaecologists multicentre randomized trial of cervical cerclage. MRC/RCOG Working Party on Cervical Cerclage', 1993) .
- A short tocolytic regimen may be indicated for patients with acute preterm labor, while patients with asymptomatic cervical dilatation may be treated with cervical cerclage, and patients with a short cervix may be treated with vaginal progesterone or possibly a cerclage or pessary.
- Systematic reviews of randomized trials of hospitalization or bed rest in twin pregnancies have failed to show that any intervention increases gestational age at delivery (Crowther and Han, 2010;

Sciscione, 2010; da Silva Lopes *et al.*, 2017) , while the lying down it can to increase him danger venous thromboembolism (Abdul Sultan *et al.*, 2013) .

- Although elevated fetal fibronectin levels can predict pregnancies at particularly high risk of preterm birth, this test is not performed in asymptomatic women, as the predictive value is low in the absence of symptoms and no intervention has been clearly shown to be effective in reducing preterm birth rates. in this population (Goldenberg *et al.*, 1996; Gibson *et al.*, 2004; Singer *et al.*, 2007) .
- Home uterine activity monitoring (HUAM) effectively detects premature contractions. However, the use of HUAM does not lead to a reduction in the rate of preterm birth or an improvement in any measure of neonatal outcome (Urquhart *et al.*, 2017) .
- Delayed labor may play a role in carefully selected twin pregnancies at early gestational age (<24 weeks) in which only the presenting fetus is delivered by spontaneous vaginal delivery due to preterm labor (Oyelese et al., 2005; Cheung et al ., 2020).) .

➢ **Use of tocolytic drugs for acute preterm labor**

Although not evaluated in large randomized trials of twin pregnancies, a brief administration of tocolysis in patients with acute preterm labor is reasonable to allow antenatal corticosteroids. It is preferable to use calcium channel blockers or indomethacin (if gestational age is <30 to 32 weeks) and avoid beta-adrenergic agonists, as the risk of pulmonary edema is higher in women with twin pregnancies because they have a larger blood volume and lower colloid osmotic pressure from women carrying a fetus (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, Society for Maternal - Fetal Medicine, 2021) .

Approach to pregnant women with asymptomatic cervical dilatation

For women with twin pregnancies with asymptomatic cervical dilatation before 24 weeks, physical examination-indicated cervical cerclage is recommended after amniocentesis is performed in the sac of the presenting twin to rule out subclinical infection. Alternatively, the woman may be observed for several hours for clinical signs of infection (e.g., fever, uterine contractions). Women who refuse cerclage are offered vaginal progesterone therapy, as are women with a short cervix.

This approach is based on the findings of the only randomized trial of physical examination-indicated cerclage in twin pregnancies, which found a reduction in spontaneous preterm birth (sPTB) and perinatal mortality (Roman *et al.*, 2020) , in agreement with previous observational data (Li, Shen and Hua, 2019) . In this trial, 30 twin pregnancies with asymptomatic cervical dilatation of 1 to 5 cm at 16 $^{+0}$ to 23 $^{+6}$ weeks' gestation were randomized to undergo cerclage or not. The use of tocolytics and antibiotics was at the discretion of the physician who placed the cerclage, although the 14 women who underwent cerclage placement received prophylactic antibiotics (cephalosporin in 12 women, clindamycin-gentamicin in one woman, and azithromycin in one) and indomethacin (50 to 100 mg loading dose followed by 25 to 50 mg every six hours for 48 hours). Before randomization, patients with vaginitis or UTI were treated, and subclinical chorioamnionitis was ruled out by either amniocentesis or 12-hour follow-up for signs of labor or infection. The cerclage group had reductions in :

- sPTB <24 weeks (29 vs 85%, RR 0.35, 95% CI 0.16-0.75)
- sPTB <28 weeks (41 vs 85%, RR 0.49, 95% CI 0.26-0.89)
- sPTB <32 weeks (65 vs 100 %, RR 0.65, 95% CI 0.46-0.92)
- sPTB <34 weeks (71 vs 100 %, RR 0.71, 95% CI 0.52-0.96)
- perinatal mortality (18 vs 77%, RR 0.23, 95% CI 0.10-0.49)

Cerclage increased the mean gestational age at delivery (29 vs. 22.5 weeks). There were no intraoperative complications. The trial was terminated early by the data safety monitoring committee due to a significant reduction in perinatal mortality in the cerclage group. Because of this, no subanalysis could be performed based on degree of cervical dilatation, gestational age at placement, and use of progesterone or surgical techniques. Although this trial was small, with only 30 women enrolled at eight sites over four years, the data suggest a clear benefit in appropriately selected women.

➢ Approach to pregnant women with a short cervix

The management of short cervix in twin pregnancies continues to evolve, with little consensus among authorities.

- Choice of pregnant women for **vaginal progesterone:**

For women with a twin pregnancy and a short, closed cervix on second-trimester transvaginal ultrasound, vaginal progesterone therapy is recommended to reduce the risk of preterm delivery, especially in women with no prior history of preterm delivery. Some researchers use a cervical length <20 mm as a threshold to define a short cervix in the second trimester in women without previous spontaneous labor (Conde - Agudelo *et al.*, 2010; Lim *et al.*, 2011) , while other researchers use the cervical length ≤25 mm for all pregnant women (Romero *et al.*, 2022) . Since there are no high-quality data to support one of these thresholds over the other, the choice of threshold rests with the clinician's judgment of the risks and benefits of overtreatment versus undertreatment.

In a meta-analysis of individual women's data from six randomized trials of women with a twin pregnancy and a second-trimester cervical length ≤25 mm, vaginal progesterone reduced preterm delivery before 33 weeks compared with no treatment/placebo (OR 0.60, 95% CI 0.38-0.95, 20 of 52 [38.5 %] vs 24 of 43 [55.8 %]), preterm delivery before 32, 30 and 28 weeks as well as neonatal morbidity and mortality (Romero *et al.*, 2022) . However, not providing progesterone supplementation in this circumstance is also reasonable, as these findings are not conclusive.

- Selection of pregnant women for **cervical cerclage:**

  Cervical cerclage is also an option on a case-by-case basis when the cervix is too short, and the physician believes that the suture can be placed safely. Some researchers use a threshold of ≤15 mm to consider cerclage (Li, Shen and Hua, 2019; Liu *et al.*, 2021) and others use a threshold of <20 mm, taking into account the woman's obstetric history. For example, cerclage is more likely to be considered in a patient with a prior history of preterm labor and vaginal progesterone in a woman without a prior history, as cervical insufficiency is more likely in a patient with a prior history of preterm labor. In singleton pregnancy, ultrasound-indicated cervical cerclage is placed in patients with a previous spontaneous preterm birth and cervical length on transvaginal ultrasound ≤25 mm before 24 weeks in the current pregnancy. A meta-analysis of randomized trials found that cerclage in this setting reduced preterm delivery <24, 28, 32, 35 and 37 weeks (eg OR for delivery <35 weeks: 0.70, 95% CI 0, 55-0.89) (Berghella *et al.*, 2011) .

The data supporting the benefit of cerclage for a short, closed cervix are not strong. Therefore, not placing a suture is also reasonable. In a meta-analysis of ultrasonographically indicated cerclage in twin pregnancies (three randomized trials and three cohort studies), compared with no cerclage, cerclage was associated with prolonged gestation in those women with a cervical length ≤ 15 mm (mean difference 3.89 weeks of gestation, 95% CI 2.19-5.59) and reduction in preterm birth <37 weeks of gestation (RR 0.86, 95% CI 0.74-0.99), < 34 weeks (OR 0.57, 95% CI 0.43-0.75) and <32 weeks (OR 0.61, 95% CI 0.41-0.90) (Li, Shen and Hua, 2019) . No benefit was seen in pregnancies with a cervical length of 16 to 24 mm and no improvement in neonatal outcome was demonstrated. Most patients in the overall analysis were in retrospective cohort studies. Importantly, when only patients in randomized trials were analyzed, ultrasound-indicated cervical cerclage was associated with higher rather than lower risks of birth weight <1500 g and <2500 g, although the number of pregnancies in these trials was small.

- The role of the **pessary:**

  The use of a cervical pessary may be considered in twin pregnancies with a short cervix, based on the favorable results and trends in the randomized trials described below. However, no consistent benefit in neonatal morbidity has been established for any cervical length threshold. Further study is needed to demonstrate a clear and consistent benefit before recommending a cervical pessary for short cervix in asymptomatic women or after threatened preterm delivery. The American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics, 2021c recommends not using a cervical pessary to prevent preterm labor in twin pregnancies with a short cervix (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics, 2021c) .

  - In a multicenter randomized trial in Spain, pessary placement in 137 asymptomatic women with a twin pregnancy and a short cervix (≤25 mm) at 18 to 22 weeks reduced the rate of sPTB <34 weeks: 16.2 (11/68) vs. 39, 4% (26/66) with close follow-up (OR 0.41, 95% CI 0.22-0.76). This reduction was associated with a trend towards a reduction in neonatal morbidity that was not statistically significant (adverse neonatal outcomes: 5.9 [8/68] vs 9.1 % [12/66], RR 0.64, 95% CI 0 .27-1.50) (Goya *et al.*, 2016) .

- In a subsequent randomized trial by the same investigators, including 132 women with twin pregnancies who remained free of labor 48 hours after threatened preterm labor and had a short cervix (≤20 mm), pessary use reduced preterm labor <34 weeks (11 / 67 [16.4%] vs. 21/65 [32.3%] with usual care) but not before 28 or 37 weeks. There was also a reduction in the number of neonates <2500 g at birth (24/134 [17.9 %] vs 92/130 [70.8 %], RR 0.25, 95% CI 0.15-0.43) (Merced *et al.,* 2019) .
- •In a randomized trial in Vietnam comparing the efficacy of cervical pessula with vaginal progesterone for the prevention of preterm birth in asymptomatic women with a twin pregnancy and a short cervix (≤28 mm), pessula reduced preterm birth <34 weeks' gestation by 53 % (21 [10/47] vs 46 [16/35] %, RR 0.47, 95% CI 0.24-0.90) and a composite of poor perinatal outcomes by 62 % (19 vs 50 %, RR 0.38, 95% CI 0.1 0.47). For cervical length <38 mm, the reduction in poor perinatal outcomes was statistically significant, but the reduction in preterm birth <34 weeks was not (Dang *et al.,* 2019) .

- **Use of corticosteroids and magnesium sulfate in pregnancies at risk of preterm birth**

The corticosteroid regimen is the same for both singleton and multiple pregnancies thought to be at increased risk of preterm delivery within seven days between 24 and 34 weeks ('Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consens Statement ', 1994) . The American College of Obstetricians and Gynecologists recommends a single rescue course of antenatal corticosteroids in pregnancies <34 weeks who are at immediate risk of preterm delivery within the next seven days and have had prior treatment with antenatal corticosteroids at least seven days prior (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, Society for Maternal - Fetal Medicine, 2021) . In the monoamniotic twin pregnancy, in the absence of threatened preterm labor before 28 weeks' gestation, a course of antenatal corticosteroids is administered at the time of admission, which is typically at 28 weeks. For patients who remain nulliparous after three weeks, a single steroid rescue regimen is reasonable. The exact time between 31 weeks and delivery should be decided on a case-by-case basis. Routine prophylactic administration in all twin pregnancies should be avoided and may have adverse effects (Murphy *et al.,* 2002) .

Magnesium sulfate appears to reduce the severity and risk of cerebral palsy in infants if given before preterm delivery <32 weeks' gestation, regardless of fetal number. Dosage is the same as in singleton pregnancies (Martin *et al.,* 1991; Costantine, Weiner, and Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal–Fetal Medicine Units Network (MFMU), 2009; Doyle Doyle *et al.,* 2009) .

- **Premature rupture of membranes**

Premature rupture of membranes (PROM) typically occurs in the presenting sac. A dichorionic placenta appears to protect against the spread of infection from the presenting to the non-presenting gestational sac (Phung *et al.,* 2002) . However, PROM can develop in the non-presenting twin sac, especially after invasive procedures (e.g., amniocentesis, fetoscopy).

Several studies have examined perinatal outcome after preterm (before 37 weeks) premature rupture of membranes (PPROM) in twin versus singleton pregnancies (Phung *et al.,* 2002; Jacquemyn *et al.,* 2003; Trentacoste *et al.,* 2008; Fishel Bartal *et al.,* 2021) . Findings included a shorter median latency in twins compared to singleton pregnancies. However, in a large cohort study of pregnancies at 23 to 34 weeks' gestation, composite maternal or neonatal morbidity per fetus after PROM and median gestational age at delivery were similar for twin and singleton pregnancies (Fishel Bartal *et al.,* 2021) .

The management of PPROM and PROM is generally similar in twin and singleton pregnancies.

As discussed in patients with preterm labor, there may rarely be a role for delayed labor in carefully selected twin pregnancies at early gestational age (<24 weeks) in which only the first (presenting) fetus is spontaneously delivered vaginally due to PPROM.

Triplet pregnancy

Preterm birth is the most common cause of death and morbidity in triplet pregnancies. Iatrogenic preterm labor is as common as spontaneous preterm labor in some series (Razavi *et al.,* 2017) .

In 2020, 98.7% of triplets were born before 37 weeks' gestation in the United States, and 65.8% were born before 34 weeks' gestation (Osterman *et al.,* 2021) . 95 % of triplets had low birth weight (<2500 g) and 36 % had very low birth weight (<1500 g). In comparison, 2.1 % of singleton fetuses were born before 34 weeks and 1.1 % weighed <1500 g. The mean gestational age for triplets is approximately 32 weeks versus 38.7 weeks for singleton pregnancies (Martin *et al.,* 2011) .

- **Possibly useful interventions**

Many interventions have been investigated to reduce the risk of preterm birth. None have been shown to be effective. However, administration of corticosteroids and magnesium sulfate may reduce neonatal morbidity, as in singleton pregnancies.

- **Corticosteroids** for fetal maturation:

  For non-monoamniotic triplets, a course of betamethasone is given if clinical findings are thought to indicate an increased risk of delivery within the next seven days, as steroids are most effective in this time frame. Examples include patients who experience rupture of membranes or threatened preterm delivery, or who develop a maternal or fetal disorder that may require preterm delivery within days. Universal administration of steroids in triplet pregnancies is not justified, as the overall incidence of delivery within seven days was <10% before 32 weeks in one study (van de Mehen *et al.,* 2016) . Thus, many triplet pregnancies that received early steroid therapy would need repeat treatment to ensure exposure near delivery.

  However, for monoamniotic triplets, a regimen of antenatal corticosteroids is routinely given at 26 weeks when the patient is admitted to the hospital for intensive fetal monitoring. These pregnancies are at high risk for premature, unexpected birth.

  Standard doses of betamethasone are given, as there is no convincing evidence that the dose should be increased with increasing number of fetuses.

  A second course of antenatal corticosteroids is recommended if more than one week has passed since the previous treatment, the patient is at increased risk of preterm delivery within the next seven days, and the gestation is less than 34 weeks. Steroids are not given after 34 weeks, as no data are available on efficacy in multiple pregnancies late in pregnancy.

  The value of antenatal corticosteroid therapy is well established in singleton pregnancies, but neonatal outcomes after intrauterine corticosteroid exposure have not been examined in randomized trials of triplet pregnancies, and the magnitude of benefit in these pregnancies is less clear (Blickstein *et al.,* 2005; Roberts *et al.,* 2017) . In the United States, the National Institutes of Health recommends the administration of one course of prenatal corticosteroids (unless contraindicated) regardless of the number of fetuses ('Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consens Statement', 1994) .

- **Magnesium sulfate** for neuroprotection :

  Magnesium sulfate is recommended for neuroprotection in triplet pregnancies at risk of imminent delivery (i.e., within 24 hours) between 23 $^{+0}$ and 31 $^{+6}$ weeks. Marret et al suggest the 4 g regimen bolus of magnesium sulfate in 30 minutes without continuous infusion (Marret *et al.,* 2007) , because omitting the continuous infusion may reduce the risk for pulmonary edema, which may be more common in triplet pregnancies receiving this drug (Poggi *et al.,* 2003) . Other shapes (e.g., 4 g bolus with 1 g /hour continuous infusion) can also be used.

- **Delayed delivery** :

  Typically, all triplet fetuses are delivered at short intervals. However, in rare selected cases, the viable birth of one or two fetuses may not require delivery of the other fetus (Ghorbani and Moghadam, 2015) . This is called delayed delivery and can improve neonatal survival and reduce morbidity from very early preterm birth.

➢ **Unconfirmed interventions**

- **Tocolytic drugs** for the treatment of preterm labor

  No tocolytic drug has been shown to improve neonatal outcome compared with placebo (Crowther, Hiller and Doyle, 2002; King *et al.,* 2003, 2005; Anotayanonth *et al.,* 2004) and the use of tocolytics in multiple pregnancies leads to a higher frequency of adverse effects, such as pulmonary edema (Pisani and Rosenow, 1989) . Other doctors do not use tocolytic drugs to treat preterm contractions or preterm labor in triplet patients, while others may give a tocolytic for 48 hours to allow betamethasone to be administered. A calcium channel blocker or nonsteroidal anti-inflammatory drug, depending on gestational age, is the preferred tocolytic.

- Prophylactic administration **of tocolytic drugs**

  There is no role for the prophylactic use of tocolytic agents in any multiple pregnancy, including triplets. No reduction in the incidence of preterm birth, low birth weight, or neonatal mortality has been demonstrated (Yamasmit *et al.,* 2015) . In addition, prolonged use of beta-adrenergic agonists has been associated with an increased risk of adverse maternal cardiovascular events including maternal death (US Food and Drug Administration, 2011) .

- Prophylactic **cervical cerclage**

  Prophylactic cerclage (defined as a suture placed only because of a triplet pregnancy) in women without a history of cervical insufficiency does not appear to prolong pregnancy or improve

neonatal outcomes (Rebarber *et al.*, 2005) . In the rare clinical scenario of a woman who has a history of cervical insufficiency and is now carrying triplets, it is also recommended that cerclage is not indicated by history, as there is no proven benefit and studies have suggested possible harm in multiple pregnancies with cerclage. Consideration of multiple pregnancy reduction in these cases is strongly recommended.

There have been no randomized trials examining prophylactic cerclage in triplet pregnancies. The largest study used a national database to compare the outcome of triplet pregnancies with cerclage (248 cases) versus those without cerclage (3030 cases) (Rebarber *et al.*, 2005) . Both groups had similar rates of preterm birth <28 and <32 weeks. There were no significant differences between groups in terms of gestational age at delivery, live birth, birth weight, very low birth weight, neonatal intensive care unit admission, or neonatal hospital days. A limitation of this study was that only patients who reached 23 to 24 weeks of gestation were entered into the database. Therefore, any effects of cerclage on early pregnancy loss were not measured. Smaller studies have reported mixed results (Goldman *et al.*, 1989; Bernasko *et al.*, 2006) .

In small observational studies of triplet pregnancies with asymptomatic cervical shortening during serial ultrasound monitoring of cervical length, placing ultrasound-guided cerclage for cervical length <25 mm did not lead to any improvement in neonatal outcome in compared with close monitoring (Moragianni *et al.*, 2009; Young *et al.*, 2014) . Worryingly, in twin pregnancies that underwent cerclage for cervical length <25 mm before 24 weeks, the rates of very low birth weight and respiratory distress syndrome were higher compared to a control (unbanded) group (Saccone *et al.*, 2015) .

- Prophylactic **pessary**

  It is not recommended to use a pessary to reduce the risk of premature birth. The largest randomized trial of condom use in more than 800 unselected multiple pregnancies reported that the intervention did not reduce the incidence of poor perinatal outcomes (Liem *et al.*, 2013) .

- **Lying down**

  There is no conclusive evidence that bed rest improves pregnancy outcome and may even be harmful due to the risk of thrombosis. In a 2017 systematic review of six randomized trials that assessed the effectiveness of strict or partial bed rest at home or in hospital compared with no activity restriction in women with multiple pregnancies (twins or triplets), the intervention did not

reduce preterm birth or perinatal mortality, but the quality of the evidence was low (da Silva Lopes *et al.,* 2017) .

- **Progesterone**

  Progesterone supplementation is not recommended to reduce the risk of preterm birth. In a 2016 meta-analysis of individual women's data from three placebo- controlled, randomized trials of hydroxyprogesterone caproate supplementation in asymptomatic women with triplet pregnancies, progesterone did not result in a statistically significant reduction in preterm delivery <28, 32, or 34 weeks or adverse perinatal outcome (Combs *et al.,* 2016) . Of note, one trial found that progesterone supplementation resulted in a significant increase in the number of fetal losses in the second trimester (13 of 56 versus 0 of 25 in the placebo group) (Combs *et al.,* 2010) .

4.3.1.b. Intrauterine growth restriction and fetal growth discordance

Twin pregnancy

Assessment of fetal growth is particularly important in twin pregnancies because growth restriction and preterm delivery are the main causes of higher morbidity and mortality rates in twins compared to singleton pregnancies (Demissie et al., 2002 ; *Hartley,* Hitti and Emanuel, 2002; Branum and Schoendorf, 2003; Adegbite *et al.,* 2004; Amaru *et al.,* 2004; Blickstein and Keith, 2004; Garite *et al.,* 2004; Kingdom, Nevo and Murphy, 2005; Yinon *et al.,* 2005; Inklaar *et al.,* 2014) . However, as in singleton pregnancy, ultrasound examination to distinguish the growth-restricted fetus from the normal small fetus is limited.

- **Normal development**

In the first and second trimesters, the growth rate of twins does not differ significantly from that of singleton pregnancies (Alexander *et al.,* 1998) . In the third trimester, particularly after 30 to 32 weeks' gestation, most studies have described slower fetal growth in uncomplicated twin pregnancies than in uncomplicated singleton pregnancies (Alexander *et al.,* 1998; Grantz *et al.,* 2016) . A prospective cohort study reported that nearly 40% of dichorionic twins at term would be classified as small for gestational age if a singleton gestation growth pattern were used (Grantz *et al.,* 2016) . The slower growth rate has been attributed to abnormal umbilical cord insertion and placental abruption (poor early growth due to close proximity of the placentas).

Growth curves, which have been derived specifically for twins, are of limited utility as they are derived from relatively small populations and generally have not taken into account chorionicity and amnionicity

or outcome. In contrast, singleton growth curves are the best predictor of adverse pregnancy outcome and growth in twin pregnancies and should be used to evaluate twins for growth abnormalities (Gleason *et al.*, 2021) . On the other hand, proponents of the use of twin growth curves state that singleton pregnancy growth curves diagnose growth abnormalities, which can lead to unnecessary maternal stress, extra prenatal testing, and possibly iatrogenic preterm delivery without improving neonatal outcome (Shea et al . *al.*, 2021) .

- **Diagnosis of fetal growth restriction and discordance**

Estimated fetal weight and/or abdominal circumference can be used to monitor growth. Developmental abnormalities manifest in three ways:

- A twin may be small for gestational age (called selective fetal growth restriction [sFGR])
- Both twins may be small for gestational age, or
- One twin may be significantly smaller than the other twin (i.e., growth discordance) even though neither is small for gestational age. In nearly two-thirds of discordant twins, the smaller twin has a birth weight < 10th percentile (Blickstein and Keith, 2004) .

There is no consensus on the optimal threshold for defining growth discordance in twins. Birth weight discordance ranging from 15 to 40% has been considered predictive of adverse outcome (Hartley, Hitti and Emanuel, 2002; Branum and Schoendorf, 2003; Amaru *et al.*, 2004; Yinon *et al.*, 2005; Breathnach *et al.*, 2011; D'Antonio *et al.*, 2013; Jahanfar, Lim and Oviedo-Joekes, 2016; Di Mascio *et al.*, 2019) . An estimated weight difference of ≥20% is used as the threshold for defining discordance, but a threshold of ≥25% is also commonly used. Both cutoffs have low sensitivity (about 50 %) but good specificity (about 90 %) for predicting birth weight difference (Jahanfar *et al.*, 2021) . An abdominal girth difference of ≥20 mm, regardless of gestational age is another threshold for defining growth discordance and has been reported to have an 83% positive predictive value for detecting a birth weight difference of ≥20% (Sperling and Tabor, 2001) . Discordance in other biometric measures has also been described to be subsequently associated with adverse obstetric and neonatal outcome (Fox *et al.*, 2011; Allaf *et al.*, 2014) .

- **Management of fetal growth restriction and discordance**

The management of fetal growth restriction and discordance depends on the chorionicity of the twin pregnancy:

- **Monochorionic twins**

  The management of monochorionic twins with sFGR is discussed separately below.

- **Dichorionic twins**

  Growth restriction is generally treated as in singleton pregnancies: determination of cause, repeated ultrasound assessment of fetal growth, ongoing assessment of fetal well-being (biophysical profile [BPP] or cardiotocography [NST] with amniotic fluid volume estimation and Doppler velocimetry), and determination of delivery time based on a combination of factors (gestational age, umbilical artery Doppler, BPP score, ductus venosus Doppler and presence or absence of risk factors or signs for uteroplacental insufficiency).

  In dichorionic twins, a systematic review found that the risk of fetal death increased with increasing growth discordance: ≥15% (OR 9.8, 95% CI 3.9-29.4), ≥20% (OR 7, 0, 95% CI 4.15-11.8), ≥25% (OR 17.4, 95% CI 8.3-36.7), ≥30% (OR 22.9, 95% CI 10.2 -51.6) compared to no discordance (D ' Antonio *et al.,* 2018) . The younger twin was at greater risk of fetal death than the older twin. The risk of fetal death did not increase when the weights of discordant twins remained appropriate for gestational age (AGA), although the small number of cases may have underestimated this association. There were several limitations of the observational studies, including differences in definitions, populations, and use of estimated fetal weight versus birth weight, as well as a lack of standardized criteria for antenatal management. Therefore, AGA but discordant twins should still be considered at risk for adverse perinatal outcome and closely monitored. According to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), sFGR in dichorionic twins should be monitored as in singleton pregnancies (A. Khalil *et al.,* 2016) .

Triplet pregnancy

The development of the fetuses is monitored by ultrasound examination. Onset and frequency are guided by the type of placentation.

Fetal growth restriction is diagnosed using the same criteria used for singleton pregnancies. Because triplet development begins to diverge from singleton fetal development in the third trimester (Weissman *et al.,* 1990; Alexander *et al.,* 1998; Blickstein, Jacques and Keith, 2002; Min *et al.,* 2004) , the use of these criteria may overdiagnose fetal growth restriction. For this reason, several authors have published growth charts specific to triplet pregnancies (median, 10th and 90th percentile) (Fountain *et al.,* 1995; Kuno *et al.,*

1999; Rodis *et al.,* 1999; Vora *et al.al.,* 2006) . Whether these arrays perform better in detecting fetuses at increased risk of adverse fetal or neonatal outcome is unknown.

Discordant triplet fetal growth is usually defined as a 20 to 25% difference in ultrasound estimated fetal weight (EFW) of the smallest compared to the largest fetus (difference of largest minus smallest EFW divided by largest EFW). Discordance may be an indicator of structural or genetic abnormalities, infection, TTTS, or placental insufficiency.

Based on twin studies, evidence of growth restriction in one or both fetuses is a stronger predictor of adverse neonatal outcome than growth discordance alone. Management of growth restriction and growth discordance is based on etiology.

4.3.1.c. Congenital anomalies

The incidence of congenital anomalies is three to five times higher in monozygotic twins than in dizygotic twins or singletons. It is also higher in monozygotic monochorionic twins compared to monozygotic dichorionic twins (Bahtiyar *et al.,* 2007; Glinianaia, Rankin and Wright, 2008; Weber and Sebire, 2010) , as well as in monoamniotic monochorionic twins compared to diamniotic monochorionic twins (Chen *et al.,* 1992; Campana and Roubicek, 1996; Liesbeth Lewi *et al.,* 2007; Ishii, 2015) . In one study, the incidence of congenital anomalies in monochorionic twins was 634/10,000 versus 344/10,000 for dichorionic twins versus 238/10,000 for singleton fetuses (Glinianaia, Rankin and Wright, 2008) . Major anomalies have been reported in 7 to 28% of monoamniotic monochorionic twin pregnancies compared to 6% of diamniotic monochorionic twin pregnancies (Heyborne *et al.,* 2005; Liesbeth Lewi *et al.,* 2007; Baxi and Walsh, 2010; Ishii, 2015 ; Glinianaia *et al.,* 2019) .

Twins are not predisposed to any particular type of congenital anomaly, although congenital heart disease is more common in monochorionic twins, particularly those with TTTS (Bahtiyar *et al.,* 2007) . Congenital heart defects are also more common in monoamniotic twins than in singletons and probably more common than in diamniotic twins (KE Hack *et al.,* 2009; Herskind, Almind Pedersen and Christensen, 2013) . The increased risk of abnormalities may be related to delayed separation and/or circulatory imbalances in the placental anastomotic vessels. Additionally, although some studies have reported an increased risk of congenital heart disease in twins conceived by assisted reproductive technology, particularly IVF, compared to twins conceived spontaneously (Tararbit *et al.,* 2011; Panagiotopoulou *et al.,* 2016) , others do not support this correlation (Bahtiyar *et al.,* 2010; Davies *et al.,* 2012; Iwashima, Ishikawa and Itoh, 2017; Schofield *et al.,* 2017) .

Concordance rates for any congenital malformation in monozygotic and dizygotic twin pairs were 37 and 17%, respectively, in a study of nearly 3400 twin pairs (Jung *et al.*, 2021) . Cases of termination of pregnancy before 20 weeks of gestation, fetal chromosomal abnormalities, fetal abnormalities associated with unique fetal complications (e.g., twin-twin transfusion syndrome [TTTS], sequence of twin reverse arterial perfusion [TRAP]) were excluded. Enough cases reports have described discordant abnormalities in monoamniotic twins (Sepulveda *et al.*, 2011; Mayumi *et al.*, 2013; Ng *et al.*, 2013; Quinlan *et al.*, 2014; Tavares *et al.*, 2015) . Abnormalities are consistent in less than 25% of cases (Post and Heyborne, 2015) .

Diagnosing a **congenital anomaly in one fetus** is particularly problematic as decisions about monitoring, treatment, and delivery affect both fetuses. Simple monitoring, intrauterine therapy, termination of pregnancy, and selective fetal termination are options that should all be discussed as appropriate for the type of abnormality and gestational age. Patients who choose to continue the pregnancy should understand how the abnormal fetus may affect the outcome of the other twin (e.g., preterm birth, organ damage), including the role of chorionicity:

- Dichorionic twins - In dichorionic twins, selective termination of the abnormal fetus is a safe and effective option in expert hands, although there is a risk of miscarriage or premature delivery of the co-twin. Because of these risks, close monitoring may be a safer option if the twin with the abnormality is not expected to have prolonged survival or a favorable outcome (e.g., trisomy 18) (Rustico *et al.,* 2005) . Anencephaly is an exception, since it is associated with polyhydramnios and premature birth. If polyhydramnios develops in the anencephalic twin, selective termination of one fetus or amnioablation (especially at maternal respiratory risk) appears to result in longer gestation and higher birth weight in the non-anomalous twin than simple monitoring (Vandecruys et al ., 2006; Lust *et al.*, 2008) .
- Monochorionic Twins - In monochorionic twins, selective termination of the fetus can be performed, but the technique is different from that in dichorionic twins and is more demanding. Occlusion of an umbilical cord (e.g., radiofrequency or laser ablation, bipolar coagulation, ligation) is required instead of intravascular injection of potassium chloride or digoxin in order to reduce the risk due to shared circulations in the other fetus (Evans et al., *1999* ; Diehl and Hecher, 2007) .

4.3.2. Complications that characterize monochorionic multiple pregnancies

4.3.2.a. Twin-Twin transfusion syndrome (TTTS)

Introduction

Twin-twin transfusion syndrome (TTTS) is a serious complication of monochorionic (MC) twin pregnancy. Only MC twins have this complication because, unlike dichorionic twins, the circulatory systems of nearly all MC twins have placental anastomoses that result in vascular connections between the twins.

TTTS is characterized by relative hypovolemia of one twin and hypervolemia of the other as a result of an imbalance in the direction of flow through the placental anastomoses. The key prenatal finding is monochorionic placentation with discordant amounts of amniotic fluid (maximum pocket <2 cm in one amniotic sac and >8 cm in the other amniotic sac).

Prevalence

The best estimate of the prevalence of TTTS is 9 to 15 % of monochorionic (MC) diamniotic (DA) twin pregnancies (Sebire *et al.,* 1997) and 6% of monoamniotic twin pregnancies (Baxi and Walsh, 2010) . These figures may underestimate the true prevalence because they rely heavily on data from live births and ultrasounds in the second half of gestation, which miss early fetal losses that may be associated with TTTS (Sebire *et al.,* 1997) .

Pathophysiology

- **Types of vascular connections**

Postpartum placental perfusion studies in MC twins have identified four types of vascular connections: arteriovenous (AV), venoarterial (VA), arterioarterial (AA), and venous (VV). The nomenclature describes first the donor fetal vessel and then the recipient fetal vessel.

- **Prenatal TTTS syndrome**

The three key parameters involved in the pathogenesis of TTTS are unbalanced volume flow, release of vasoactive mediators, and absence of AA anastomoses.

- The **AVs anastomoses** occur through the placental cotyledon when the chorionic plate surface arterial vessels from one twin and the chorionic plate surface venous vessels from the other twin descend into the placental parenchyma and join in the underlying cotyledon to form a capillary

network (that is, the cotyledon is supplied by an artery of one twin and blood is drained through a vein of the other twin).

If there are more or larger AV anastomoses than VA anastomoses (i.e., unbalanced anastomoses), then uncompensated hydrostatic and osmotic forces will result in a net transfer of fluid from one twin (donor) to the other twin (recipient), resulting in the phenotype TTTS. If the number and size of AV anastomoses and therefore blood flow in one direction is the same as the number and size and therefore blood flow in the opposite direction (i.e., balanced anastomoses), then TTTS does not develop.

The initial developmental process leading to the formation of the unbalanced vasculature and the subsequent TTTS phenotype in some MC twin pregnancies but not in others has not been determined. Dichorionic (DC) twins do not develop TTTS (with rare exceptions (Quintero *et al.*, 2010)), because each has its own placenta without interlocking anastomoses, even when the placenta has a fused appearance.

AA and VV anastomoses are very different from AV and VA anastomoses in that they occur exclusively on the surface of the placenta (not deep), are terminal (not capillary) anastomoses, and allow bidirectional (not unidirectional) blood flow. Thus, they do not cause the TTTS phenotype.

- **Vasoactive mediators** are released in response to changes in intravascular volume and affect cardiovascular and renal function in both twins.

  Hypoperfusion of the kidneys of the chronically hypovolemic twin (called the donor twin) results in activation of the renin-angiotensin-aldosterone system (RAAS) and release of angiotensin II, renin, aldosterone, and vasopressin in a sustained effort to restore intravascular volume and maintain his blood pressure (Mahieu - Caputo *et al.*, 2000; Bajoria, Ward and Sooranna, 2004) . This leads to oliguria, with anhydramnios and the 'conjoined twin' phenotype in severe cases.

  Chronic hypervolemia in the recipient twin causes its heart atria to stretch and release atrial natriuretic peptide. Abdominal distension results in the release of brain natriuretic peptide (Bajoria, Ward and Chatterjee, 2002) . These hormones promote vasodilation, natriuresis, and RAAS inhibition, leading to polyuria and polyhydramnios. However, over time, the recipient may develop hypertensive cardiomyopathy as a result of continued volume overload, increased levels of endothelin I, and increased levels of RAAS mediators acquired from the donor through the AV anastomoses, even though their own RAAS system is suppressed (Bajoria, Sullivan and Fisk, 1999; Barrea *et al.*, 2005; Donepudi *et al.*, 2017) . Venous hypertension is a late stage of the

process and results in movement of intravascular fluid into the interstitial spaces and functional lymphatic obstruction, leading to hydrops fetalis (van den Wijngaard *et al.,* 2005) .

- The **AA anastomoses** are thought to be protective against the development of TTTS by correcting the volume imbalance interaction caused by unbalanced AV anastomoses. The observation that AA anastomoses are rare to absent in TTTS supports this theory (Denbow *et al.,* 2000) .

➢ **Intrapartum TTTS syndrome**

In a minority of cases, acute intrapartum TTTS occurs at birth from a rapid and large transfusion of blood from the donor to the recipient (Lopriore *et al.,* 2014) . This leads to immediate anemia and possibly hypovolemic shock in the donor twin and immediate polycythemia in the recipient twin. The reported incidence is 1.5 to 2.5% of all MC twins, regardless of mode of delivery (Verbeek, Slaghekke, *et al.,* 2017) .

Acute transfusion is thought to occur through AV and AA anastomoses, but it is not clear why a balanced state becomes acutely unbalanced. Hypotheses include changes or maturation of the placenta late in pregnancy, hemodynamic changes that occur after the birth of one twin and before the birth of the second twin, and the timing of cord clamping (Lopriore and Oepkes, 2008) .

Monitoring

Twin pregnancies are often first diagnosed when a pregnant woman undergoes a first-trimester ultrasound to date the pregnancy, assess for vaginal bleeding, or measure nuchal translucency as part of screening for Down syndrome (trisomy 21). When diagnosing twins, determination of chorioamnionicity is essential to guide follow-up, which is different for monochorionic (MC) versus dichorionic (DC) twins.

In monochorionic twin pregnancies, repeated fetal ultrasound examinations are necessary to monitor the development of TTTS, as well as twin anemia-polycythemia sequence (TAPS) and selective single-fetal growth restriction (sFGR), because these disorders collectively affect 15 up to 20% of MC pregnancies, have high morbidity and mortality and are amenable to interventions that can reduce morbidity and mortality. Their clinical findings overlap, so identifying the differences between them will aid in the differential diagnosis.

Table 1 presents an ultrasound screening protocol for monochorionic twins to screen for TTTS, TAPS and sFGR. This protocol is based on guidelines published by the Society for Maternal-Fetal Medicine and the

International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) (Sueters *et al.*, 2006; Society for Maternal-Fetal Medicine and Simpson, 2013; A. Khalil *et al.*, 2016) .

In the first trimester, chorionicity is determined and nuchal translucency and CRL are measured in both twins as part of routine obstetric ultrasound evaluation. In meta-analyses, intertwin nuchal translucency discordance >20%, nuchal translucency >95th percentile in one or both fetuses, CRL discordance ≥10%, and abnormal ductus venosus (DV) flow on the first ultrasound trimester were associated with the development of TTTS, but with low sensitivity (Stagnati *et al.*, 2017; Mackie *et al.*, 2018) . Nuchal translucency discordance and abnormal DV flow had the highest sensitivities at 53 and 50%, respectively (Stagnati *et al.*, 2017) . However, first-trimester DV Doppler is not recommended for predicting TTTS because Doppler in early pregnancy exposes twins to higher ultrasound power with no clear benefit in predicting or reducing complications from TTTS.

Monitoring for TTTS begins in the second trimester, at 16 weeks' gestation, and continues until 36 weeks (table 1). The onset of TTTS is usually gradual and during the second trimester at 16 weeks or later, but can occur suddenly and later in pregnancy (Sueters *et al.*, 2006; Lewi, Gucciardo, *et al.*, 2008) . The onset of the disorder peaks at around 20 weeks, with a decline in incidence at 26 weeks and only rare cases are reported thereafter up to 30 weeks. TAPS, as well as sFGR, usually develop at the end of the second or third trimester (Lewi, Gucciardo, *et al.*, 2008) .

Gestational age	Purpose of ultrasound examination and frequency

11 to 14 weeks	• One examination for:
	  • Assessment of gestational age and estimated date of delivery
	  • Assessment of chorioamnionicity
	  • Measurement of nuchal translucency*

16 AND 18 weeks	• Fetal size • Early fetal anatomic survey, including presence and size of fetal bladders • MVP of amniotic fluid • Doppler measurement of MCA-PSV • Doppler measurement of end-diastolic velocity in the UA • Assessment for PDE
20 weeks	• Fetal size • Detailed fetal anatomic survey, including presence and size of fetal bladders • MVP • Doppler measurement of MCA-PSV • Doppler measurement of UA end-diastolic flow velocity • PDE • Evaluate placental cord insertion sites (proximate cord insertion is defined by a distance between cord insertions below the fifth percentile for gestational age or by 3.3 to 4.0 cm at any gestational age)
20 to 22 weeks	• Transvaginal ultrasound measurement of cervical length • Fetal echocardiogram

22 to 32 weeks	• Serial examinations of fetal growth every 4 weeks
	• Serial examinations of the following every 2 weeks:
	  • MVP
	  • Presence and size of fetal bladders
	  • Doppler measurement of MCA-PSV
	  • Doppler measurement of UA end-diastolic flow velocity
	  • PDE

32 to 36 weeks	• Continue serial examinations of fetal growth every 4 weeks
	• Weekly examinations:
	  • Biophysical profile score
	  • Doppler measurement of MCA-PSV
	  • Doppler measurement of UA end-diastolic flow velocity
	  • PDE

Table 1. Ultrasound control protocol for monitoring monochorionic multiple pregnancies.

MVP: maximum vertical pocket; MCA: middle cerebral artery; PSV: peak systolic velocity; UA: umbilical artery; PDE: placental discordance echogenicity.

Increased nuchal translucency has been associated with trisomy 21, a variety of congenital anomalies, developmental and genetic syndromes, and TTTS. Amendment by (Sueters et al., 2006; Society for Maternal-Fetal Medicine and Simpson, 2013; A. Khalil et al., 2016)

Diagnosis

TTTS is usually diagnosed in an ultrasound exam performed in the early to mid-second trimester.

- **Diagnostic criteria**

Prenatal diagnosis of TTTS is based on ultrasonographic evidence of a single MC placenta with oligohydramnios/polyhydramnios sequence in twins, after exclusion of other amniotic fluid discordant disorders. The maximum amniotic fluid pockets for oligohydramnios and polyhydramnios are usually defined as <2 cm and >8 cm, respectively. Alternatively, the Fetal foundation Medicine Foundation of the United Kingdom uses criteria based on gestational age to define polyhydramnios (≥6 cm at 15 to 17 weeks, ≥8 cm at 18 to 20 weeks and >10 cm at ≥20 weeks) (The Fetal Medicine Foundation ' MC twins : twin - to - twin transfusion syndrome ') .

When severe, oligohydramnios in the donor sac results in a “conjoined twin” appearance: The fetus appears stuck to the uterine wall because there is little or no fluid in its sac and its amniotic membrane is in its body. Instead, the recipient moves freely within a large volume of amniotic fluid, which also compresses the sac of the donor twin.

- **Postdiagnostic fetal evaluation and potential findings**

Once a diagnosis of TTTS is made based on the recognition of amniotic fluid discordance, the following evaluations of both twins are performed to rule out other disorders in the differential diagnosis. Other findings possibly related to TTTS are looked for, the stage is defined, on which the monitoring and management of the pregnancy is based. TTTS is not associated with an increased risk for chromosomal abnormalities or genetic syndromes, so fetal genetic testing is not offered unless there is another reason for such testing.

At 16 to 18 weeks:

- **Doppler studies** of the umbilical artery (UA), umbilical vein (UV), and ductus venosus (DV) are required to classify disease severity, while middle cerebral artery peak systolic flow velocity (MCA - PSV) is required to assess of TAPS (defined as: MCA - PSV 1.5 times above the median [multiples of median, MoM] in one twin and less than 0.8 MoM in the other twin), which sometimes coexists with TTTS .
- **Comprehensive anatomic screening-** Twins are at increased risk for congenital anomalies and MC twins are at increased risk compared to DC twins. Abnormalities that could lead to growth failure or oligohydramnios are of particular importance as they may affect the differential

diagnosis of TTTS versus sFGR versus upper or lower urinary tract abnormalities resulting in amniotic fluid disharmony.

- **Evaluation for hydrops fetalis-** One or both fetuses may show signs of hydrops (combination of ascites, pleural or pericardial effusions, and skin edema). If one twin is hydropic, it is usually the donor. Dropsy is a factor in grading the severity of the disease.
- **Evaluation of bladder size-** The size of the donor bladder may be normal or reduced. The size of the recipient cyst may be normal or enlarged. Bladder size is a factor in classifying the severity of the disease.
- **Biometry** – Growth restriction is a potential complication of TTTS, developing in over 50% of donor twins (Van Winden *et al.,* 2015) , and also a key component of sFGR .
- **Fetal heart ultrasound**
    - **Recipient twin-** Abnormalities of the right ventricular outflow tract, including functional or anatomic pulmonary atresia or stenosis, have been observed in approximately 10% of recipient twins (Lougheed *et al.,* 2001; Karatza *et al.,* 2002; Herberg *et al.,* 2006) . Hypertrophy may develop in one or both fetal heart ventricles. (Hypertrophy is measured by ultrasound and is defined as thickness of the abdominal wall or intra-abdominal septum greater than two standard deviations [SD] for gestational age).

      Right-sided myocardial dysfunction is two to three times more common than left-sided dysfunction, although echocardiographic studies have revealed that in the early stages of TTTS left ventricular filling pressures may be elevated and systolic function may be reduced before left ventricular function right ventricle becomes abnormal (Wohlmuth *et al.,* 2018) . Right-sided dysfunction is not surprising, as the right ventricle is the dominant ventricle in the fetal heart. Depression of myocardial contractility and severe tricuspid regurgitation can be detected, as well as a-wave inversion on DV Doppler examination. Functional occlusion of the pulmonary artery is signaled by reverse filling of the ductus arteriosus from the aortic arch (Barrea *et al.,* 2005) .
    - **Twin donor-** The donor generally has a normal echocardiogram. In advanced stages, the donor may have low-output heart failure.

Differential diagnosis

- **Early form of TTTS** should be considered when the findings do not meet the diagnostic criteria. Second-trimester MC pregnancies with polyhydramnios of one sac and normal amniotic fluid volume in the other sac or amniotic fluid volume discordance that do not meet the diagnostic criteria for TTTS are at increased risk of progression to TTTS, especially if one twin is growth restricted (Huber *et al.*, 2006; Chon *et al.*, 2014) . Contrary to the routine screening protocol (table 1), in this case weekly ultrasound examinations to determine the maximum vertical pool of amniotic fluid are recommended until the presence or absence of TTTS is clear. An early ultrasound examination is also recommended in patients with polyhydramnios in a sac who become acutely symptomatic.
- The **before the end premature rupture of membranes (PPROM)** of a sac can cause amniotic fluid discordance. PPROM is easily diagnosed or ruled out by testing for amniotic fluid in the vagina.
- **Congenital anomalies** can lead to amniotic fluid discordance (e.g., renal agenesis in the suspected donor twin can cause oligohydramnios, upper gastrointestinal obstruction in the suspected recipient can cause polyhydramnios). Renal abnormalities causing amniotic fluid discordance can usually be easily diagnosed or ruled out by an anatomical study of the fetus, but gastrointestinal abnormalities, such as esophageal atresia, are more difficult.
- **Congenital infection** of the fetus may be severe enough to cause growth restriction with or without amniotic fluid abnormalities. Testing for infection is not recommended when TTTS is suspected unless there are fetal findings associated with infection, such as cerebral calcifications, cerebral ventriculomegaly, echogenic fetal bowel, hepatosplenomegaly, and/or hepatic calcifications.
- The term **selective fetal growth restriction (sFGR)** is used in the scenario where the difference in estimated fetal weight between twins is >25% and the estimated weight of the younger twin is <10th percentile, with or without reduced amniotic fluid volume. The older twin has a normal volume of amniotic fluid. Amniotic fluid discordance (when present) increases the likelihood of TTTS. In a series of 324 cases referred to a specialist center because TTTS was suspected, the diagnosis was confirmed in 77 % (249 cases) and the remaining patients had either discordant amniotic fluid volume that did not meet the criteria for TTTS (56 %) or sFGR (44%) (Gandhi *et al.*, 2012) .

  Distinguishing TTTS complicated by IUGR in the donor twin from sFGR can be difficult, as in both cases the fetus with FGR may have oligohydramnios. The key to distinguishing between the two entities is based on ultrasound findings in the normal-sized twin: In pregnancies with sFGR, the other twin will grow appropriately and have a normal amniotic fluid volume (defined as a maximum vertical

pocket >2 cm and <8 cm), whereas when FGR is part of TTTS, the appropriately growing twin usually has polyhydramnios (maximum pocket >8 cm), since it is the recipient.

Determining the true diagnosis between TTTS and sFGR is paramount in making decisions about treatment options. Laser photocoagulation of placental anastomoses is the treatment of choice for TTTS with or without concomitant FGR. Treatment for individual sFGR is based on expert opinion, varies (conservative management with fetal monitoring, early delivery) and depends on gestational age (e.g., selective reduction at predicted gestational ages).

Staging

Staging systems have been established to provide a standardized means of describing the increasing severity of TTTS. The use of different systems should be considered when comparing reported pregnancy outcomes.

- **Classic staging**

The five classical stages of the disease are based on findings from two-dimensional ultrasound and Doppler measurement of the UA, UV, and DV. In the influential publication by Quintero and colleagues, oligohydramnios was defined as a maximum pocket ≤2 cm and polyhydramnios was defined as a maximum pocket ≥8 cm (Quintero *et al.,* 1999) .

- Stage I
  - Sequence of oligohydramnios and polyhydramnios
  - The bladder of the donor twin is visible
  - Doppler indices (UA, UV, DV) in both twins are normal
- Stage II
  - Sequence of oligohydramnios and polyhydramnios
  - The donor's bladder is not visible
  - Doppler indices (UA, UV, DV) in both twins are normal
- Stage III
  - Sequence of oligohydramnios and polyhydramnios
  - Abnormal Doppler indices: At least one of the following is present in both twins: absent end-diastolic wave or inversion in UA, inversion of DV α-wave, or pulsatile flow in UV
- Stage IV

- Sequence of oligohydramnios and polyhydramnios
- One or both fetuses have hydrops

- Stage V
  - Sequence of oligohydramnios and polyhydramnios
  - One or both fetuses are dead

Although this classical staging represents a standardization method, there are several important limitations. Informal presentations may occur. For example, the donor may have both a persistent cyst and abnormal umbilical artery Doppler flow. Furthermore, although higher stages are generally associated with a worse perinatal prognosis, the clinical picture of a particular case does not always follow a smooth progression of stages. For example, a stage I case may progress rapidly in a few days to stage III, but disease regression may occur in up to 15% of stage I cases and 60% of stage II disease (Taylor, Govender, et al., 2002) .

➢ **Other classification systems**

Given the limitation of classical staging to predict disease progression, some experts have suggested the use of fetal heart ultrasound assessment (cardiovascular score), mainly of the receiver twin, to provide the information needed to distinguish between pregnancies progressing to severe TTTS versus those with stable early TTTS that can be managed with monitoring.

- **(CVPS)**

  This score was originally developed for use in hydropic fetuses to predict congestive heart failure and fetal outcome. Incorporates heart size, cardiac function, and Doppler blood flow studies of UA, UV, and DV into the scoring profile. For each category, 2 points are assigned for normal findings and either 1 or 0 points for abnormal findings, depending on severity (Hofstaetter *et al.*, 2006) .

  In a study of CVPS to assess cardiac status and outcome in 62 postintervention recipient twins, the overall neonatal survival rate was 61% (76/124) and recipient survival rates were better with higher CVPS (74% [25/34] for CVPS 10 vs 31 % [5/16] for CVPS <9) (Shah *et al.*, 2008) . Classical staging was not predictive of recipient survival. The authors concluded that cardiac assessment by CVPS can improve clinical decision-making and the timing of fetal interventions. However, the results are difficult to interpret, as the initial treatment for TTTS was a treatment no longer used (amnioablation) in 51 % (32/62) of cases, with over a third in Quintero stage III.

- **CHOP rating**

The Children's Hospital of Philadelphia has developed a cardiovascular scoring system based on echocardiographic and peripheral Doppler findings in a study of 150 donor and recipient fetuses (Rychik *et al.,* 2007) . When four grades of progressive worsening of cardiovascular abnormalities were compared with classical staging, significant differences were noted. For example, when fetuses classified as stage II were reclassified by cardiovascular score, the distribution of cardiovascular score grades from least to most severe was grade 1 (35%), grade 2 (30%), grade 3 (25%), and grade 4 (10 %). However, a subsequent prospective evaluation of 158 cases of TTTS before laser treatment at another center failed to find an association between increasing CHOP score and perinatal survival (Stirnemann *et al.,* 2010) .

- **Cincinnati Amendment**

The Cincinnati modification of the classic staging system is another cardiovascular grading system (Crombleholme *et al.,* 2010) . This system divides stage III into A, B, and C classifications based on progressively worsening echocardiographic findings of three parameters in the recipient fetus (presence and severity of AV valve insufficiency, ventricular wall thickening, and ventricular function as assessed by myocardial performance index [MPI, myocardial performance index]). Cases are upgraded from the classic stage based on the presence of these fetal echocardiographic findings.

Although cardiovascular evaluation has provided further insight into the pathophysiology and severity of TTTS, available scoring systems do not appear to be predictive of disease progression or perinatal outcome after laser photocoagulation. Furthermore, many of the proposed components of fetal heart ultrasound evaluation are technically difficult to perform (such as MPI, which is used to assess whole ventricular function). This raises concern about the feasibility and effectiveness of cardiovascular scoring systems as potential screening tests in widespread clinical populations.

Maternal clinical manifestations

TTTS is usually suspected initially because of the characteristic fetal findings on ultrasound examination, as discussed above. The mother is usually asymptomatic, but symptoms associated with uterine hyperdistension may occur, including supine discomfort, insomnia, early satiety, lower abdominal pain, orthopnea, and pelvic pressure (in patients with advanced cervical change). (Sueters *et al.,* 2006) . Mirror syndrome (i.e., generalized maternal edema usually associated with hypertension) has been reported in cases with a hydropic fetus (Chai *et al.,* 2014) .

Premature cervical shortening occurs in some patients, although cervical length in TTTS is normally distributed, with mean ± SD: 38 ± 10 mm at 16 to 24 weeks' gestation (Papanna *et al.*, 2015) . The pathogenesis of cervical shortening is unclear. Although uterine overdistension is the presumed etiology, no correlation was found between intra-amniotic pressure and cervical length before treatment or gestational age at delivery (Bergh *et al.*, 2019). A pretreatment cervical length <28 mm in patients with TTTS in this gestational age range has been associated with an increased risk for preterm delivery, but the optimal management of these patients is unclear given the lack of data from randomized trials. It is thought that using progesterone 200 mg vaginally daily or pessary is a reasonable approach, but no cervical cerclage is performed. In the largest cohort study, cervical cerclage did not prolong pregnancy or improve perinatal survival (Papanna *et al.,* 2012) . Additionally, there is evidence that cerclage may reduce the time to birth in this population (Buskmiller *et al.,* 2022) . However, practice standards vary widely both in defining the treatment that warrants cervical length (e.g., <10, 20, or 28 mm) and in the intervention offered (vaginal progesterone, pessary, or band).

Syndrome management

The three main approaches to the management of TTTS are monitoring, ligation of placental anastomoses via amnoscopy and laser, and amnioablation. Selective fetal reduction is another option but is rarely performed in the absence of discordant malformations or severe selective fetal growth restriction. The choice of approach depends on the stage, maternal symptoms and signs, gestational age, and the availability of the required technical expertise.

- **Management of stage I TTTS**

The choice of treatment for stage I TTTS is based primarily on the severity of maternal discomfort from uterine distension and the length of the cervix. No randomized trials have compared treatment approaches for stage I TTTS.

In a 2020 meta-analysis of observational studies evaluating the outcome of 610 stage I TTTS pregnancies by intervention type, the fetal survival rate of at least one twin was 84.9% (94 of 112) in cases treated with observation, 86.7 % (249 of 285) in those treated with laser therapy and 92.2 % (56 of 60) in those treated with amnioablation, while the double survival rate was 67.9 (73 of 108), 69.7 (203 of 285), and 80.8% (49 of 60), respectively (Di Mascio, Khalil, D' Amico, *et _ al .*, 2020) . Survival findings alone are not

sufficient to make a strong recommendation for one type of management over another. Maternal symptoms and risk of progression should also be considered.

- **Women without or with tolerable symptoms and normal cervical length**
  - **Choice of treatment**

    For women with stage I TTTS and no maternal symptoms or with tolerable symptoms and cervical transvaginal length >25 mm, it is recommended to avoid intervention and monitor the status of TTTS with weekly ultrasound examinations to detect progression to more severe disease. In addition to the morbidity associated with any intervention, unnecessary intervention may influence treatment options later in pregnancy if intervention becomes the indicated choice due to progressive disease. For example, amnioablation performed as first-line treatment of minimally symptomatic stage I disease may result in inadvertent septal stoma or bloody amniotic fluid, which would make it difficult to perform subsequent laser therapy when indicated due to worsening TTTS.

    This approach is based on limited but reassuring data on the outcome of well-defined stage I disease in the absence of any intervention. In a 2016 systematic review of 18 observational studies evaluating progression in 172 pregnancies and survival in 433 pregnancies, conservative management was associated with a pooled rate of worsening of 27% (95% CI 16-39%) and an overall survival of 79% (95% CI 62-92 %) (Asma Khalil *et al.,* 2016) . Overall survival with amnioablation, laser therapy only if deterioration occurs, and laser therapy as first-line therapy was 77, 68, and 84%, respectively. Although these findings suggest that laser surgery as first-line therapy may have little benefit, they are limited by the biases inherent in observational data.

    An international randomized trial comparing conservative management with laser therapy in the management of women with stage I TTTS who were asymptomatic and had a cervix length >15 mm showed no difference in overall disease-free survival at six months for conservative management (77%) versus direct laser surgery (78 %). However, 60% of conservatively treated cases had serious complications and led to surgery (Stirnemann *et al.,* 2021) . Severe neurological morbidity may be lower in those treated with immediate laser surgery versus follow-up, but the data did not allow a clear conclusion (2.6 vs 4.6 %, RR 0.574, 95% CI 0.117-2.81). The trial was stopped early (at 117 of 200 planned inclusions) due to a slow rate of patient enrollment.
  - **Prenatal monitoring and care**

Pregnancies with stage I TTTS and no maternal symptoms or with tolerable symptoms and cervical transvaginal length >30 mm are monitored for disease progression by ultrasound:

- ✓ Amniotic fluid volume is assessed weekly. The North American Fetal Therapy Network reported that the average duration from diagnosis of stage I TTTS to change of status was 11.1 days. In those cases that worsened, the average duration was 9 days (Emery *et al.*, 2016) .
- ✓ Fetal growth is assessed every three to four weeks. If selective fetal growth restriction is identified (i.e., a fetus with estimated fetal weight <10th percentile), weekly umbilical artery and ductus venosus Doppler blood flow studies are obtained.
- ✓ Beginning at 18 weeks, Doppler blood flow studies to assess middle cerebral artery peak systolic flow velocity (MCA-PSV) are incorporated into the monochorionic multiple pregnancy screening protocol, along with umbilical artery (UA) Doppler blood flow studies and of the vein (UV) and the ductus venosus (DV) (Townsend and Khalil, 2018) . Different values between fetuses indicate TAPS syndrome, a milder form of TTTS that occurs spontaneously in 5% of monochorionic twins. Discordance is defined as MCA-PSV >1.5 times the median value (MoM) in one fetus combined with a value <1.0 MoM in the other.
- ✓ Starting at 30 weeks, the biophysical profile is performed weekly.

If TTTS stage and symptoms remain stable, the American College of Obstetricians and Gynecologists and the International Society of Ultrasound in Obstetrics and Gynecology recommend planning delivery at 34^{+0} to 37^{+6} weeks of gestation, in the absence of complications requiring preterm delivery (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, Society for Maternal - Fetal Medicine, 2021) . According to a meta-analysis, uncomplicated monochorionic diamniotic twins are born at 37^{+0} weeks (Cheong - See *et al.*, 2016) .

If TTTS progresses, then management depends on maternal symptoms, the condition of the cervix and the stage of TTTS.

- **Women with debilitating symptoms or a short cervix at 16 to 26 weeks' gestation**
  - **Choice of treatment**

For women with stage I TTTS at 16 to 26 weeks' gestation with debilitating symptoms (e.g., significant respiratory distress and/or premature contractions) or a short cervix (≤25 mm) due to severe polyhydramnios, laser ligation of placental anastomoses is recommended, in agreement with most experts in the international medical community (Wagner *et al.*, 2009; Wilson, Johnson and Ryan, 2009; Molina *et al.*, 2010) . Cervical length <28 or 30 mm before laser surgery was predictive of preterm delivery in two studies (Robyr *et al.*, 2005; Papanna *et al.*, 2015) . Conservative management is not a reasonable option given the maternal distress and increased risk of preterm delivery.

Amnioscopic laser ligation of placental anastomoses is an effective treatment of TTTS and, unlike amnioablation, is unlikely to require repeat procedures. In a systematic review evaluating the progression of stage I TTTS with various interventions, no pregnancies treated with laser therapy progressed to a more advanced stage, whereas 30% of pregnancies treated with amnioablation progressed to a later stage of TTTS . (Rossi and D' Addario, 2013).

- **Prenatal monitoring and care after laser treatment**

There are few data on which to base specific recommendations for prenatal monitoring and care after laser treatment. The following protocol for routine post-laser fetal monitoring is described:

- ✓ Weekly ultrasounds are performed according to the ISUOG Society for the first two weeks and then every other week after laser treatment until 30 weeks of gestation, to evaluate for complications and response to treatment (A. Khalil *et al.*, 2016) :
  - The amniotic fluid and fetal membranes are evaluated for signs of separation of the membranes, involuntary septal stoma, rupture of membranes, unexpected changes in amniotic fluid volume, and evidence of therapeutic response. Normalization of amniotic fluid volume occurs at week 5 in the donor amniotic sac and at week 8 in the recipient amniotic sac in more than 95% of cases (Assaf, Korst and Chmait, 2010) .
  - MCA-PSV is measured to detect TAPS due to residual placental anastomoses. TAPS usually occurs in the first six weeks after laser treatment. As discussed above, TAPS is diagnosed when the MCA-PSV is >1.5 MoM in one fetus combined with a value <1.0 MoM in the other.
- ✓ Fetal weight is estimated every three to four weeks to detect severe growth restriction (i.e., a fetus with estimated fetal weight <10th percentile), which usually occurs in the twin-former donor. Doppler blood flow studies of the umbilical artery in the growth-restricted

fetus are obtained weekly once viability is achieved. If absent or reversed end-diastolic flow in the umbilical artery is observed, ductus venosus Doppler flow studies are added to the monitoring protocol.

Growth-restricted donor twins often show growth after laser treatment. One study reported that the percentage of donor twins with growth restriction decreased from 65 to 29 % after the procedure (Chmait *et al.,* 2008) . However, if preterm delivery due to growth restriction seems likely, an antenatal course of glucocorticoids is given.

- ✓ Starting at 30 weeks of gestation, the biophysical profile is performed weekly.

Fetal magnetic resonance imaging (MRI) is not usually scheduled after laser. Although 2 to 6% of fetuses will have an ischemic hemorrhagic lesion on MRI at 30 to 32 weeks' gestation after laser treatment, one study noted that 82% of these cases were identified by ultrasound before MRI (Stirnemann *et al.,* 2018) . Additionally, monochorionic twins are known to have white matter injury, even those without a known diagnosis of TTTS, so if an injury is found, it will not be known if it is due to the procedure. Finally, few centers have specialized people on site to read/interpret fetal MRI.

However, MRI may be informative in cases with post-laser fetal death. In theory, all vascular communications between the twins should be closed so that the surviving fetus is not at risk of hypotension or embolism at the time of death, but since recurrent TTTS is likely, the ISUOG guidelines recommend review of MRI imaging 4 to 6 weeks after detection of a death (A . Khalil *et al.,* 2016) .

Delivery is planned up to 37 $^{+0}$ weeks of gestation, in the absence of complications requiring premature delivery. Preterm delivery is indicated because of the risk of unexplained fetal death at the end of pregnancy. Although the ISUOG recommends delivery as early as 34 weeks, there is no evidence of an increased risk of fetal death after 34 weeks in pregnancies treated with laser surgery.

- **Women with debilitating symptoms after 26 weeks of pregnancy**
  - **Choice of treatment**

For women with stage I TTTS after 26 weeks' gestation with debilitating symptoms (e.g., significant respiratory distress and/or premature contractions) or a short cervix (≤25 mm) due to severe polyhydramnios, amniocentesis is recommended to reduce uterine hyperdistension and

thereby relieve from maternal symptoms (Wagner *et al.,* 2009; Wilson, Johnson and Ryan, 2009) . Amnioectomy may also improve TTTS.

The US Food and Drug Administration's investigational device exemption for fetoscopes limits their use in the treatment of TTTS from 16 to 26 weeks gestation. In practice, laser ligation at later gestational ages is subject to several technical limitations: Fetal sebum in the amniotic fluid reduces optimal visualization, placental vessels are larger in diameter and more difficult to coagulate successfully, and current fetoscopes may not they easily cross longer distances in the womb. However, some centers outside the United States offer the laser after 26 weeks' gestation, and there is increasing evidence that procedures performed at later gestational ages can lead to results comparable to those performed at the traditional 16-26 week period (JM Middeldorp *et al.*, 2007; Valsky *et al.,* 2012; Baud *et al.,* 2013; Lecointre *et al.,* 2014) .

- **Prenatal monitoring and care**

  The following protocol is described for routine follow-up after amnioectomy:

  - ✓ After amniocentesis, weekly fetal ultrasound examination is performed to assess for complications, progression to a more advanced stage of TTTS, and response to treatment. The amniotic fluid and fetal membranes are evaluated for signs of separation of the membranes, involuntary septal stoma, rupture of membranes, unexpected changes in amniotic fluid volume, and signs of therapeutic response.

    Amniocentesis is repeated if the pregnant woman becomes symptomatic (contractions or respiratory distress) due to uterine overdistension from recurrent polyhydramnios.
  - ✓ Fetal development is assessed every three to four weeks. If selective fetal growth restriction is identified (i.e., a fetus with estimated fetal weight <10th percentile), weekly umbilical artery Doppler blood flow studies are obtained in the growth-restricted fetus. If absent or reversed end-diastolic flow is noted, ductus venosus Doppler flow studies are added to the monitoring protocol. If a discordance in fetal growth is detected and preterm delivery is likely, a prenatal course of glucocorticoids is administered.
  - ✓ Beginning at 28 weeks, weekly Doppler blood flow studies are obtained to assess MCA - PSV. As discussed above, discordant values are indicative of TAPS, a milder form of TTTS that occurs spontaneously in 5% of monochorionic twins. TAPS is diagnosed when the MCA - PSV is >1.5 MoM in one fetus combined with a value <1.0 MoM in the other.
  - ✓ Starting at 30 weeks of gestation, the biophysical profile is performed weekly.

Delivery is planned up to 37 $^{+0}$ weeks of gestation, in the absence of complications requiring premature delivery. Early delivery is indicated due to the risk of unexplained fetal death during the period of "term" pregnancy (37 to 42 weeks).

- **Management of stage II - IV TTTS**

Intervention for stage II to IV pregnancies is indicated because reports suggest a poor prognosis with follow-up alone. Overall perinatal survival at stage II or greater was only about 30% in a literature review of 28 studies involving a total of 68 pregnancies with untreated TTTS between 1966 and 1991 (Berghella and Kaufmann, 2001) . In comparison, perinatal survival was approximately 60% in two large series with therapeutic intervention (Crombleholme *et al.,* 2007; Chmait *et al.,* 2011) .

- **Choice of treatment at 16 to 26 weeks of gestation**

Fetoscopic laser ligation of placental anastomoses is the preferred procedure for the definitive treatment of stage II to IV TTTS between 16 and 26 weeks' gestation (Society for Maternal - Fetal Medicine and Simpson, 2013) .

Although a 2014 meta-analysis of randomized trials comparing laser ablation with amnioablation found no statistically significant improvement in survival with laser treatment, the two trials had different conclusions [Eurofetus reported better survival with laser ablation (Senate *et al.,* 2004) , which did not occur in the United States trial (Crombleholme *et al.,* 2007)], whereas in both trials the laser ablation group was more likely to be alive without neurological complications at six years of age (Roberts *et al.,* 2014) . However, there were several limitations to these data: Fewer than 200 pregnancies were studied. Approximately 90% of pregnancies in both trials had stage II or III disease, but the proportions of stage I and stage IV disease randomized were insufficient to answer the question of benefit. The Eurofetus trial enrolled patients at all stages of TTTS. Of the 142 randomized cases, 11 were stage I (6 randomized to laser and 5 to amnioablation) and 2 were stage IV cases (1 randomized to laser and 1 to amnioablation). In the United States trial, stage I cases were excluded. Of the 42 randomized cases, 4 were stage IV (3 randomized to laser and 1 to amnioablation). Thus, the pregnancies in the United States trial were at the more severe end of the disease spectrum. Both trials were stopped early: Eurofetus was stopped early because a planned interim analysis showed a significant benefit in the laser group. The United States trial was stopped early because referring clinicians were no longer willing to refer patients to participating centers for randomization after

publication of the Eurofetus report. Decreased enrollment together with the finding of a statistical trend in adverse outcomes in laser-treated donor twins led to the decision to stop the trial.

Additional support for the efficacy of laser therapy was provided by a 2013 meta-analysis of brain injury following laser therapy versus amnioablation, which included four observational studies involving 357 children in the amnioabotomy group and 269 children in the laser group (van Link *et al.,* 2013) . Brain injury in live infants in the amnioablation group was more than sevenfold that of live infants in the laser group (95% CI 2.8–20.0). After excluding neonatal deaths from the analysis, infants from pregnancies treated with amnioablation still had a significant increase in neurological injury (RR 3.23, 95% CI 1.45–7.14) compared with the group with a laser. Gestational age at the time of intervention was comparable, 20 to 22 weeks. However, the median gestational age at delivery was lower in the amniocentesis group compared with the laser group, 28 to 31 versus 32 to 34. The authors hypothesized that the increased risk of brain damage in the amniocentesis group was due to the higher rate of prematurity.

- **Prenatal monitoring and care**

  Antenatal monitoring and care is identical to that in stage I TTTS pregnancies treated with laser ablation.

- **Choice of treatment after 26 weeks of gestation**

Amniocentesis is the preferred intervention for the treatment of stage II to IV TTTS after 26 weeks' gestation in the United States. As discussed above, the US Food and Drug Administration's investigational device exemption for fetoscopes limits their use in the treatment of TTTS to 16 to 26 weeks' gestation. In practice, laser ablation at later gestational ages is subject to several technical limitations: fetal sebum in the amniotic fluid reduces optimal visualization, placental vessels are larger in diameter and more difficult to coagulate successfully, and greater distances to the uterus may not easily crossed by current fetoscopes. However, some centers offer laser ablation after 26 weeks' gestation, and there is increasing evidence that procedures performed at later gestational ages can lead to results comparable to those performed at the traditional 16–26-week period, as stated above.

- **Prenatal monitoring and delivery time**

Antenatal follow-up and timing of delivery are identical to those in stage I TTTS patients treated with amnioablation.

- **Management of stage V TTTS**

If one fetus has died, the main concerns for the other fetus are death (10% risk) or neurological damage (10 to 30% risk) due to their shared circulation (Society for Maternal - Fetal Medicine and Simpson, 2013) . Management is the same as in monochorionic twin pregnancies without TTTS.

In these cases, neither laser treatment nor amnioablation can prevent brain damage in the surviving twin, as the insult occurs at the time of the twin's death. The goal is to optimize the outcome for the surviving twin and avoid the complications of iatrogenic prematurity. A detailed ultrasound examination of the surviving twin should be performed, including middle cerebral artery peak systolic velocity (MCA-PSV) Doppler blood flow studies. Exclusion of fetal anemia (MCA-PSV) in the context of acute death of the other fetus virtually eliminates the possibility that major hemorrhage has occurred and probably has a favorable prognosis (Shek, Hillman and Kilby, 2014) . Before 37 weeks of gestation, conservative management with repeated fetal ultrasound examinations every three to four weeks is aimed at monitoring fetal development and the central nervous system. MRI examination three to four weeks after fetal death is indicated to detect intracranial damage. Emergency delivery in the preterm setting does not improve outcome.

Intrauterine transfusion to correct fetal anemia within 24 hours of intrauterine fetal death has been offered in some centers, but the benefit of this intervention has not been established (Quarello *et al.,* 2008) . Intrauterine transfusion is performed after acute death when fetal anemia is documented with MCA-PSV >1.5 times the median value. A fetal blood sample is obtained for hemoglobin/hematocrit and a slow transfusion is initiated pending the results, which are used to determine the transfusion volume.

- **Fetoscopic laser ablation of anastomotic vessels**

Fetoscopic laser ablation is a procedure in which a laser is inserted through an fetoscope and used to ablate the superficial blood vessels on the surface of the placenta that cross the membrane between the twins. Although the anastomoses are present deep in the placenta, their afferent and efferent branches are superficial. In theory, coagulation of the superficial vessels should eliminate unbalanced twin transfusion. Contraindications are center-specific and may include preterm premature rupture of membranes, preterm labor, suspected abruption, significant separation of the membranes, fetal death of one twin, fetal chromosomal or congenital abnormalities, and previous amnioablation (Baud et al., *2013* ; Akkermans *et al.,* 2015; Sasso *et al.,* 2019) .

- **Patient preparation**

Fetoscopic laser ablation is generally performed as an outpatient procedure under local anesthesia with intravenous sedation, although some clinicians use regional anesthesia. General anesthesia with endotracheal intubation may be required in selected cases due to maternal respiratory distress from extreme polyhydramnios. A cephalosporin is given within one hour of starting the procedure. Nifedipine 10 mg is given orally just before the procedure to suppress uterine contractions. After 24 weeks of gestation, an antenatal course of corticosteroids is administered in case of preterm delivery. Although some clinicians administer indomethacin short-term (<48 hours) or long-term (>48 hours) (Mustafa *et al.,* 2022) instead of nifedipine, others do not use indomethacin because of reports of an increased risk of kidney damage in the donor twin when multiple doses of this agent were used to treat hydramnios in the recipient twin. Long-term use of indomethacin can also cause premature closure of the ductus arteriosus.

A thorough obstetric ultrasound examination is performed, including the determination of the distance between the two points of insertion of the umbilical cord of the placenta. If the sites are very close together (defined as <2 cm), vascular anastomoses may be difficult to locate and ligate (Gandhi *et al.*, 2011; Zhao, Peeters, *et al.,* 2013) and may require alternative intervention or conservative management. However, proximal cord prolapse is uncommon, occurring in only 1 to 2% of TTTS cases.

- **Process of laser ablation**

The suspected vascular equator between twins is located in the area between the two points of emergence of the umbilical cords of the placenta. The position of the "bonded" donor twin typically parallels this equator. An entry location in the receiver sac is chosen at 90 degrees to the equator. The Power Doppler is used to locate an avascular area in the uterine wall.

The skin is primed with hexachlorophene and anesthetized with a local anesthetic (e.g., 0.25% bupivacaine). Percutaneous entry can be done via the Seldinger technique or with a sharp trocar. For the Seldinger technique, an 18-gauge needle is inserted, followed by insertion of a J- wire through the needle and then removal of the needle. Next, a 9 to 12 French intravenous catheter is placed percutaneously over the guide wire under ultrasound guidance. Alternatively, a sharp metal trocar can be placed on the catheter and used to enter the uterus.

mm diameter fetoscope is then inserted through the catheter. If the placenta is anterior and centrally located, entering the uterus from an extreme lateral approach may result in puncture of the placental edge or the enlarged adnexal vascular complex. Specialized fetoscopes with 30- and 70-degree lenses have been developed that allow better visualization of the anterior placenta in these cases. In rare cases where percutaneous access is not possible due to the vascularity of the appendages, a laparoscopically assisted approach may be used. This method directs the fetoscope through the posterolateral uterine wall under direct visualization (Johanna M. _ Middeldorp *et al.,* 2007) .

An attempt is made to visualize all four distal extremities of both fetuses. This is particularly important in cases of TTTS complicated by polycythemia anemia sequence (TAPS), where the twin with polycythemia may show signs of limb thrombosis (e.g., skin blisters and blanching of the affected limb) (Schrey *et al.,* 2012) .

The equatorial dichorionization (Solomon) technique is preferred, which has three components:

- **Locating the vascular equator and mapping the anastomoses**

  The intertwin membrane on the surface of the placenta is identified as a landmark. The vascular equator is then identified, and the types of anastomoses are mapped. The type of anastomosis is determined based on various features as visualized through the fetoscope.

  Arteriovenous (AV) or venoarterial (VA) anastomoses appear as a single vessel originating from the donor or recipient. This vessel disappears in the placental mass, and a second vessel can be identified in close proximity to the disappearing vessel leading back to the twin. The arterial component of the anastomosis is dark red blue (deoxygenated blood), while the venous component is bright red (oxygenated blood). If the color differentiation cannot be easily discerned, a vessel can be traced back to its origin from the umbilical cord to the placenta.

  Arterioarterial (AA) anastomoses appear as dark tortuous vessels connecting the twin circulations on the surface of the placenta. Often, pulsating color changes can be seen by fetoscopy as the blood components of the two twins oscillate in the vessel.

  Venous (VV) anastomoses are rare. When present, they appear as relatively straight vessels that run between the two fetal circulations on the surface of the placenta.

  In most cases, the vascular equator may be located in the recipient sac. However, it is occasionally irregular with an element in the donor sac. The uterine wall at each end of the placenta is carefully examined to ensure that an eccentric communicating vessel does not roll out of the placental mass.

- **Cauterization of all visible anastomoses**

Laser energy (20 to 40 watts from a diode or YAG laser) is applied through a 400-to-600-micron quartz fiber inserted through an operating channel in the fetoscope. A second channel allows continuous irrigation to promote visualization. The anastomotic vessels are then catalyzed in a specific sequential sequence (called sequential selective laser photocoagulation): Arteriovenous (AV, donor artery to recipient vein), then veno-arterial (VA, donor vein to recipient artery), and finally arterio-arterial (AA) and veno-venous (VV) anastomoses.

Sequential selective ablation has been associated with a 40 to 50% reduction in the risk of intrauterine death of the donor or recipient twin compared with selective ablation, the older standard technique. The sequential selective technique requires a specific order of catalysis of the type of anastomoses, as mentioned above, while catalysis of the anastomoses with the selective technique is done without a specific order (Quintero *et al.*, 2007; Chmait *et al.*, 2011) . It has also been associated with a nearly doubling of the double perinatal survival rate. However, these results should be interpreted cautiously because the pregnancies that underwent the standard procedure in these studies did so due to technical difficulties that prevented them from receiving the full sequential selective treatment, potentially introducing systematic errors into the results (Chmait et al ., 2011) .

- **Cauterization of the vascular equator (dichorionism of the equator)**

After cauterization of all visible anastomoses, a thin line of placental surface at the vascular equator is cauterized. This line runs from one edge of the placenta to the other and connects the white areas resulting from the ligation of the individual anastomoses. The two parts of the chorionic surface of the placenta are completely separated.

In a multicenter randomized trial comparing this Solomon technique with standard laser ablation (i.e., no ablation of the vascular equator) in 274 patients with stage II, III, or IV TTTS, equatorial bichorination resulted in lower rates of TAPS (3 vs. 16 %, odds ratio [OR] 0.16, 95% CI 0.05-0.49) and TTTS recurrence (1 vs 7 %, OR 0.21, 95% CI 0.04-0.98) (Slaghekke, Lopriore, *et al.*, 2014) . When postpartum placentas were perfused to look for residual anastomoses, fewer residual anastomoses were found when equatorial ablation was performed (Slaghekke, Lewi, *et al.*, 2014) . However, this did not lead to significant differences in perinatal mortality or severe neonatal morbidity, and neurodevelopmental outcomes at two years of age were similar for both approaches (Slaghekke, Lopriore, *et al.*, 2014; van Link *et al.*, 2016) .

The fetoscope is then removed and amniocentesis is performed until the volume of amniotic fluid appears normal in the recipient sac (maximum pocket <8 cm). No more than 3 liters are removed because of the potentially increased risk of detachment.

- **Complications of laser therapy**

Preterm premature rupture of membranes (PPROM), TAPS, and intertwin rupture of membranes are the most common complications of fetoscopic laser ablation procedures. Intra-amniotic bleeding may also occur and prevent completion of the procedure due to poor visualization.

In a 2019 systematic review including 6746 fetoscopic laser photocoagulation procedures, serious maternal complications occurred in 1.51 % (95% CI 0.01-2.25) and placental abruption accounted for 130 of 141 events (Sacco *et al.*, 2019) . The incidence of minor maternal complications was 4.03 % (95% CI 2.73-5.56). Intraoperative bleeding and chorioamnionitis were the two most common secondary complications, accounting for 148 and 68, respectively, of the 241 secondary events. In this review, obstetric complications such as PPROM, separation of the chorionic membranes and preterm delivery were not considered maternal complications.

Other rare complications that have been reported include recurrent TTTS, reverse TTTS, and leakage of amniotic fluid into the maternal peritoneal cavity (Yamamoto *et al.*, 2005) . Persistent or recurrent TTTS can be treated with conservative management, repeated fetoscopic laser ablation, or amnioablation, depending on the stage and gestational age. Reverse TTTS is a rare post-laser phenomenon in which each twin receives the previous phenotype of the other twin (e.g., the former donor develops hydramnios and the former recipient develops oligohydramnios). It is not clear how the apparent reversal of the transfusion gradient occurs, but when present, the outcome is compromised with overall survival rates below 50% (Wee *et al.*, 2004; Fox *et al.*, 2009) . Finally, intraperitoneal leakage is self-limiting but often causes maternal discomfort, which can be controlled with analgesics.

- **Outcome**
  - **Perinatal survival**

In a 2020 meta-analysis that included 610 stage I, 692 stage II, 1146 stage III, 247 stage IV, and 4 stage V TTTS cases (Di Mascio, Khalil, D' Amico, *et _ al* ., 2020) :

The frequency of survival of at least one twin per stage was:

- ✓ stage I - 86.9 %
- ✓ stage II - 85 %
- ✓ stage III - 81.5%
- ✓ stage IV - 82.8%
- ✓ stage V - 54.6 %

The incidence of non-survivor by stage was:

- ✓ stage I - 11.8 %
- ✓ stage II - 15.0 %
- ✓ stage III - 18.6 %
- ✓ stage IV - 17.2%
- ✓ stage V cases - 45.4%

In a recent study, twins with TTTS who underwent fetoscopic laser treatment were compared with a group of uncomplicated monochorionic diamniotic twins from the Trial of Progesterone in Twins and Triplets to Prevent Preterm Delivery (STTARS, Trial of Progesterone in Twins and Triplets to Prevent Preterm Birth). Gestational age at delivery was lower in the TTTS group compared to the uncomplicated monochorionic twin pregnancy (31.0 ± 4.6 vs. 33.5 ± 2.4 weeks, $p<0.001$). Respiratory distress syndrome and transient tachypnea of the newborn were at higher rates in the TTTS than in the uncomplicated monochorionic diamniotic group. After multivariate logistic regression, the only factor significantly associated with the composite adverse outcome was lower gestational age at delivery (OR 0.61, 95% CI 0.58–0.7).

- **Neurodevelopmental disorders**

In a 2021 meta-analysis of risk factors for neurodevelopmental impairment after fetoscopic laser photocoagulation for TTTS (9 studies, 1499 surviving fetuses from TTTS) (Hessami *et al.*, 2021) :

- ✓ The overall incidence of neurodevelopmental impairment was 14% (95% CI 9-18).
- ✓ Risk factors for neurodevelopmental impairment were later gestational age at treatment, early gestational age at birth (especially before 32 weeks: SD 2.25 [95% CI 1.02–4.94]) and low birth weight of birth.
- ✓ TTTS stage, recipient or donor status, post-laser TAPS or recurrent TTTS, small-for-gestational-age fetus, and death of the other twin had no statistically significant effects on neurodevelopmental outcome.

The overall risk of neurological damage after laser treatment is not significantly different from the baseline risk in monochorionic twins without TTTS or dichorionic twins matched for gestational age at delivery (Lenclen *et al.,* 2009; Ortibus *et al.,* 2009; Spruijt *et al.,* 2012) . In another study, the Age Stages Questionnaire (Rossi, Vanderbilt and Chmait, 2011; Spruijt *et al.,* 2012; Vanderbilt *et al.,* 2012, 2014) (ASQ, Ages Stages Questionnaire), a developmental screening tool that accurately detects developmental progress in children aged one month to 5 ½ years, was significantly higher in TTTS who underwent laser surgery compared to uncomplicated monochorionic twins. Almost all of the risk of neurological damage in surviving fetuses is due to complications associated with preterm birth, rather than a direct result of TTTS or laser therapy (Rossi, Vanderbilt and Chmait, 2011; Spruijt *et al.,* 2012; Vanderbilt *et al.,* 2012, 2014) . In the largest study of long-term pediatric outcomes in twins treated with fetoscopic laser ablation for TTTS (number = 417), the incidence of behavior problems was no greater than among children in the general population at two years of age (Brandsma *et al.,* 2020) but an increased rate of mild-to-moderate cognitive impairment and severe neurological impairment was observed in 73 children who were also followed up to age 5, suggesting that the absence of impairment cannot be confidently ruled out before school age (Knijnenburg *et al.,* 2022) . The presence of behavioral problems appeared to be mainly associated with severe neurodevelopmental impairment. Perioperative fetal hemodynamic changes, such as increased MCA-PSV >1.5 MoM and change from normal umbilical artery pulsatility index, appear to be associated with an increased risk for severe brain injury (Gijtenbeek, Haak, Huberts, *et al.,* 2020) .

- **Renal effects**

Chronic hypovolemia in the donor can lead to vascular remodeling and chronic kidney disease (Cheung *et al.,* 2000) , which can be prevented by laser therapy (Gardiner *et al.,* 2003) . One series reported renal failure in 7% of 101 neonates who underwent fetoscopic laser ablation compared with 20% who underwent amnioablation (Lenclen *et al.,* 2007) . Another series reported short-term neonatal renal dysfunction (creatinine levels >100 micromol/L) in 7% of the laser group versus 38% of the no-laser group (Verbeek, Joemmanbaks, *et al.,* 2017) . In a study of the long-term renal effects of laser-treated TTTS, all 18 surviving twin pairs had normal markers of renal function in serum and urine, and no significant differences were observed between donors and recipients at a mean age of three years (Beck *et al.,* 2005) .

- **Cardiovascular effects**

Fetoscopic laser photocoagulation usually improves cardiovascular function in both twins. Optimal initiation of this therapy has shortened disease duration compared to previous decades, which appears to provide time for cardiac remodeling before delivery (Wohlmuth *et al.*, 2016) . However, congenital heart disease, particularly mild to severe right ventricular outflow tract obstruction, is detected postnatally in 8 to 16% of cases and may require postnatal intervention (Herberg *et al.*, 2006; Moon-Grady *et al.*, 2011; Pruetz *et al.*, 2011; Springer *et al.*, 2014; Gijtenbeek, Haak, Eschbach, *et al.*, 2020) . A series of 51 recipient twins who survived laser treatment noted that 8% had pulmonary artery stenosis at the time of birth, a 200-fold increase over the rate in the general population (Herberg *et al.*, 2006) . Half of the cases required balloon valvular dilatation for treatment. However, when childhood cardiac function was assessed at a median age of 10 years, it was normal in the majority of surviving donors and recipients (Herberg *et al.*, 2014) .

- **Long-term maternal effects**

No adverse long-term maternal effects have been observed regarding subsequent fertility and obstetric and gynecological outcomes following fetoscopic laser therapy (Vergote *et al.*, 2018) .

- **Amnioectomy**

Amnioablation reduces uterine hyperdistension, which is a risk factor for preterm labor and preterm premature rupture of membranes (PPROM). It also reduces the pressure inside the amniotic cavity and thus can improve the uteroplacental perfusion (Urig, Clewell and Elliott, 1990; Bower *et al.*, 1995) .

- **Amnioablation procedure**

A variety of amnioablation techniques have been described, however no randomized trial has evaluated whether one is safer and more effective than another. There is no consensus on how much fluid should be removed, how quickly the fluid should be removed, the use of tocolytic drugs, or the use of antibiotics.

A reasonable approach is to anesthetize the skin with a long-acting local anesthetic (e.g., bupivacaine). Under ultrasound guidance, a long 18-gauge needle is inserted into the amniotic sac with polyhydramnios, avoiding the placental tip if possible. The placenta may thin significantly on ultrasound imaging due to the distension of the uterus by excess amniotic fluid.

The needle is placed as close to the midline of the uterus as possible with a slight angulation towards the maternal xiphoid process to reduce the risk of needle displacement as the size of the uterus

decreases with drainage of amniotic fluid. The needle can be attached to one end of specialized tubing included in a disposable thoracentesis disc (male to male ends) while the other end of the tubing is attached to a short 18-gauge needle placed in a disposable vacuum bottle. This setup maintains a closed system, avoids excessive needle manipulation, and allows flow rate control with the in-line rollerball valve.

Some authors recommend removing the fluid until there is no more polyhydramnios (maximum vertical pocket <8 cm). Others recommend removing no more than 5 liters of amniotic fluid in about an hour (Leung *et al.,* 2004) . Uterine decompression with rapid removal of a large volume of fluid may cause placental abruption or fetal bradycardia. Therefore, removal of no more than 3 liters of fluid is recommended in severe TTTS.

- **Outcome of amniocentesis**

The International Amnioreduction Registry reported results from the largest series of TTTS patients undergoing amnioreduction (Mari *et al.,* 2001) . A total of 223 twin pregnancies from 20 fetal medicine units were diagnosed with TTTS before 28 weeks' gestation and treated with 760 amnioablatives. The major findings of this series were:

- Complications related to the procedure included PPROM within 48 hours of the procedure (6%), spontaneous labor (3%), fetal distress (2%), fetal death (2%), placental abruption (1.3%), and chorioamnionitis (1 %).
- Both twins were born alive in 55% of pregnancies, one twin was born alive in 31%, and both twins were stillborn in the remaining 14%. During the first four weeks of neonatal life, an additional 30% of twins born alive succumbed.
- Intracranial abnormalities were seen on neonatal cranial ultrasound in 24% of recipient twins and 25% of donor twins that survived to four weeks of age.

➢ Selective fetal reduction

Selective reduction of one twin is an option that may improve the prognosis of the other twin if a technique that does not affect its circulation is used. While perinatal outcomes are comparable between the various procedures (bipolar cord coagulation, cord laser coagulation, and radiofrequency ablation [RFA]), RFA is the preferred technique for selective reduction of monochorionic twins because the smaller device reduces maternal morbidity (Yinon *et al.,* 2015) .

The fetus predicted to have the least chance of survival is usually selected for the reduction procedure. For example, a recipient with advanced cardiac findings or ascites or a growth-restricted donor with >30% abnormal fetal weight and abnormal umbilical artery Doppler is selected (Snowise *et al.*, 2015) .

- **TTTS**

Available data show no difference in survival depending on whether the donor or recipient is targeted (Lewi *et al.*, 2006) . If bipolar coagulation is used, reduction of the recipient twin is technically easier, as its umbilical cord is easily seen floating in the excess amniotic fluid. The oligohydramnios around the donor makes this twin a more difficult target, although the donor cord can be caught through the intertwin membrane after entering the recipient's amniotic cavity. This can lead to a diaphragmatic stoma and the risk of subsequent cord entanglement. However, if the donor is the primary target, amniocentesis may be performed to improve access for bipolar forceps. Radiofrequency ablation does not require amniocentesis (Moise *et al.*, 2008) .

Experience in selective reduction for TTTS is limited. A study including 15 cases of TTTS treated with bipolar cord cauterization reported an overall twin survival of 87%, but preterm premature rupture of membranes occurred in 20% of pregnancies within three weeks of surgery (Taylor , Shalev, et al., 2002) . Another study looking at 22 cases of TTTS in which bipolar coagulation was performed found an overall survival of 77% (Robyr, Yamamoto and Ville, 2005) . One infant had developmental delay at 16 months of age. In a third series of 24 cases of TTTS, overall survival was 92 % (one fetal death and three neonatal deaths) (Lewi *et al.*, 2006) . One infant developed mild motor delay at 18 months.

- **Selective fetal growth restriction**

Selective reduction is also considered according to the ISUOG Society in monochorionic twins with selective fetal growth restriction when the fetal death of the younger twin is likely far from the " term " period of gestation (eg before 26 weeks) (A. Khalil _ *et al.*, 2016) . The goal is to reduce the risk of morbidity and mortality in the surviving twin.

Special populations

- **Monoamniotic twin pregnancy**

Monoamniotic twins have a lower rate of TTTS than diamniotic twins [2 to 6 % (K. E. Hack *et al.*, 2009) versus 9 to 15 % (Sebire *et al.*, 1997; L. _ Levi *et al.*, 2007)], but the risk is sufficient to warrant population control starting in the second trimester (table 1). While TAPS can be seen in up to 6% of monochorionic diamniotic twins, the rate in monochorionic monoamniotic twin pregnancies is expected to be lower

because of the larger vascular anastomoses in these pregnancies. Only one case report of TAPS in monochorionic monoamniotic twins was found (Diehl *et al.,* 2013) .

The management of TTTS and TAPS in monoamniotic twins is similar to that in diamniotic twins. Although visualization of the equator between the twins is more difficult due to the absence of membranes, blood vessels can be traced distally from their origin at the two sites of cord emergence. These pregnancies are at high risk of perinatal mortality and preterm delivery before 32 weeks (Murgano *et al.,* 2020) .

- **Triplet pregnancy**

Triplet pregnancy (monochorionic triamniotic and dichorionic triamniotic triplets) but also any multiple pregnancy with a common chorionic sac puts the involved fetuses at risk for TTTS, selective growth restriction and TAPS. An ultrasound protocol similar to that commonly used to monitor monochorionic twin pregnancies is followed (table 1) (A . Khalil *et al.,* 2016) . Pregnancies with monochorionic diamniotic and dichorionic diamniotic triplets, which share an amniotic sac, are also at risk for TTTS. In contrast, in trichorionic triamniotic triplets, monitoring for TTTS and TAPS is not necessary as the placenta is not common.

Discrepant amount of amniotic fluid (sequence of polyhydramnios/oligohydramnios) suggests TTTS.

Laser ablation is an effective treatment, even in triplets. Fetoscopic laser therapy for the treatment of TTTS in dichorionic triamniotic triplets appears to result in similar perinatal and neonatal survival rates compared with monochorionic diamniotic twins. A systematic review of perinatal outcome after laser fetoscopic surgery for TTTS in triplet pregnancies reported the following main findings (126 triplet pregnancies, 104 dichorionic triamniotic [DCTA] and 22 monochorionic triamniotic[MCTA] triplet pregnancies) (D ' Antonio *et al.,* 2016) :

- Fetal loss: DCTA 19.9 %, MCTA 28.9 %.
- Perinatal loss: DCTA 23.6 %, MCTA 75.0 %.
- Preterm delivery <28 weeks: DCTA 16.9 %, MCTA 37.1 %.
- Preterm delivery <32 weeks: DCTA 50.0%, MCTA 69.5%.
- Survival: In the DCTA group, all three fetuses survived in 56% of pregnancies, two fetuses survived in 27% of pregnancies, and only one fetus survived in 17% of pregnancies. In the MCTA group, the comparable survival rates were 56, 19 and 25%, respectively.
- Abnormal neurologic outcome: DCTA 0 to 37%, MCTA 0 to 50%.

- **Life-threatening abnormality of a fetus**

Selective reduction has been performed to treat TTTS when a fetus has a very poor prognosis (e.g., life-threatening malformation, severe growth restriction, severe heart failure, evidence of brain damage).

- **Conjoined twin above the vascular equator**

Laser ablation may not be possible when a conjoined twin overlaps the site of the placental anastomoses. Selective reduction is an option in these cases.

4.3.2.b. Twin anemia-polycythemia sequence (TAPS)

Introduction

Twin anemia-polycythemia sequence (TAPS) is a complication of monochorionic (MC) twin pregnancies, characterized by a highly discordant hemoglobin difference between them and, in contrast to twin-twin transfusion syndrome (TTTS), the amniotic fluid volume of each gemini is normal in the classic, pure form of the syndrome (Lopriore *et al.*, 2007; Couck and Lewi, 2016; Moaddab *et al.*, 2016; Tollenaar *et al.*, 2016) . It may be considered an atypical chronic form of TTTS caused by unbalanced slow transfusion of red blood cells through a few very small (<1 mm diameter) placental arteriovenous (AV) anastomoses (Lopriore *et al.*, 2007) , leading to large hemoglobin differences between twins resulting in anemia in one twin and polycythemia in the other twin. Diagnosis can be difficult because TAPS, TTTS, and a third disorder, selective fetal growth restriction (sFGR), are not necessarily mutually exclusive and can occur together in any combination.

Types of TAPS and their pathophysiology

- **Automatic TAPS**

Spontaneous TAPS refers to a type of chronic TTTS. It has been reported in 3 to 6% of previously uninvolved third-trimester MC diamniotic twins (Lewi, Jani, *et al.*, 2008; Slaghekke *et al.*, 2010) . TAPS has also been rarely reported in monozygotic, dichorionic pregnancies in which fine anastomoses between placental masses lead to chronic red blood cell exchange (Kanagaretnam, Nayyar and Zen, 2021; Tollenaar, Prins, *et al.*, 2021) .

- **Pathophysiology**

MC placentas usually contain arteriovenous (AV), arterioarterial (AA), and venovenous (VV) anastomoses. AV anastomoses are unidirectional, while both AA and VV anastomoses are bidirectional.

Placentas in cases of spontaneous TAPS have an average of three to four very small (<1 mm) AV anastomoses [comparatively eight AV anastomoses are found, on average, in normal MC placentas (Zhao, de Villiers, *et al.*, 2013)]. These tiny one-way unbalanced anastomoses allow slow passage of red blood cells [5 to 15 mL per 24 h (Tollenaar *et al.*, 2016)] from the donor twin to the recipient twin, gradually leading to highly discordant hemoglobin levels (Robyr *et al.*, 2006) . The donor becomes anemic (which can lead to hydrops fetalis), while the recipient becomes polycythemic (which can lead to fetal and placental thrombosis) (Lopriore *et al.*, 2009; Assaf, Benirschke and Chmait, 2011) . The slowness of this process allows hemodynamic compensation across the maternal-fetal placental interface, which is hypothesized to be the reason for the absence of the amniotic fluid volume discordance seen in classic TTTS (Lopriore *et al.*, 2008) .

AA anastomoses occur in 10 to 20% of TAPS placentas and are smaller in these placentas than in the placentas of uncomplicated MC twins and placentas in TTTS, both of which have more of these anastomoses. The small number and size of AA anastomoses also contribute to the development of TAPS, because bidirectional blood flow in normal AA anastomoses allows blood to balance interaction.

Furthermore, in MC twins without TAPS, the younger twin usually has a smaller portion of the shared placenta compared to the older twin. In TAPS, however, the donor is usually smaller than the recipient, but often has a larger share of the placenta (Tollenaar *et al.*, 2016) .

- **TAPS after laser ablation**

TAPS after laser ablation refers to potential consequences of using laser ablation to treat TTTS (Habli *et al.*, 2009) . It occurs in 2 to 13% of such pregnancies, usually within a month but up to 17 weeks after surgery (Robyr *et al.*, 2006; Lisanne S. _ A. _ Tollenaar *et al.*, 2020) . The wide range of incidence has been attributed to the use of different laser treatment techniques and different definitions and criteria for TAPS. Risk factors include TTTS with few anastomoses and no AA anastomoses before laser treatment (Donepudi *et al.*, 2016) .

- **Pathophysiology**

Based on placental perfusion studies from TTTS pregnancies treated with laser ablation, post-laser TAPS appears to be caused by incomplete laser surgery resulting in some very small (<1 mm) residual anastomoses, usually AV anastomoses without accompanying AA anastomoses. The use of the Solomon technique with coagulation between the anastomoses at the ends of the placenta helps reduce the risk of post-laser TAPS (Slaghekke, Lopriore, *et al.*, 2014) .

As with auto-TAPS, these small unbalanced residual AV anastomoses allow slow passage of RBCs, usually from the former recipient twin to the former donor twin, gradually leading to highly discordant hemoglobin levels (Robyr *et al.*, 2006) . The former recipient becomes anemic, while the former donor becomes polycythemic, a reversal of the previously net blood flow during TTTS (Lopriore *et al.*, 2009; Assaf, Benirschke and Chmait, 2011) . However, residual anastomoses may also be in opposite directions, leading the former recipient to polycythemia and the former donor to anemia.

Population control

MC twins are monitored for development of TTTS, TAPS and sFGR (table 1). To screen for TAPS, repeated measurements of middle cerebral artery peak systolic velocity (MCA-PSV) are recommended starting at 16 weeks, as well as assessment for placental discordance in echogenicity and for cardiomegaly. There is a lack of consensus among different companies regarding MC twin screening for TAPS. The Society for Maternal-Fetal Medicine (SMFM) recommends against routine screening for TAPS due to poor understanding of the natural history and management of the disease, but recommends screening for TTTS (Society for Maternal-Fetal Medicine for Maternal - Fetal Medicine and Simpson, 2013) . In stark contrast, the ISUOG guidelines recommend screening for TAPS (in addition to TTTS) every two weeks starting at 16 weeks (A. Khalil *et al.*, 2016) .

Diagnostic criteria

- **Diagnosis after birth**

At birth, the obstetrician should suspect TAPS when a striking color difference is observed on the maternal side of the placenta: one side (donor) is pale and the other side (recipient) is dark (Tollenaar *et al.*, 2017) .

TAPS should then be suspected if one twin is anemic (hematocrit <45 %) and the other is polycythemic (hematocrit >65 %). The postnatal diagnosis of TAPS is based on an intertwin hemoglobin difference of

≥8.0 g/dL combined with a twin reticulocyte ratio >1.7 (reticulocyte count of the donor twin divided by the reticulocyte count of the recipient twin)

Additionally, placental injection examination will show a few very small (1 mm) AV anastomoses with flow in only one direction, but is not required for diagnosis (Slaghekke *et al.,* 2010) .

- **Prenatal diagnosis**

The following criteria reflect the characteristics of TAPS in its classic, pure form. However, prenatal diagnosis can be difficult because TAPS, TTTS, and sFGR are not necessarily mutually exclusive and can occur together in any combination.

The accuracy of the prenatal diagnosis of TAPS is not verified due to the risks of the confirmatory test, namely umbilical vein sampling for fetal hemoglobin/hematocrit determination.

- **MCA-PSV**

Prenatal diagnosis of TAPS is based on ultrasonographic evidence of anemia in one twin with concurrent evidence of polycythemia in the other twin.

- **Traditional criteria-** TAPS is traditionally diagnosed when the middle cerebral artery peak systolic velocity (MCA-PSV) is >1.5 times the median value (MoM) in one twin (suggesting anemia) and <0.8 MoM in the other twin (indicates polycythemia) (Robyr *et al.,* 2006; Assaf, Benirschke and Chmait, 2011; Sainz *et al.,* 2014; Slaghekke *et al.,* 2015) . The criteria are not the same in all studies [some authors report an MCA - PSV threshold of <1.0 MoM for the diagnosis of polycythemia (Slaghekke *et al.,* 2010)], creating variations in clinical practices (Brock *et al.,* 2020) .
- **Emerging Criteria-** The prenatal diagnosis of TAPS is shifting from reliance on the strict MCA-PSV cut-offs described above to a system based on the absolute MCA-PSV discordance between twins (MCA-PSV delta) because it appears to have a stronger correlation with the postnatal diagnosis of TAPS (Fishel - Bartal *et al.,* 2016; Tollenaar *et al.,* 2019) . A delta MCA - PSV threshold of ≥1 MoMs has been suggested for the diagnosis of TAPS (A. Khalil _ *et al.,* 2016) , with some authorities recommending a MCA-PSV delta >0.5 (Tollenaar *et al.,* 2019) or >0.37 MoMs for diagnosis (Tavares de Sousa, Fonseca and Hecher, 2019) .

The use of MCA-PSV delta rather than strict MCA-PSV thresholds is supported by prospective data from children postnatally diagnosed with TAPS (Fishel - Bartal *et al.,* 2016) . Although MCA-PSV was significantly greater in anemic than normal fetuses (1.15 MoM vs. 1.02 MoM), MCA-PSV did

not differ between polycythemic and normal fetuses (0.95 MoM vs. 1.02 MoM), and among the 25 children with polycythemia, nine (36 %) had MCA-PSV >1. Thus, many cases did not meet the traditional criteria for TAPS. On the other hand, the MCA-PSV delta was positively associated with the inter-twin differences in hematocrit required for the postnatal diagnosis of TAPS.

Although the MCA-PSV delta appears to have better diagnostic accuracy than using each twin's MCA-PSVs, the optimal cutoff needs to be determined. In a retrospective cohort study of 35 twin pregnancies with a postnatal diagnosis of TAPS, an MCA-PSV delta >0.5 was 85% sensitive, 100% specific, and had a negative likelihood ratio of 0.17 for the diagnosis of TAPS (Tollenaar et al ., 2019) . Validation studies are needed.

- **Supporting findings**
  - Anomalous **placental echogenicity** is a common but nonspecific finding that supports the diagnosis: The anemic donor placental region is thickened and hyperechoic, whereas the exuberant recipient placental region is normal in appearance, with a clear demarcation between the donor and recipient regions (Bamberg *et al.*, 2018) .
  - The donor may have **cardiomegaly** with tricuspid insufficiency and ascites.
  - The recipient may have **a starry sky liver** (i.e., bright echogenic dots in a background of reduced echogenicity of the liver parenchyma). The bright dots are due to the increased echogenicity of the walls of the portal veins. (LSA Tollenaar, Lopriore, Middeldorp, *et al.*, 2020) .

Postdiagnostic assessment of pregnancy

Once the diagnosis of TAPS is established by MCA-PSV velocity, Doppler flow studies of the umbilical artery (UA), umbilical vein (UV), and ductus venosus (DV) should be performed to classify disease severity, which it forms the basis for further monitoring and management. The natural history of fetuses without evidence of severe disease (cardiac disorder, hydrops) remains unknown.

TAPS is not associated with an increased risk for chromosomal or structural abnormalities or genetic syndromes, so fetal genetic testing is not offered unless otherwise indicated.

Classification of disease severity

- **Severity of disease based on traditional criteria:**

- Stage 1- MCA-PSV >1.5 times the median value (MoM) in the donor and <1.0 MoM in the recipient, with no other signs of fetal distress.
- Stage 2- MCA-PSV >1.7 MoM in the donor and <0.8 MoM in the recipient, with no other signs of fetal distress.
- Stage 3- Stage 1 or 2 plus donor cardiac disorder with any of the following:
  - AU:
    - ✓ Absence or reversal of end-diastolic flow
    - ✓ Pulsed flow
  - DV:
    - ✓ Increased pulse rate
    - ✓ Reverse flow
- Stage 4- Stage 1 or 2 plus hydrops in the donor
- Stage 5- The death of one or both fetuses after TAPS

➢ **Severity of disease based on emerging criteria:**

- Stage 1- Delta MCA-PSV >0.5 MoM, no signs of fetal distress
- Stage 2- Delta MCA-PSV >0.7 MoM, no signs of fetal distress
- Stage 3- Stage 1 or 2 MCA-PSV delta findings plus cardiac damage of the donor or recipient fetus based on abnormal Doppler flow studies in the UA or DV or amniotic fluid (predominantly in the donor fetus)
- Stage 4- Intrauterine death of one or both fetuses after TAPS

➢ **Severity of disease based on postnatal hemoglobin difference (g/dL) between twins:**

- Stage 1 - >8
- Stage 2 - >11
- Stage 3 - >14
- Stage 4 - >17
- Stage 5 - >20

Differential diagnosis

Although there is some overlap between the findings for TAPS and TTTS, there are several features that favor either diagnosis:

- MCA-PSV discordance is diagnostic of TAPS and is absent in pure TTTS.
- Amniotic fluid discordance (alternation of oligohydramnios and polyhydramnios) is essential in pure TTTS and absent in pure TAPS.
- Spontaneous TAPS has been diagnosed between 14 and 35 weeks of gestation, in contrast to TTTS, which is usually diagnosed in the early to mid-second trimester (Weingertner *et al.*, 2010; Tollenaar, Slaghekke, *et al.*, 2021) .
- Postnatally, an intertwin reticulocyte ratio >1.7 is required to diagnose TAPS, because a large hemoglobin difference alone at delivery may represent acute intrapartum TTTS rather than TAPS. Accurate diagnosis is important because anemia caused by TAPS is typically under normal blood volume, whereas anemia in intrapartum TTTS requires rapid correction of hypovolemia (Tollenaar *et al.*, 2017) .

Intrauterine infection with parvovirus B19 can cause fetal anemia. However, both fetuses tend to be anemic (von Kaisenberg *et al.*, 2007) .

Prognosis

TAPS can result in the delivery of two healthy neonates with individual hemoglobin differences between the twins that may require neonatal blood transfusion or partial exchange transfusion. However, brain injury or death of one or both twins are other possible outcomes. Spontaneous resolution has been observed in 16% of cases (LSA Tollenaar, Slaghekke, *et al.*, 2020) .

- **Short term:**
  - A meta-analysis of 506 pregnancies in 38 studies reported the following pregnancy outcomes in auto and after TAPS laser, respectively (Giorgione *et al.*, 2021) :
    - Intrauterine death: 5.2 vs. 10.2%
    - Neonatal death: 4.0 vs. 9.2%
    - Severe neonatal morbidity: 29.3 vs. 33.3%
    - Serious neurological morbidity: 4.0 vs 11.1%
    - Preterm labor (spontaneous and iatrogenic): 86.3 vs. 100%

The limitations of the observational data preclude clear conclusions about the better prognosis of spontaneous TAPS and the superiority of any management approach (conservative, laser, intrauterine transfusion, selective reduction). Also, the case reports and retrospective nature of the original studies in the systematic review limit the ability to assess accurate risk.

- **Long term:**
  - In a long-term outcome study (mean age 48 months) of 49 twin pregnancies in which spontaneous TAPS occurred (L. S. A. Tollenaar, Lopriore, Slaghekke, *et al.*, 2020) :
    - Neurodevelopmental impairment occurred in 30% (22 of 74) of survivors and was more common in anemic fetuses (44 vs. 18%, OR 4.1, 95% CI 1.8–9.1).
    - Severe neurodevelopmental impairment was detected in 9% of survivors and was also more frequent in anemic fetuses (18 vs. 3%), although the difference did not reach statistical significance.

In multivariate analysis, independent risk factors for neurodevelopmental impairment were gestational age at delivery and severe anemia.

- In a study of long-term neurodevelopmental outcomes (24 to 96 months of age) of 33 TAPS twin pregnancies after fetoscopic laser ablation for TTTS (Slaghekke, van Klink, *et al.*, 2014) :
  - Mild to moderate cognitive delay (score <85) occurred in 8 of 47 children (17 %) and severe cognitive delay (score <70) occurred in 2 of 47 children (4 %) assessed.
  - Overall, severe neurodevelopmental impairment occurred in 4 of 47 children (9 %): cerebral palsy (1), severe motor delay (1), severe cognitive delay (2). These four children were born at 28, 29, 29 and 32 weeks, which may account for at least some of these lesions.

The small sample size and variety of tests used for neurodevelopmental assessment limit the interpretation of these findings.

Pregnancy management

- **Approach**

  Management is similar for both auto and post-TAPS laser therapy (LSA Tollenaar, Slaghekke, *et al.*, 2020) .

  - **Stage 1 TAPS** (MCA-PSV >1.5 times the median value [MoM] in the donor and <1.0 MoM in the recipient or delta MCA-PSV >0.5 MoM without signs of fetal distress)

- These pregnancies are managed conservatively with weekly Doppler studies to assess stage progression.
- In the absence of progression, delivery between 34 $^{+0}$ and 37 $^{+0}$ weeks of gestation is recommended (Breathnach *et al.,* 2012) . In more complex cases it is earlier within this range and in less complex cases later within this range.
- Progression is treated according to stage and gestational age.

- **Stage 2 TAPS** (MCA-PSV >1.7 MoM in donor and <0.8 MoM in recipient or delta MCA-PSV >0.7 MoM without signs of fetal distress)
  - Patients between 24 $^{+0}$ and 32 $^{+0}$ weeks of gestation are given an antenatal course of corticosteroids to reduce the risks of the neonates in case of preterm delivery.
  - These pregnancies <32 $^{+0}$ weeks are managed conservatively with twice-weekly Doppler studies to assess persistence or progression (characterized by development of fetal heart failure, as well as secondary signs of TAPS [placental echogenicity discordance, stellate liver]).
    - ✓ Persistent stage 2 TAPS beyond 32 to 34 weeks' gestation is an indication for delivery.
    - ✓ Stage 2 persistent TAPS (i.e., lasting more than one to two weeks) <32 weeks or disease progression is treated as stage 3 or 4 TAPS.

- **Stage 3 or 4 TAPS** (based on MCA-PSV criteria plus cardiac distress [absence or reversal of end-diastolic flow in umbilical artery (UA), pulsatile flow in umbilical vein (UV), increased pulsatility index and/or reflow in DV, hydrops] or death of the donor twin) - There is no consensus on the optimal treatment. Conservative management, laser surgery, intrauterine transfusion, selective fetal reduction and preterm delivery have been used (LSA Tollenaar, Slaghekke, *et al.,* 2020; Tollenaar, Slaghekke, *et al.,* 2021) . The decision about the best approach is made on a case-by-case basis based on gestational age and severity of TAPS:
  - In a patient who develops TAPS after laser treatment within two weeks of the procedure, if termination of pregnancy is an option, it should be considered. Otherwise, repeat laser treatment is offered up to 28 $^{+0}$ weeks of gestation (Valsky *et al.,* 2012; Baud *et al.,* 2013) . A repeat laser treatment can often be difficult due to bloody amniotic fluid as a result of the previous procedure.

- In spontaneous cases of TAPS that develop before 28 $^{+0}$ weeks, fetoscopic laser ablation is probably the best option. Because of the reduced accessibility and visibility of the placental surface after treatment of TTTS, amniocentesis and/or amnioablation can be used to improve visualization of the fine anastomoses across the membrane between the twins. Alternatively, intrauterine red blood cell transfusion (IUT) can be performed on the anemic fetus. Both intravenous (IV) and intraperitoneal (IP) transfusion are acceptable methods for correcting fetal anemia. IP transfusion is preferred because the slow reabsorption of red blood cells commonly seen with IP transfusion may more closely mimic fetal physiology. A combination approach is sometimes used: IV transfusion to correct severe anemia with IP transfusion of a portion of blood for slower absorption to limit the need for frequent, multiple transfusions.
- In cases of TAPS that develop between 28 $^{+0}$ and 32 $^{+0}$ weeks of gestation, either option is reasonable. Some centers perform intrauterine red blood cell transfusion (IUT) in the anemic fetus, while others perform IUT plus a partial exchange transfusion of the polycythemic twin to potentially reduce hyperviscosity-related complications. In these cases, 5 mL blood samples are removed and replaced with equal volumes of sterile saline. Repeat transfusion or partial exchange transfusions are based on subsequent MCA- PSVs.
- The appearance or persistence of stage 2, 3 or 4 TAPS beyond 32 $^{+0}$ weeks' gestation is an indication for delivery.

➢ **Proof**

In a series of 370 MC twin pregnancies diagnosed prenatally with TAPS stage 1 to 4 in 17 fetal treatment centers (L. S. A. Tollenaar, Slaghekke, *et al.*, 2020) :

- With all management approaches, perinatal mortality was significantly higher in pregnancies with post-laser TAPS compared with those with spontaneous TAPS.
- Perinatal mortality occurred in 17% (39 of 225) of pregnancies in the conservative management group, 18% (38 of 215) in the laser group, 18% (25 of 140) of the IUT group, 10% (9 of 86) of delivery group and 7 % (2 of 30) of the other fetuses in the selective reduction group.
- Serious neonatal morbidity occurred in 49% (41 of 84) of the delivery group, 46% (56 of 122) of the IUT group, 31% (60 of 193) of the conservative management group, 31% (57 of 182) of the laser ablation group and 25 % (7 of 28) of the selective fetal reduction group.

- The median time from diagnosis to birth was longest after selective reduction (10.5 weeks), followed by laser surgery (9.7 weeks), conservative management (7.8 weeks), IUT (4 weeks), and delivery (0.3 weeks).

No results were reported by stage. Because of extensive heterogeneity in the management of TAPS among embryology centers, optimal management has been unclear. Laser surgery addressed the cause of TAPS and prolonged the overall interval from diagnosis to birth in the absence of fetal reduction, thereby allowing more time for fetal maturation, but was technically difficult and did not clearly improve or worsen perinatal outcome compared with conservative treatment. Because conservative management likely results in continued exposure to the potential deleterious effects of TAPS, and the risks for perinatal mortality and morbidity increase with increasing TAPS stage, definitive laser therapy may be the optimal intervention away from the "term" period (≥ 37 weeks of gestation) to improve perinatal outcome.

Triplet pregnancy

Polycythemia vera sequence (TAPS) is uncommon in triplets. Few cases have been reported (Davidoff *et al.*, 2013; Griersmith, Fung and Walker, 2014) . Treatment is the same as in twin pregnancies complicated by TAPS.

4.3.2.c. Selective fetal growth restriction (sFGR)

Introduction

Selective fetal growth restriction (sFGR) refers to the restriction of the growth of a fetus of a monochorionic twin pair. It is a common complication of monochorionic twins resulting from discordant placental distribution and is distinct from placental-based growth restriction resulting from deficient uteroplacental perfusion in dichorionic twin and singleton pregnancies (Burton and Jauniaux, 2018) . sFGR is of major importance because it is associated with a significant risk for perinatal morbidity and mortality (Buca *et al.*, 2017; D' Antonio _ *et al.*, 2018; Weiner *et al.*, 2018) .

Pathophysiology

The "vascular equator" is an imaginary line that can be drawn along the vascular anastomoses between twins sharing a monochorionic placenta. This line can be used to estimate the percentage of placental area that belongs to each fetus. In sFGR, placental area is unequally distributed between twins: one twin

benefits from having the larger share of the placenta, while the growth-restricted twin is supported by a smaller portion of the placenta (Fick et al., 2006; Lewi, Gucciardo, *et al.*, 2008; De Paepe *et al.*, 2010) . Furthermore, when the placental share is significantly different, the number and size of vascular anastomoses between twins are also different (Denbow *et al.*, 2000; Lanna *et al.*, 2015; Sun *et al.*, 2016) , which affects the volume exchange between the twins and the transport of nutrients and oxygen. Increasing discordance in placental share increases net volume flow between twins, leading to more interdependent circulations (Liesbeth Lewi *et al.*, 2007; Hack, Nikkels, *et al.*, 2008; Konno *et al.*, 2018) . This affects the natural history of the disease: clinical deterioration is often less predictable and slower than would be expected in FGR complicating singleton or dichorionic twin pregnancies (Rustico *et al.*, 2017; Shinar, Xing, *et al.*, 2022) .

Other factors can also contribute to limiting growth. For example, a membranous insertion of the placental cord can further impair the smaller twin's ability to access the placental area. Membranous insertion of the placental cord occurs in approximately 30% of monochorionic twins and is strongly associated with both sFGR (OR 9.24, 95% CI 2.05-58.84) and developmental discordance >25% (OR 6, 81, 95% CI 1.67-34.12) (Lopriore *et al.*, 2012; Kalafat *et al.*, 2018; Konno *et al.*, 2018) .

Incidence

sFGR affects 10 to 15 % of monochorionic twin pregnancies (Sebire *et al.*, 1997; Lewi, Jani, *et al.*, 2008) .

Clinical picture

Ultrasound examinations are systematically performed in multiple pregnancies. Accurate determination of chorionicity and gestational age is crucial for appropriate monitoring and management of these pregnancies.

Cephalo-urethral length (CRL) discordance of monochorionic twins on first-trimester ultrasound may be the first sign of developing sFGR (Memmo *et al.*, 2012) . If the CRLs are discordant, it is important to use the CRL of the older twin to determine gestational age in naturally conceived pregnancies.

Most sFGR is detected during routine ultrasound monitoring of monochorionic pregnancies, which begins in the early second trimester. The protocol is illustrated in table 1 and determines sFGR, feto-fetal transfusion syndrome and polycythemia sequence.

Diagnosis

The diagnosis of sFGR is typically made in the second trimester based on fetal biometrics, growth discordance, and umbilical artery (UA) Doppler parameters. Third trimester diagnosis is less frequent and associated with more favorable outcomes (Curado *et al.*, 2020? Y. _ Wang *et al.*, 2022) .

sFGR is defined as follows (A . Khalil *et al.*, 2016; Khalil *et al.*, 2019) :

- Estimated Fetal Weight (EFW) < 3rd percentile of a fetus

the

- At least two of the following four criteria:
  - EFW <10th percentile for a twin
  - Abdominal circumference <10th percentile for one twin
  - UA pulsatility index >95th percentile for the younger twin
  - Weight Discordance ≥25%

The percentage weight difference is calculated using the following equation:

(EFW of older twin - EFW of younger twin) / (EFW of older twin × 100)

- **Doppler technique**

It is important that the interpretation of UA Doppler is not the same as in singleton or dichorionic multiple pregnancies, as it not only reflects the relative size differences in the share of the placenta, but also the size of the hemodynamically significant vascular communications between the twins (Bennasar *et al.*, 2017) .

Proper acquisition of the UA waveform is required for accurate evaluation and interpretation.

- The reproducibility of the measurements is greater if the measurement is taken in a free loop of the umbilical cord with an echo angle close to 0 degrees during fetal rest.
- Focal zone, gain and pulse repetition rate should be adjusted to maximize frame rate.
- The scan rate should initially be set to display four to six waveforms and should occupy approximately 75% of the Doppler screen (Bhide *et al.*, 2021) . To assess the variation or oscillation of end-diastolic velocity in UA, the scan speed must be slowed to visualize the classic pattern in more than 6 waveforms.
- Maternal breath holding may be required to exclude interference during waveform measurement (Gratacós, Lewi, *et al.*, 2004) .

- Both UAs should be examined, as the flow pattern may differ. However, interarterial anastomoses, if present, can equalize blood flow between arteries, even though the areas of the placenta supplied by the umbilical arteries are different (Raio *et al.,* 2001) .
- UA waveforms are best recognized close to the placental cord insertion, where the interlocking placental anastomoses have the greatest impact on umbilical artery Doppler flows, particularly in the case of narrow placental cord interferences. Assessment for proximal placental abruption (distance between the cords below the fifth centile or 3.3 to 4.0 cm) is prudent, as intermittent absence or reversal of end-diastolic velocity (as in type 3 sFGR, discussed below) is more common in this case (Eschbach *et al.,* 2020) .

Classification

The waveform pattern of the umbilical artery (UA) and the end-diastolic flow of the smaller fetus are used to classify sFGR into three types that are predictive of the expected clinical course and risk profile (Pasquini *et al.,* 2015; Eschbach *et al.,* 2020; Batsry *et al.,* 2021) . This is an important determination to make as it is used to guide advisory and management decisions.

➢ **Type 1 sFGR**

It is characterized by persistent forward end-diastolic UA velocity without change in waveform with normal or increased resistance. It is associated with the most stable course and a typically favorable outcome. The mean gestational age at birth was 35.4 weeks in a large series (Gratacós *et al.,* 2007) . In a meta-analysis of observational studies including 786 monochorionic pregnancies complicated by sFGR, type 1 sFGR, when managed conservatively, was associated with the lowest risk of unexpected fetal death: 3.1% (95% CI 1.1-5, 9) and a high rate of intact survival: 97.9 % (95% CI 93.6-99.9) (Townsend *et al.,* 2019) .

Late-onset sFGR (i.e., recognized after 26 weeks) is typically type 1. Although these fetuses usually have a benign course, they are at increased risk for hemoglobin differences at birth (i.e., polycythemia vera twin sequence), which occurs up to 38 percent of cases (Gratacós *et al.,* 2007) .

➢ **Type 2 sFGR**

It is characterized by stable absent or stable retrograde end-diastolic flow in the UA without waveform change in the smaller twin. It is associated with deterioration of the midtrimester growth-restricted fetus. The mean gestational age at birth was 30.7 weeks in the same large series described above.

Although pregnancies with sFGR type 2 are expected to have a predictable pattern of deterioration and a longer latency between diagnosis and deterioration than with sFGR type 3, they are considered to have the worst prognosis because of the significant risk of single-fetal death and preterm delivery (Vanderheyden *et al.,* 2005; Townsend *et al.,* 2019) .

In the meta-analysis described above, when type 2 sFGR was treated conservatively, fetal death occurred in 16.6% (95% CI 6.9–29.5) of cases, with neonatal death in an additional 6.4% (95% CI 0.2-28.2) (Townsend *et al.,* 2019) . For surviving neonates, 89.3% (95% CI 71.8-97.7%) were neurologically intact.

- **Type 3 sFGR**

It is characterized by a pathognomonic UA waveform that has a variable flow pattern that alternates between forward, absent, and reversed flow over a short interval, called intermittent absent/reversed end-diastolic flow (iAREDF). This results from a large artery-to-artery anastomosis (AAA) on the surface of the placenta and represents bidirectional volume flow in these vessels. It is more often observed in the UA of the smaller fetus, as the interface of the two waveforms is shifted towards the smaller twin, and the AAA has a greater proportional effect in the fetus with a smaller share of the placenta (X . Wang *et al.,* 2022) . The AAA allows oxygen and nutrients to diffuse from the larger fetus to a portion of the placenta of the smaller twin. Consequently, sFGR type 3 is associated with the greatest degree of discordance in the placental region (Wee *et al.,* 2003; Groene *et al.,* 2018) .

These cases have the most unpredictable clinical course, and unpredictable fetal loss can occur in a short period of time, even after a reassuring ultrasound assessment. In the meta-analysis described above, when sFGR type 3 was treated conservatively, fetal death occurred in 13.2 % (95% CI 7.2–20.5), with neonatal death in an additional 6.8 % (95% CI 0.7-18.6) (Townsend *et al.,* 2019) . In a large multicenter study of 328 pregnancies with type 3 sFGR, singleton fetal loss occurred in 5.8% and twin death occurred in 4.9% of conservatively managed patients (Shinar *et al.,* 2021) . Normalization of umbilical artery Doppler flow occurred in 13.7% of cases and was associated with improved fetal growth of the smaller twin (Shinar, Xing, *et al.,* 2022) .

These pregnancies are also at the highest risk for neurological morbidity, particularly of the older twin. Only 61.9 % (95% CI 38.4-81.9) have been reported to have intact survival, probably due to the more unstable hemodynamic environment (Gratacós, Lewi, *et al.,* 2004). (Townsend *et al.,* 2019) .

Diagnostic evaluation

TAPS twin polycythemia anemia sequence, a systematic approach to evaluation is required to establish the correct diagnosis and initiate management planning (Gratacós, Ortiz and Martinez, 2012) . All the variables that determine these conditions must be ascertained. The final diagnosis should describe the full range of findings.

- When sFGR or discordant fetal growth is suspected, the **first step** is a detailed anatomical study to evaluate structural fetal abnormalities, which can complicate up to 7% of monochorionic twin pairs and contribute to abnormal growth (Glinianaia, Rankin and Wright, 2008; Rustico *et al.,* 2018) . Among sFGR cases, a significant fetal abnormality in at least one twin (usually the younger twin) has been noted in 16% of cases (Couck *et al.,* 2020) .

  Viral infection may affect one or both fetuses and result in growth restriction, so maternal history of signs/symptoms or ultrasound markers of viral infection other than single FGR require additional investigation, such as maternal serum testing for CMV and toxoplasmosis (Yinon *et al.,* 2006) .

  Rarely, monochorionic twins have discordant karyotypes. This is most often seen in the context of discordant fetal anomalies (Rock *et al.,* 2017) . Screening or diagnostic testing for aneuploidy is recommended in abnormal fetuses when the findings will influence clinical decision-making (Lewi, Lewi, *et al.,* 2008) .
- The **second step** is to evaluate the amniotic fluid for an oligohydramnios/polyhydramnios sequence to diagnose or rule out coexisting TTTS (Quintero *et al.,* 1999) . Distinguishing TTTS complicated by growth restriction of the donor twin from sFGR can be difficult as in both cases the growth restricted fetus may have oligohydramnios. If the amniotic fluid criteria for TTTS are met (defined as a maximum vertical pocket <2 cm for the donor and >8 cm for the recipient), appropriate management is needed for the disease depending on the stage, regardless of coexisting sFGR or twin weight discordance (Senat *et al.,* 2004) .
- The **third step** is to assess middle cerebral artery systolic velocity (MCA-PSV) in both twins to diagnose or rule out co-existing TAPS.

Fetal anemia in monochorionic twins can also be caused by parvovirus infection, alloimmunization, hemoglobinopathy (e.g., alpha-thalassemia major), or massive fetal transfusion. When TTTS and TAPS were not present at diagnosis of sFGR, TTTS subsequently developed in 10% of cases, whereas TAPS subsequently developed in 3% of cases in a retrospective series of 177 cases of sFGR (Couck *et al.*, 2020) .

Pregnancy management

The goal in managing pregnancies with sFGR is to identify those that can be safely managed conservatively versus those that could benefit from fetal intervention. The strategy for risk assessment and management that has evolved is based on gestational age, prognosis, technical considerations, and patient values and preferences (Gratacós, Ortiz and Martinez, 2012) .

- **Classification-based approach**

The approach described below is based on expert opinion and data from observational studies. No randomized trials have been performed.

- **sFGR type** 1

Conservative management with weekly ultrasound monitoring (umbilical artery [UA], middle cerebral artery [MCA]) is the preferred approach for these mild cases detected in the second trimester. Weekly Biophysical Profile (BPP) score is added at 28 to 32 weeks. If the UA pulsatility index rises above the 95th percentile or the MCA pulsatility index falls below the 5th percentile, fetal well-being assessment will be increased to twice weekly and monitoring will also be done for waveform abnormalities of the ductus venosus (DV). Deterioration of the Doppler pattern of the UA in the growth-restricted fetus is seen in up to 26% of these cases (Rustico *et al.*, 2017) . However, this usually takes months to develop and the likelihood of severe fetal deterioration (venous Doppler abnormalities, low BPP score or oligohydramnios) or death is low when UA flow is consistently forward (Gratacós *et al.*, 2007) .

If the fetal status remains reassuring, as is usually the case, delivery at 34 $^{+0}$ to 35 $^{+6}$ weeks is recommended, as sFGR pregnancies are not "uncomplicated" twins and these have a higher rate of unexpected death than uncomplicated monochorionic twins in which to delay childbirth until 37 $^{+6}$ weeks (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, Society for Maternal - Fetal Medicine, 2021) . Earlier delivery is indicated if typical maternal or fetal signs of labor develop.

ISUOG recommends timing of delivery in sFGR based on assessment of fetal well-being, growth, BPP, DV waveform, and/or NST and notes that the risk of fetal death in these pregnancies is increased, and therefore the delivery may be indicated even before fetal deterioration becomes apparent (A. Khalil *et al.,* 2016) .

- **sFGR type 2 and 3**

The approach to moderate and severe sFGR is more complicated due to higher rates of adverse outcomes, particularly fetal death (Buca *et al.,* 2017) (Rustico *et al.,* 2018) . The death of one twin can lead to acute fetal transfusion and tumor displacements, leading to double fetal death or neurological damage in the surviving twin in up to 30% of cases (Gratacós, Carreras, et al., 2004; Hillman , *Morris* and Kilby, 2011; Ishii *et al.,* 2011; JMM van Klink *et al.,* 2015; Mackie *et al.,* 2019) .

Earlier than the lower limit of viability, physicians can intervene with either selective fetal reduction (Lewi *et al.,* 2006; Bebbington *et al.,* 2012; Parra - Cordero *et al.,* 2016) or by fetoscopic laser ablation of overlapping placental vascular anastomoses in cases with fetal deterioration [progression from type 2 to type 3 sFGR, vein Doppler abnormalities (Gratacós *et al.,* 2007; Ishii *et al.,* 2009) , or oligohydramnios in the growth-restricted fetus (Ishii *et al.,* 2011; Monaghan *et al.,* 2019)]. Coexistence of oligohydramnios has been associated with impending fetal death. Fetoscopic laser therapy is associated with high mortality for the fetus with sFGR and does not guarantee survival for the normally developing fetus, but may protect this fetus from the consequences of the death of the other twin (Quintero et al., 2001; Gratacós *et al.,* 2008; Chalouhi *et al.,* 2013; Ishii *et al.,* 2015, 2019; Peeva *et al.,* 2015; Koch *et al.,* 2017; Miyadahira *et al.,* 2018) . Increased peak cerebral artery systolic velocity (MCA - PSV) and abnormal venous Doppler have been suggested as strong predictors of death in the growth-restricted fetus after laser (Chmait *et al.,* 2022) . The procedure may be more technically difficult compared to fetoscopic laser ablation for the treatment of feto-fetal transfusion syndrome and may not always be possible in cases of pure sFGR (Gratacós *et al.,* 2008; Ishii *et al.,* 2011, 2015) . If laser treatment is performed, then these pregnancies are treated similarly to dichorionic twin pregnancies.

In patients who refuse these interventions, weekly Doppler assessment of fetal well-being of the UA, MCA, and DV is performed starting at diagnosis while BPP is performed with each ultrasound assessment performed at ≥28 weeks. If Doppler findings remain stable and BPP is reassuring, weekly outpatient follow-up until delivery is reasonable. If Doppler findings worsen (e.g., worsening UA

Doppler pattern, such as progressive reverse end-diastolic flow, or DV pulsatility index >95th percentile) or if oligohydramnios develops, Doppler/BPP assessment of fetal well-being is increased to two to three times per week and considered admission to the hospital for daily fetal monitoring with NST if labor was considered for fetal evidence (Weisz *et al.,* 2011) .

These pregnancies are offered delivery at 32 $^{+0}$ weeks for inverted end-diastolic UA flow and up to 34 $^{+0}$ weeks for absent end-diastolic UA flow, with earlier delivery for typical obstetric indications (Valsky *et al.,* 2010; Bennasar *et al.,* 2017 ; Shinar *et al.,* 2021) .

- **Antenatal corticosteroids**

Betamethasone or dexamethasone is given if the fetal condition worsens or before planned preterm delivery. Doppler flow in the UA may improve transiently after administration of betamethasone (Chang *et al.,* 2012) .

Outcome

A set of results is available for studies investigating the management of these pregnancies (Townsend *et al.,* 2020) .

- **Outcome by sFGR severity**

In a review including 177 cases of sFGR, isolated sFGR (without subsequent TTTS syndrome or TAPS sequence) had a survival rate of 91 %. Survival was lower in sFGR associated with a major abnormality (70 % survival) or subsequent development of TTTS (65 % survival) (Couck *et al.,* 2020) . The majority of cases were type 1 sFGR (110/177) and had a survival rate of 96%, compared to a survival rate of 55% (12/22) in those pregnancies with type 2 sFGR and 83% (55/66) in those with type 3 sFGR.

- **Neurodevelopmental outcome**

A systematic review on the impact of sFGR or birth weight difference on long-term neurodevelopment in monochorionic twins found that survivors of sFGR are at increased risk for neurodevelopmental impairment, with the smaller twin having the worst outcomes, but highlighted the paucity of available data. (Rustico *et al.,* 2018; Groene *et al.,* 2019) . For the fetus with sFGR, the analysis reported long-term rates of moderate and severe neurological morbidity of 3 and 6%, respectively. For the older twin, these rates were 1 and 5% respectively.

4.3.2.d. Twin reversed arterial perfusion sequence (TRAP)

Introduction

Twin reversed arterial perfusion sequence (TRAP) or acardiac twin refers to a rare complication, unique to monochorionic twin pregnancies, in which one severely abnormal twin with an absent or atypical heart ("acardiac twin") is passively and reversibly bled from the other twin ("pump twin") through anomalous arterioarterial anastomoses. The acardiac twin is entirely dependent on circulatory support from the pump twin, and its upper body and head are often underdeveloped, if not completely developed. Thus, the acardiac twin has no potential for ex utero survival. As a result of the circulatory burden of supporting the acardiac twin, the pump twin is at risk of developing heart failure and other complications, which can lead to preterm birth or death, which are often unassisted. TRAP sequence can also occur in monochorionic triplet and higher order multiple pregnancies.

Incidence

A 2015 study estimated the incidence of TRAP sequence at 2.6% of monochorionic twin pregnancies and 1 in 9500 to 11,000 pregnancies, based on mathematical models (van Gemert, van den Wijngaard and Vandenbussche, 2015) .

TRAP sequencing has historically been reported to occur in approximately 1% of monochorionic twin pregnancies and 1 in 35,000 pregnancies (Gillim and Hendricks, 1953) . These historical figures are widely reported but are based on data available up to 1953. In modern obstetrics, the incidence appears to be higher due to factors such as the use of first-trimester obstetric ultrasound screening, which can detect early fetal death, and assisted reproductive technology, which has increased the incidence of multiple pregnancies, including monochorionic twins.

Pathophysiology

- **Normal fetal circulation**

In normal fetal circulation, relatively oxygen-rich blood from the placenta flows through the umbilical vein to the fetus. From there, the ductus venosus drains 80% of placental blood flow into the inferior vena cava, where it mixes with venous return from the lower extremities and kidneys before entering the right atrium. Once blood enters the right atrium, the two sides of the fetal heart act in parallel via intra- and extracardiac shunts (foramen ovale, ductus arteriosus) to fill the aorta and supply blood to the systemic

circulation. The abdominal aorta terminates in the left and right common iliac arteries, each of which divides into internal and external iliac branches. The umbilical arteries carry relatively deoxygenated blood from the internal iliac arteries back to the placenta.

- **Fetal circulation in the TRAP sequence**

In the TRAP sequence, the pump twin maintains the normal fetal circulatory pattern described above. In addition, a portion of the cardiac output travels through one or more arterio-arterial anastomoses and then continues retrogradely to one or both umbilical arteries and the systemic circulation of the twin acardia, thus creating a "reverse" circulatory perfusion. While arterio-arterial anastomoses between the twin circulations in the TRAP sequence are usually present along the placental surface, a number of vascular atypias have been described, and other abnormalities are possible, such as direct umbilical artery to umbilical artery communications that bypass the chorionic plate (Steffensen *et al.*, 2008; van Gemert *et al.*, 2016) . Venovenous anastomoses may also be present but play a secondary role.

Reverse circulation involving relatively deoxygenated blood from the pump twin contributes to the development of a wide range of gross structural abnormalities in the acardiac twin (Van Allen, Smith and Shepard, 1983) . The lower half of the acardiac twin is believed to receive a preferential share of the circulatory support of the pump twin and this may account for the relatively better development of the fetal abdomen, pelvis, and lower extremities than the trunk, upper extremities, and head, often showing varying degrees of necrosis, poor growth and absence.

Among the presentations of protean acardiac twins, a common subtype is acardiac acephalus, in which the acardiac twin has well-formed lower extremities and pelvis, but a severely malformed head and thorax. In other manifestations, the acardiac duodenum may not have normally recognizable structures, and instead appear as a mass of amorphous tissue. Because of abnormal circulatory patterns and the lack of a normally functioning excretory system, acardiac twins are also at risk for subcutaneous edema, which can be dramatic.

Since the pump twin must supply its own body as well as that of its noncardiac twin, the resulting hemodynamic burden puts it at risk for high-output heart failure. Heart failure can lead to cardiomegaly, polyhydramnios, ascites and other pathological fluid collections, fetal hydrops, preterm labor and perinatal death. The pump twin is also at increased risk for congenital malformations, which is true of all monochorionic twins, with a particular increase in the risk of cardiovascular abnormalities.

Pathogenesis

The exact pathogenesis of TRAP sequence is unknown and there are two theories. In one theory, abnormal arterio-arterial anastomoses in early embryogenesis provide deoxygenated blood to an acardiac fetus without direct perfusion of the placenta. In the other theory, an acardiac twin with defective early cardiac embryogenesis has low systemic blood pressure, allowing retrograde blood flow from the pump twin. Regardless of the exact cause, the net result is that the acardiac twin is dependent on the pump twin for circulatory support from the beginning of the first trimester.

It should be emphasized that the presence of placental vascular anastomoses alone is not sufficient for the development of TRAP sequence, as almost all monochorionic twins have some degree of placental anastomoses, while TRAP sequence remains a rare phenomenon. Retrograde blood flow through an arterio-arterial anastomosis is essential for the diagnosis of TRAP sequence in a suspected anomalous monochorionic twin pregnancy.

Ultrasound findings

TRAP occurs only in monochorionic multiple pregnancies and usually with twins. Although very rare, TRAP sequence can occur in a monochorionic triamniotic triplet pregnancy, as a literature review identified 11 case reports of this phenomenon (Pan *et al.*, 2017) . In monochorionic triplet pregnancies, there may be more than one pump fetus or more than one acardiac fetus.

- **Cardiac fetus**
  - The heart is either absent or a rudimentary pump structure.
  - The skull may be absent or present with major defects such as anencephaly, holoprosencephaly, or other major neuroanatomical malformations.
  - The lower limbs, pelvis and abdomen may be well developed, or limb defects and anterior abdominal wall defects may be present.
  - Lungs, kidneys, spleen and/or liver may be present or absent.
  - The head (if present), trunk, and upper extremities (if present) may be severely oedematous, more so than can be attributed to autolysis after fetal death.
  - An amorphous mass of tissue may be the only finding, with no easily identifiable fetal parts.
  - The umbilical cord contains two vessels in 70% of cases (Benson *et al.*, 1989; Healey, 1994) .

- **Pump fetus**

The pump fetus may be normal or have signs of high-output heart failure, such as:

- Polyhydramnios
- Cardiomegaly
- Pericardial collections
- Pleural collections
- Ascetic
- Subcutaneous swelling/swelling per flesh
- Amniotic fluid
- Tricuspid valve insufficiency

- **Doppler measurement (acardiac twin)**

Color Doppler examination of the umbilical artery of the acardiac fetus shows blood flowing toward, rather than away from, the acardiac twin (Benson *et al.,* 1989) . This reverse flow is required for ultrasonographic demonstration of the TRAP sequence. Doppler can be used to locate fetal vessels and demonstrate arterio-arterial anastomosis (Bornstein *et al.,* 2008) .

Prenatal diagnosis

TRAP sequence is diagnosed prenatally based on the characteristic ultrasound findings described above. The three main findings are:

- Monochorionic multiple pregnancy.
- A fetus with either absent cardiac activity or a rudimentary pump structure
- Doppler study demonstrating retrograde arterial flow in the acardiac fetus (pathologic finding).

Prenatal diagnosis can be made as early as the first trimester (Bornstein *et al.,* 2008) . In a classic vignette of an early TRAP presentation, a woman diagnosed with a first-trimester "disappeared" (dead) twin on ultrasound returns for a second-trimester fetal anatomy study only to discover that the presumed fetal loss has continued to increase, so TRAP is also diagnosed.

To avoid this initial misdiagnosis, a color Doppler study should be performed for all early cases of suspected 'disappearing' twins in early monochorionic twin gestation. The finding of reverse perfusion in a presumably stillborn twin allows early detection of TRAP sequence. When performing color Doppler

studies in first-trimester pregnancies, the goal should be to focus the study on the potentially acardiac fetus and limit exposure to the viable twin as much as is practicable.

- **Differential diagnosis**

In real-time ultrasonography of monochorionic twins (or higher order multiple gestation), the differential diagnosis of TRAP sequence includes a severely abnormal fetus or fetal death. An anomalous twin unrelated to TRAP can be excluded by Doppler assessment of arterial flow in that twin: it will be reversed in TRAP but normal in a purely anomalous twin. A dead twin will have no limb movement, no retrograde arterial flow seen on color Doppler imaging, and will not continue to grow on repeated ultrasound examinations, whereas an acardiac twin may show some or all of these findings.

Additionally, a severely amorphous "acardiac" mass of tissue may be mistaken for a placental mass, such as a chorioangioma.

Prognosis

Among TRAP sequence cases with poor prognostic features treated conservatively, perinatal twin mortality rates of ≥50% were reported in two series (Moore, Gale and Benirschke, 1990; Quintero *et al.*, 2006) . It is worth noting that the interpretation of these data is limited, as a series (Moore, Gale and Benirschke, 1990) described cases more than three decades ago and the second series (Quintero *et al.*, 2006) had only a small number of cases of conservative management.

The main reasons for the high mortality are the development of heart failure, which can lead to pregnancy loss in any trimester, and the consequences of premature birth, which can be iatrogenic or spontaneous. Intrauterine therapy improves survival rates to about 80% or higher.

- **Poor prognostic factors**

One or more of the following poor prognostic factors increase the risk of mortality in pump-twins (Moore, Gale and Benirschke, 1990; Brassard *et al.*, 1999; Quintero *et al.*, 2006; Sugibayashi *et al.*, 2016) :

- In the fetus-water pump or high-performance heart failure.
- Abnormal fetal-pump Doppler velocity studies that include persistent absence or reversal of end-diastolic blood flow in the umbilical artery, pulsatile blood flow in the umbilical vein, and/or reversed α-wave in the ductus venosus, which may be indicative of overt heart failure.

- Acardiac twin weight to pump twin weight ratio greater than 0.70 (i.e., the estimated noncardiac fetal weight is ≥70% of the pump twin weight). This can be estimated subjectively or using a regression equation (Moore, Gale and Benirschke, 1990) :

Weight (grams) = (-1.66 x longest length [cm]) + (1.21 x longest length [cm]$^{2)}$

In one study, when the ratio of the weight of the acardiac twin to that of the pump twin exceeded 0.70, the risks of heart failure, preterm birth, and polyhydramnios were 30, 90, and 40%, respectively, versus 10, 75, and 30 %, respectively, when this ratio was below 0.70 (Moore, Gale and Benirschke, 1990) .

Other formulas have been proposed for sonographic assessment of the weight of the noncardiac twin, as conventional biometric formulas are not valid for assessing the size of a noncardiac fetus. Given the many different possible cardiac twin body shapes, no formula can accurately estimate weight for all cardiac twins. Therefore, subjective assessment is also important in estimating atrial twin size.

- Polyhydramnios (defined as a maximum vertical pool of amniotic fluid ≥8 cm).
- Monoamniotic pregnancy (carrying an additional risk of entanglement of the cord).

Pregnancy management

After the diagnosis of TRAP sequence, women should be referred to an experienced fetal diagnosis and treatment center for further evaluation and to discuss management strategies. The option of terminating the pregnancy should be offered. For women who choose to continue the pregnancy, strategies include conservative management or targeted cord occlusion.

- **Assessment for birth defects**

As pregnancies complicated by the TRAP sequence appear to have an increased risk of birth defects (Moore *et al.*, 1987; Hartge and Weichert, 2012) , an invasive procedure (eg amniocentesis, chorionic villus sampling) is recommended to obtain fetal cells for genetic testing (karyotype, microarray). This information may influence the patient's decisions about continuing the pregnancy, cord occlusion, and/or other aspects of prenatal, intrapartum, or postnatal care.

- **Ultrasound monitoring**

There are no reliable data to support any specific, evidence-based, follow-up strategy for pregnancies complicated by the TRAP sequence. Close ultrasound evaluation is recommended after the diagnosis of TRAP sequence, with repeat ultrasound examinations usually every one to two weeks depending on the perceived severity of the clinical presentation and gestational age.

For example, in a relatively small cardiac mass with an otherwise normal fetus-pump in the early second trimester monitoring every 2 weeks is recommended as significant deterioration between studies is unlikely. Weekly monitoring is recommended for women with relatively large cardiac twins, those in whom there are concerns about the development of poor prognostic factors, and those who are at or near viable gestational age because poor prognostic factors or fetal deterioration can lead to consideration of cord obstruction or, in some cases, labor. In other scenarios, such as cases where the fetus-pump is suspected to be at risk before the usual gestational age limit for cord occlusion therapy, twice-weekly follow-up may be offered to optimize the timing of therapeutic intervention.

- **Antenatal corticosteroids**

Given the increased risk of preterm delivery, pregnancies complicated by TRAP sequence at viable gestational ages may be considered for antenatal corticosteroid administration. The timing of this intervention should be individualized based on signs of threatened preterm labor, the presence of preterm premature rupture of membranes (PPROM), or concern for fetal-pump compromise, which may require delivery within the next seven days.

- **Cord occlusion treatment**

The goal of cord occlusion therapy for the management of the TRAP sequence is to interrupt the vascular communication between the twins, thereby relieving the twin-pump of the hemodynamic burden of supporting the acardiac fetus. As the acardiac twin has no potential for substantial long-term independent survival, treatment for the TRAP sequence is entirely focused on optimizing outcomes of the twin-on-pump.

Intervention offers a better prognosis than conservative management, especially in pregnancies with one or more poor prognostic features. In a meta-analysis including 26 retrospective studies of the TRAP sequence, intervention with cord occlusion or ablation was associated with a higher likelihood of live birth than conservative management (odds of miscarriage/fetal death with conservative management versus intervention: OR 2.22, 95% CI 1.23-4.01), with the greatest benefit in pregnancies with poor prognoses

(odds of miscarriage/fetal death with conservative treatment versus intervention: OR 8.58, 95% CI 1.47-49.96) (Mone, Devaseelan and Ong, 2016) .

Because of the need for highly specialized training and equipment, cord occlusion procedures are available in only a small number of institutions. Patients with pregnancies complicated by TRAP sequence should be offered referrals to these centers for further evaluation and care.

If referral to a center providing cord occlusion is not possible, amnioablation can reduce polyhydramnios and limit its consequences. However, as amnioablation does not address the underlying pathophysiology of TRAP, it is a temporary measure at best and not a preferred strategy. Therefore, referral to a fetal treatment center experienced in cord occlusion treatment is strongly recommended when possible.

- **Candidates**

Pregnant candidates for cord occlusion therapy generally include the TRAP sequence with at least one of the poor prognostic factors described above.

Although a ratio of estimated acardiac twin to pump-twin weight greater than 0.70 is such a poor prognostic factor, many centers now offer cord occlusion therapy for ratios greater than 0.50 or with evidence of a rapidly growing acardiac twin. Ultimately, the decision to intervene must be individualized to the specifics of each pregnancy and must balance maternal and obstetric risks against potential benefits. Local legal regulations regarding termination may be an additional factor, although it should be reiterated that acardiac twins often lack a heart and a head and are universally recognized as having no chance of ex utero survival.

- **Preoperative assessment and preparation**

A comprehensive fetal anatomical evaluation, fetal heart ultrasound, and invasive diagnostic genetic testing are recommended prior to umbilical cord occlusion therapy (Blaicher, Repa and Schaller, 2000) .

There are no reliable data to support either clear benefit or harm from perioperative antibiotic prophylaxis for the treatment of percutaneous cord occlusion.

- **Choice of operation**

Three current methods of cord occlusion therapy for the management of TRAP sequence are radiofrequency ablation (RFA), bipolar cord coagulation, and intrafetal or interstitial laser coagulation (Ville et al., 1994; Deprest et al ., 2000 *;* Lee *et al.*, 2007; King *et al.*, 2017) . These procedures can be performed under local or regional anesthesia.

The choice of technique for a given pregnancy should be individualized based on operator experience, center resources, clinical presentation, gestational age, and preference. In the United States, RFA is the

most commonly used cord occlusion technique. In many treatment centers, RFA and/or bipolar coagulation are reserved for candidates with a TRAP sequence at at least 16 weeks' gestation and preferably ≥ 18 weeks' gestation, due to concerns about a higher rate of complications, such as PPROM, with earlier intervention. The optimal management of candidates presenting before 16 to 18 weeks is unclear. Conservative management until some time later in pregnancy is an option, but has been associated with a significant risk of poor obstetric outcome (Lewi *et al.*, 2010) . The use of laser therapy has been suggested for the specific indication of early TRAP presentations, as it can be performed as early as the end of the first trimester (Tavares de Sousa *et al.*, 2020) .

Because RFA ablation involves a smaller-caliber entry into the uterus than bipolar occlusion to perform the procedure, proponents of RFA believe that it may have a lower complication rate (and therefore greater efficacy) in achieving second-trimester cord occlusion in complicated monochorionic pregnancies. However, limited published data could not definitively demonstrate improved outcomes with RFA ablation (Bebbington *et al.*, 2012; Gaerty, Greer and Kumar, 2015) , despite its seemingly less invasive nature (Gabby *et al.*, 2020? Ting *et al.*, 2021) . In a meta-analysis including 481 cases of bipolar cord occlusion and 320 cases of RFA from 17 studies involving complicated monochorionic pregnancies, overall survival was 76.8% with RFA and 79.1% with bipolar occlusion (Gaerty, Greer and Kumar, 2015) . While PPROM occurred less frequently in the RFA group compared to the bipolar group, (17.7 vs. 28.2%), the mean gestational age at delivery did not differ between groups (34.7±1.7 weeks for RFA; 35.1±1.6 weeks for bipolar).

- **Intervention**
  - **RFA-** RFA is used to cauterize the abdominal wall of the acardiac twin at the level of the umbilical cord insertion, thereby causing cord occlusion. For RFA, a catheter (modern catheters are typically 17-gauge) is guided percutaneously through a small skin incision into the atrial duodenum under continuous ultrasound guidance. This procedure can be performed under regional anesthesia or by blocking local anesthesia (i.e., lidocaine) with sedation in a patient who has received preoperative oral pain medication.

    Although there are different RFA catheters, a commonly used RFA catheter uses deployable prongs that are released in a palm formation, allowing for a controlled ablation sphere that will occlude the entire umbilical vessel. Catalysis is then carried out until a certain resistance or temperatures are reached, depending on the device used. Because of significant maternal thermal injuries associated with early RFA experience, grounding pads are required prior to

ablation to protect the patient from such injuries. As with the other techniques, interruption of blood flow from the pump twin to the acardiac twin is confirmed by Doppler ultrasound before the end of the procedure (Lee *et al.*, 2007) . After the RFA procedure, indomethacin (50 mg oral loading dose followed by 25 mg orally every 6 hours for a total of 48 to 72 hours) is usually given to patients with cramping or contractions related to the procedure.

- **Bipolar coagulation-** Bipolar coagulation is performed by percutaneously guiding a surgical sheath (approximately 10- to 12- gauge) under adequate analgesia through a small skin incision in the uterus via Seldinger technique or direct trocar entry to reach the acardiac fetus. Once in the uterus, amniocentesis can be done in cases with oligohydramnios. A diagnostic fetoscope can then be used to visualize the atrial cord and identify the appropriate target site for coagulation. Alternatively, a cord target location can be identified by ultrasound evaluation.

  If an fetoscope was used, it is removed, and the bipolar forceps are advanced through the sheath and guided sonographically to grasp the cord target site. Once it is confirmed to be in place, power is applied until successful cable occlusion is achieved. Cord obstruction can be demonstrated using ultrasound and Doppler studies. Fetoscopic visualization can also be used for confirmation. Similar to RFA ablation, perioperative indomethacin tocolysis can be used.
- **Laser coagulation-** Intrafetal laser coagulation involves a freely guided 17- or 18-gauge needle directed into a target intra-fetal tissue adjacent to the vessels of the intra-fetal cord. A laser fiber is then passed through the needle and, after a series of short controlled bursts, a permanent interruption of vascular flow is achieved.

- **Complications**

Major maternal complications from cord occlusion are rare and include severe bleeding, uterine injury, need for laparotomy, thermal injury, chorioamnionitis that can lead to maternal sepsis, and disseminated intravascular coagulation. Among 98 women identified in the North American Fetal Treatment Network Registry for cord occlusion treatment with RFA for TRAP, there were no maternal deaths, no women required a blood transfusion, and most women were hospitalized for ≤1 day after surgery (Lee *et al.*, 2013) . Obstetric complications include PPROM, preterm loss, preterm labor, preterm delivery, abruption, and intrauterine infection. Perioperative death of the fetus-pump is possible and there is a theoretical risk of direct and indirect injury to it (Moldenhauer *et al.*, 2017) .

The development of congenital epidermal aplasia has been reported as a complication of the intrafetal laser coagulation procedure. Further study is needed to assess the frequency of this complication (O ' Donoghue *et al.*, 2008) .

- **Outcome**
  - **Neonatal Survival** – In published experiences describing the use of RFA for TRAP, twin-pump survival ranged from 80 to 100%, with a mean gestational age at delivery of 33 to 37 weeks (Lee *et al.,* 2007, 2013; Livingston *et al.,* 2007; Jelin *et al.,* 2010) . In the North American Fetal Treatment Network review of 98 pregnancies from multiple contributing fetal treatment centers, there was an overall 80% twin survival rate and a median gestational age at birth of 37 weeks (Lee *et al.,* 2013) .

    As previously noted, retrospective review suggests comparable efficacy for RFA and bipolar cord occlusion (Bebbington *et al.,* 2012; Gaerty, Greer and Kumar, 2015) .

    Limited published experience with intrafetal laser coagulation suggests a neonatal survival rate of approximately 80% (Pagani *et al.,* 2013; Berg *et al.,* 2014; Roethlisberger *et al.,* 2017; Tavares de Sousa *et al.,* 2020) . In the largest series of intrafetal laser for TRAP at a single center (17 cases), the live birth rate was 82 % at a mean gestational age of 37 $^{+1}$ weeks of gestation (Pagani *et al.,* 2013) . A companion literature review including data from an additional 10 studies yielded a total of 51 cases with a neonatal survival rate of 80%.
  - **Long-term results** – Data on long-term results are sparse. Cases of neurodevelopmental delay have been reported after selective feticidal cord occlusion for TRAP (Lewi *et al.,* 2006; J. _ van Link *et al.,* 2015) . In the largest series focusing on long-term neurodevelopmental outcomes among surviving pump-twins complicated by the TRAP sequence treated with RFA, information was available for 27 children at a mean age of two years and five months, and none had neurodevelopmental delay (defined as a total developmental quotient <70 points using the Infant Growth Risk Scale, a validated questionnaire) (Ozawa *et al.,* 2021) . However, some infants were as young as four months old at assessment, only 44% were children older than three years, and long-term follow-up was not available for another five children who underwent RFA.

Time of planned delivery

Although there are no reliable data to support the optimal timing of delivery for pregnancies complicated by the TRAP sequence, a reasonable approach is to consider delivery of uncomplicated cases not undergoing fetal therapy at 34 $^{+0}$ to 36 $^{+6}$ weeks of gestational age and possibly earlier if complications arise, such as jeopardizing the pump-twin or development of typical obstetric signs of preterm labor. After successful cord occlusion treatment with subsequent reassuring ultrasound and maternal monitoring, labor in "full term" gestational age (39 $^{+ 0/7}$ to 40 $^{+ 6/7}$ weeks) is the appropriate target.

Caesarean section should be performed for standard obstetric indications.

4.3.3. Complications that characterize monoamniotic multiple pregnancies

In addition to the problems of monochorionic diamniotic pregnancies described above, the following fetal complications are of particular concern in monoamniotic multiple pregnancies:

- **Umbilical cord entanglement** - Umbilical cord entanglement occurs in most, if not all, monoamniotic twin pregnancies (Dias *et al.*, 2010; Ishii, 2015) . Loose engagements likely begin in the first trimester and have the potential to tighten at any time. Intermittent occlusion of umbilical blood vessels may be associated with neurologic morbidity. Severe prolonged occlusion can be fatal (Gaffney *et al.*, 1994; MacLennan, 1999; Sebire *et al.*, 2000; Dias *et al.*, 2010) .

  In a systematic review of the effect of cord entanglement on perinatal outcome, overall survival among fetuses with cord entanglement at birth was 89% (202 of 228 fetuses), and subanalysis found no significant difference in perinatal mortality among fetuses with cord entanglement. and without rope entanglement (Rossi and Prefumo, 2013) . However, these findings should be interpreted with caution as the overall number of deaths was small and information on prenatal diagnosis and management of these pregnancies was limited. Fetal monitoring and early delivery, which has become routine in monoamniotic pregnancies, may have prevented perinatal death from cord entanglement.

  Women with monoamniotic placentation in a multiple pregnancy are recommended to be admitted to hospital at 26 weeks' gestation for intensive fetal heart rate monitoring (one hour of continuous monitoring every eight hours), to be given a course of antenatal corticosteroids, and to deliver by caesarean section at 32 to 33 weeks of pregnancy.

- **Conjoined Twins** - Described next.

4.3.4. Zygote division abnormalities

Of the monoamniotic twins just described, an interesting subset derives from embryonic division at day 9 after fertilization. These "mirror-image twins" are genetically identical but have mirror-image characteristics such as dominant hand and hair source (Post, 2015). More seriously, several aberrations in monozygotic twinning result in a spectrum of fetal malformations. These are traditionally attributed to the incomplete separation of an embryo into two separate twins. However, they are likely to result from early secondary fusion of two separate embryos. These separated embryos are either symmetrical or asymmetrical. The asymmetric category includes twin types in which one twin is substantially smaller and incompletely formed (Cunningham, 2018).

4.3.4.a. Conjoined twins

Incidence

Conjoined twins are a rare type of monoamniotic twin, estimated to occur in 1.5 per 100,000 births worldwide (Mutchinick *et al.,* 2011) . Female twins are more commonly affected than male twins.

Types

When twins are conjoined, fusion occurs between the same body parts. Conjoined twins are classified as cephalopagus, thoracopagus, omphalopagus, ischiopagus, parapagus, craniopagus, rachipagus, and pygopagus, based on the location of the fusion (Baken et al., 2013).

Prenatal diagnosis

First-trimester monoamniotic twin pregnancies should be suspected when the fetal poles are closely connected and do not change position with each other (Winkler *et al.,* 2008; Bakken *et al.,* 2013; Mahalingam and Dighe, 2014) . Fusion of fetal organs may be evident.

Other findings, not all of which are specific to conjoined twins, include side-by-side fetuses with a single mean heartbeat, increased nuchal translucency or cystic fluid, inseparable fetal parts, no sign of separate twin movement, fewer limbs than expected, a only umbilical cord with more than three vessels, hyperextension of the cervical vertebrae of fetuses facing each other, or both heads or hips fixed at the

same level with each other (McHugh, Kiely and Spitz, 2006; O'Brien, Nugent _ _ and Khalil, 2015) . In the second half of pregnancy, a detailed anatomical study can help determine the location and extent of the attached area.

Polyhydramnios is present in up to 50% of conjoined twins in late gestation (McHugh, Kiely and Spitz, 2006) .

Congenital anomalies are always present in conjoined twins. The prognosis is poor because these abnormalities often preclude the survival of one or both twins, even if surgical separation is performed.

- **Additional imaging studies**

Color Doppler, fetal heart ultrasound, and 3D ultrasound can confirm the diagnosis and clarify the anatomy, which is critical for assessing prognosis and making decisions before and after birth. Fetal MRI can also help define anatomy and surgical planning (Spielmann, Freed and Spritzer, 2001) . A team of surgeons at Texas Children's Hospital is using a combination of volumetric computed tomography, 3D modeling, and 3D printing for surgical planning, patient-specific simulations, and training (Mathew *et al.*, 2017) .

Management

- **Multidisciplinary Team** - Patients should be cared for in a center experienced in the management of conjoined twins. The management team includes at least specialists in maternal fetal medicine, pediatric surgery, neonatology and radiology. Management is based largely on clinical experience at such centers and on data from case reports, small series, and expert opinion.
- **Time of delivery** - There is insufficient literature to guide a specific time of delivery. However, delivery at 35 weeks after antenatal corticosteroids is a reasonable approach because of the increased risk of stillbirth or complications associated with polyhydramnios and preterm labor (O'Brien, Nugent and Khalil, 2015) . Premature delivery to avoid entanglement of the umbilical cords does not make sense because the twins do not move independently (O'Brien, Nugent and Khalil, 2015) .
- **Cesarean delivery** - The optimal uterine incision depends on patient-specific factors, including gestational age, attachment type, and neonatal prognosis. The abdominal and uterine incisions must be large enough to deliver the twins atraumatically. Therefore, a classic hysterectomy is usually required.

- **Vaginal delivery approach** - Successful vaginal delivery of undiagnosed conjoined twins has been reported, but there is a high risk of dystocia and maternal and/or fetal trauma, including uterine rupture and fetal death (Harma *et al.,* 2005; Tug *et al.,* 2009; Mitchell *et al.,* 2014) . Vaginal delivery can be attempted in the second trimester, as the mass of the twins is much smaller than at the end of pregnancy and is reasonable for non-viable twins or termination of pregnancy.

4.3.4.b. External parasitic twins

This is a severely defective fetus, or simply fetal parts, externally attached to a relatively normal twin. A parasitic twin usually consists of externally attached supernumerary limbs, often with some viscera. Classically, however, a functioning heart or brain is absent. The appendage mirrors those positions previously described for Conjoined twins. Parasitic fetuses are thought to result from the death of the defective twin. The surviving tissue adheres to and receives vascularization from the normal twin (Spencer, 2001) . In a large epidemiological study, parasitoid twins accounted for 4% of all conjoined twins and occurred more frequently in male fetuses (Mutchinick *et al.,* 2011) .

4.3.4.c. Fetus in fetu

Early in development, one fetus may wrap inside the other twin fetus. The normal development of this rare parasitic twin usually stops in the first trimester. As a result, the normal spatial arrangement and the presence of many organs are lost. Classically, the vertebral or axial bones are found in the fetal mass, while the heart and brain are absent. These masses are thought to represent a monozygotic, monochorionic diamniotic twin pregnancy and are usually supported by large parasitic vessels in the host (Spencer, 2000; McNamara *et al.,* 2016) . Malignant degeneration is rare (Kaufman *et al.,* 2007) .

4.3.5. Intrauterine death

4.3.5.a. Fetal death in a twin pregnancy

Vanishing twin syndrome

Early automatic reduction from a twin to a singleton pregnancy (i.e., disappearing twin) is common and occurs in 7 to 36% of twin pregnancies resulting from in vitro fertilization (IVF) (Romanski *et al.,* 2018; Harris *et al.,* 2020? Seong *et al.,* 2020) . It is unclear whether the rate is similar in naturally conceived pregnancies, which are not routinely imaged from the early stages of pregnancy. Although some studies

report that a vanishing twin increases the surviving fetus's risk of low birth weight and a small-for-gestational-age infant compared with pregnancies in which a singleton fetus is conceived, others have reported equivalent risks of adverse outcome (Pinborg *et al.,* 2005; Chasen, Luo, *et al.,* 2006; La Sala *et al.,* 2006; Shebl *et al.,* 2008; Almog *et al.,* 2010; Evron *et al.,* 2015; Zhou *et al.,* 2016 ; Romanski *et al.,* 2018; Harris *et al.,* 2020; Seong *et al.,* 2020) . The discordance in perinatal outcomes may be related to differences between studies in the range of gestational age of the twin that disappears at death and to differences in IVF techniques. The dead twin can affect the results of the free fetal DNA test when it is used to screen for common fetal aneuploidies.

In general, the first-trimester death of a dichorionic twin fetus does not adversely affect the surviving twin (Benson, Doubilet and David, 1994) . The first-trimester death of a monochorionic twin fetus may also have no effect on the other twin. However, second and third trimester death can have serious adverse effects, as described below.

Death of twins in the second and third trimesters

Fetal death in twin pregnancies is not rare. In a study in which both twins were alive at 11 to 13 weeks' gestation, about 97% of 4896 dichorionic twin pregnancies and 89% of 1329 monochorionic twin pregnancies had two live fetuses or two live births before 34 weeks pregnancy (Cimpoca *et al.,* 2020) . The rate of death of a single fetus before 34 weeks with the other twin alive ≥3 days later was 3.5% for monochorionic twins and 1.2% for dichorionic twins. Obviously, the incidence of fetal death is higher if losses before the 11th ^{to} 13th week are included.

Single fetal death is a serious concern in monochorionic twins due to placental vascular anastomoses. Intrauterine death of one twin in a monochorionic pregnancy may cause acute hypotension, anemia, and ischemia in the other twin due to exsanguination into the low-pressure vasculature of the deceased twin, resulting in morbidity or death of the twin. In a dichorionic pregnancy, this sequence is not a concern as there are no placental vascular anastomoses. However, the death of one twin may reflect an adverse intrauterine environment that could also put the other twin at risk of morbidity or mortality.

The outcome of twin pregnancies with singleton fetal loss was shown in a systematic review of studies that assessed the prognosis of the twin after death of the other twin after 14 weeks (monoamniotic twins were excluded) (Mackie et al., *2019)* . After intrauterine death of a twin:

- The rates of fetal death of the other twin in monochorionic and dichorionic pregnancies were 41 and 22%, respectively (comparing monochorionic versus dichorionic pregnancies: relative ratio [OR] 2.06, 95% CI 1.14–3.71).
- In monochorionic pregnancies, 20% of twin survivors had abnormal prenatal imaging of the skull.
- Preterm delivery rates in monochorionic and dichorionic pregnancies were 59 and 54%, respectively (comparing monochorionic vs. dichorionic pregnancies: OR 1.42, 95% CI 0.67-2.99).
- The rates of abnormal postnatal cranial imaging in monochorionic and dichorionic pregnancies were 43 and 12%, respectively (comparing monochorionic versus dichorionic: OR 5.41, 95% CI 1.03–28.56).
- The rates of neurodevelopmental impairment of the surviving fetus in monochorionic and dichorionic pregnancies were 29 and 10%, respectively (comparing monochorionic versus dichorionic: OR 3.06, 95% CI 0.88–10.61).
- The rates of neonatal death of the surviving fetus in monochorionic and dichorionic pregnancies were 28 and 21%, respectively (comparing monochorionic versus dichorionic: OR 1.95, 95% CI 1.00-3.79). Furthermore, in monochorionic twins, a single fetal death before 28 weeks' gestation increased the other twin's risk of fetal and neonatal death compared with a single fetal death after 28 weeks.

While the risk to the surviving twin in a monochorionic pregnancy is clear when the death of one twin occurs in the second or third trimester, the risk with the death of a twin in the first trimester is unclear. It has been hypothesized that congenital anomalies and cerebral palsy may be attributable to early fetal loss in a twin pregnancy (Pharoah, 2005) . A retrospective study with data from the United Kingdom provided support for this theory. The risk of a congenital anomaly in the surviving twin after the loss of the other fetus before 16 weeks' gestation was more than twice that in twin births (Pharoah, Glinianaia and Rankin, 2009) . These data may reflect, at least in part, the known increased risk of concordant and discordant congenital anomalies in monozygotic twins, which may lead to early intrauterine death of one twin if the anomaly is severe. Prospective studies are needed to clarify these relationships.

Compared with singleton pregnancies, additional risks to the surviving fetus after the death of a twin include a 120 g reduction in average birth weight, an increased risk of a small-for-gestational-age neonate, and an increased risk of preterm delivery (Practice Committee of American Society for Reproductive Medicine, 2012) .

➢ Management

The optimal management of pregnancies in which one twin is likely to die or has died is unclear in pregnancies that have reached the viable stage. Timing of delivery should be individualized based on the clinical scenario.

- **Dichorionic twins**

  In dichorionic twins, the death of one twin is not, by itself, a strong predictor of preterm delivery of the surviving twin. However, if there is a condition affecting both twins (e.g., preeclampsia, chorioamnionitis), then close monitoring and early delivery of the surviving twin is indicated to prevent a second fetal loss. Early delivery depends on the situation at hand (e.g., early delivery for chorioamnionitis vs. consideration of conservative management of preeclampsia without severe features before 34 weeks' gestation and with a normal surviving twin).

- **Identical twins**

  The death of one twin of a monochorionic pair can have immediate deleterious effects on the survivor due to interconnected vascular anastomoses. The hemodynamic changes that occur with the death of a twin are immediate. Therefore, early delivery after death to avoid harm to the survivor appears to be futile (Karageyim Karsidag *et al.*, 2005) . Management should be based on the maternal condition and the condition of the surviving fetus.

  When a twin dies before the limit of viability, the practice is to discuss the option of terminating the pregnancy, although, as mentioned above, the risk of neurological injury to the twin is not clear when death occurs in the first trimester [the risk of death and in both twins, however, it can be predicted (Benson, Doubilet and David, 1994) . In continuing pregnancies, ultrasound and MRI evaluation of the surviving twin may identify signs of brain damage, such as ventrilomegaly, white matter lesions, or intracranial hemorrhage, that develop over time, and may be helpful in predicting prognosis if are the results abnormal. However, both the diagnostic performance of imaging studies to predict or rule out fetal brain injury in this setting, the best imaging method to use, and the best time to perform the imaging study are unclear (Shinar, Harris, *et al.*, 2022) . In the absence of a maternal or other fetal indication for early delivery, delivery before 34 weeks' gestation is not recommended and the practice is to deliver from 34^{+0} to 36^{+6} weeks (Blickstein and Perlman, 2013) .

  On the other hand, if fetal evaluation after 26 weeks' gestation suggests imminent death (rather than death) of one twin of a monochorionic pair, early delivery of both twins is recommended rather than conservative management, given the high risk of neurological damage to the surviving twin.

It is not necessary to monitor maternal coagulation in these cases, as they are rare. Maternal hypofibrinogenemia or disseminated intravascular coagulation after the death of a multiple gestation fetus has been described in only a few case reports (Skelly *et al.,* 1982; Romero *et al.,* 1984; Chescheir and Seeds, 1988; Hasbún *et al.,* 1992; Mitra *et al.,* 1993) . Although some experts have treated these patients with short heparin therapy, spontaneous resolution of hypofibrinogenemia occurs without treatment. Heparin therapy will be considered only if there is active bleeding associated with hypofibrinogenemia, hypofibrinogenemia in a patient at high risk of bleeding, such as with placenta previa or placental abruption, or if thrombotic complications are present.

D immunoglobulin prophylaxis is recommended in all Rh - D negative women with intrauterine death and twin pregnancy.

4.3.5.b. Fetal death in a triplet pregnancy

Automatic fetal reduction

A significant number of triplet pregnancies experience spontaneous loss of one sac during the first trimester, referred to as a "disappearing twin". The rate of loss correlates with the initial number of gestational sacs. In one study, spontaneous reduction of one or more gestational sacs and/or fetuses occurred in 53% and loss of all three sacs occurred in 6% of 132 triplet pregnancies diagnosed before 12 weeks (Dickey *et al.,* 2002) . Most losses occurred before the ninth week of pregnancy.

Triplet pregnancies that showed spontaneous reduction were born earlier than normal pregnancies with the same number of fetuses (e.g., from an initially triplet pregnancy, singleton fetuses were born 10 days earlier than natural singleton fetuses, from an initially triplet pregnancy twins were born four days earlier than natural twins) (Dickey *et al.,* 2002) .

Late death of a fetus

The rate of fetal death after 22 weeks of gestation is related to chorioamnionicity. In one study, fetal death occurred in 0.8% of trichorionic triplet pregnancies (12 of 1521) versus 2.7% of monochorionic triamniotic triplet pregnancies (4 of 150) (Kawaguchi *et al.,* 2013) .

Although no studies have specifically looked at the outcomes of surviving fetuses from the death of one fetus in a triplet pregnancy, this risk likely depends on whether they shared a chorionic sac with the dead triplet. For example, monochorionic fetuses surviving the death of another fetus have higher rates of

subsequent death, preterm birth, and neurodevelopmental impairment than dichorionic survivors of the death of another fetus.

After the death of one or both triplets with a monochorionic placenta, injury to the surviving fetus or fetuses is considered to occur instantaneously. Therefore, immediate birth will not prevent the adverse outcomes associated with this event (Karageyim Karsidag *et al.*, 2005) . Timing of delivery is based on the usual patterns for the rest of the twin or singleton pregnancy, but assessment of fetal well-being with weekly biophysical profiles (NST is a reasonable alternative) and repeated ultrasound examinations of growth is applied.

5. Multifetal pregnancy reduction-Selective termination

Multiple pregnancies are at higher risk for a variety of maternal, fetal, and neonatal complications than singleton pregnancies. Ideally, multiple pregnancies should be prevented by better use of assisted reproductive technology (e.g., better management of ovulation induction and embryo transfer). In the absence or failure of preventive interventions or in the event of spontaneous conception, multifetal pregnancy reduction (MPR) procedures have been developed to reduce the total number of fetuses in the pregnancy and thereby improve maternal outcome and of outcomes in the surviving fetus(es). Fetuses selected for reduction are mostly chosen at random, but taking into account technical factors.

Selective termination (ST) also involves reducing the number of fetuses, but the ST procedure is directed at one or more specific fetuses in a multiple pregnancy due to a known genetic, structural, or other abnormality (e.g., severe growth restriction)., which has been identified by ultrasound examination or by an invasive procedure (amniocentesis, chorionic villus sampling) for diagnostic testing of the fetuses.

5.1. Multifetal pregnancy reduction

Definition

MPR (multifetal pregnancy reduction) refers to a procedure in which the total number of fetuses in a multiple pregnancy is reduced by terminating one or more fetuses chosen mostly at random, but taking into account technical factors.

Reasoning

It is well documented that the morbidity and mortality of multiple pregnancies increase with increasing number of fetuses and that adverse outcomes in the offspring are primarily a consequence of preterm

delivery (Belizán *et al.*, 1978; Doyle, 1996; Conde-Agudelo, Belizán and Lindmark, 2000; Arlettaz, Paraskevopoulos and Bucher, 2003; Kahn *et al.*, 2003; Luke and Brown, 2008) . The main justification for MPR is that the "take home" baby rate per pregnancy is increased by increasing the gestational age at birth as well as the birth weight, thereby reducing the morbidity and mortality of preterm birth (Obi č an *et al.*, 2015) . Risks for certain maternal complications, such as preeclampsia, are also reduced (Devine and Malone, 2004) .

Improved medical outcomes are not the only consideration. The economic and psychological impact of multiple pregnancy on families is also significant and may be additional reasons for MPR (Ellison and Hall, 2003; Vilska *et al.*, 2009) . The emotional stress and complexity of caring for multiple newborns, especially those with medical or developmental problems, is high. More than 25% of parents of multiples experience depression or anxiety disorders in the perinatal period (Leonard, 1998) . In addition to immediate medical costs, infants/children with complex medical and developmental issues often require specialized and coordinated care, preventing parents and family members from returning to work and thus increasing financial stress.

In response to these and other issues, an opinion of the American College of Obstetricians and Gynecologists (ACOG) committee on multiple pregnancy reduction states that “obstetricians and gynecologists should respect patients' autonomy regarding whether to continue or will reduce a multiple pregnancy' and that 'only the patient can weigh the relative importance of medical, ethical, religious and socioeconomic factors and determine the best course of action for her unique situation' (' Committee Opinion No. _ 719: Multifetal Pregnancy Reduction ', 2017) .

Candidates

- **Multichorionic triplet and higher order multiple pregnancies**

MPR should be offered for any pregnancy with three or more fetuses, as there is good evidence from meta-analyses of observational studies that it improves neonatal survival rates and outcomes in surviving fetuses (Anthoulakis *et al.*, 2017; Zipori *et al.*, 2017) .

A report by the Commission of the International Federation of Gynecology and Obstetrics (FIGO) stated that "a multiple pregnancy of an order of magnitude larger than twins poses a great risk to the health of the woman as well as to her fetuses, which are likely to be born prematurely at high risk or to die or suffer harm' and that 'where such pregnancies occur, it may be considered morally preferable to reduce the

number of fetuses than to do nothing' (FIGO Committee for the Ethical Aspects of Human Reproduction and Women 's _ Health, 2006) .

Outcome data of electively reduced pregnancies versus ongoing triplet pregnancies are discussed below.

- **Dichorionic twin pregnancies**

MPR may be considered for dichorionic twin pregnancies (DCDA), particularly if there is a medical or obstetric indication, such as maternal medical disease (e.g., heart disease, kidney disease) or a history of preterm birth or cervical insufficiency. Reduction to singleton pregnancy may also be considered in women of very advanced maternal age (≥45 years), as they are at high risk for pregnancy complications, such as preterm birth, preeclampsia, growth restriction, and possibly gestational diabetes, with twin pregnancy compared with singleton pregnancy (Meyer *et al.,* 2018) .

MPR in the absence of a medical/obstetrical indication is controversial, given that the outcome of twin pregnancies is much less poor than for higher order pregnancies (Chervenak, McCullough and Wapner, 1992; Evans *et al.,* 2001, 2003, 2004) . However, even if there is no medical or obstetrical indication for MPR, some patients believe that they can meet the needs of one additional child but not two additional children. These patients should receive objective advice about their options (' Committee Opinion No. 719: Multifetal Pregnancy Reduction ', 2017) .

Outcome data of electively reduced versus ongoing twin pregnancies are discussed below.

- **Selected monochorionic pregnancies**

The injection techniques discussed below for MPR are intended for dichorionic fetuses or for reduction of all fetuses in a monochorionic pregnancy (such as a monochorionic pair of triplets or higher order pregnancies).

Reduction of a single fetus in a monochorionic pregnancy requires specialized umbilical cord occlusion techniques to prevent death or neurological damage to the fetus from effects arising from placental vascular anastomoses. These cord occlusion techniques are associated with a higher risk of miscarriage than the injection technique described below and are therefore rarely performed for MPR. In those rare cases where a patient chooses to selectively terminate a single fetus in a monochorionic pregnancy, the technique is the same as that described below for ST of a monochorionic pregnancy.

Contraindications for multiple pregnancy reduction

There are no absolute contraindications for MPR, but there are some relative contraindications.

The inability to confidently diagnose chorionicity, although uncommon, is a relative contraindication to MPR because the death of one fetus in a monochorionic multiple pregnancy may be harmful to the coexisting fetuses in the monochorionic sac. HIV or active hepatitis is another consideration when planning an invasive intrauterine procedure because of the risk of vertical transmission. However, the true risk is unknown and probably low. Conditions that make the procedure too technically difficult, such as maternal obesity or reduced ultrasound imaging of the fetus due to previous abdominal surgery, may also be relevant contraindications, although most of these technical considerations can be overcome in experienced hands.

Cervical shortening, a relative contraindication for many other intrauterine procedures, is not necessarily considered a contraindication for MPR.

Pre-interventional assessment factors

- **Informed Consent and Counseling**

Patients should have a clear understanding of the risks of multiple pregnancy and the benefits and risks of MPR. The primary risk associated with MPR is miscarriage, but this risk should be interpreted in the context of miscarriage in expected multiple pregnancies, as the risk of miscarriage after MPR is lower than that for spontaneous loss of unreduced triplets or higher order multiple pregnancies (Obi č an *et al.*, 2015) .

- **Local settings**

MPR differs philosophically from termination of pregnancy as it is a procedure developed to increase the likelihood of a successful pregnancy and is therefore not considered a type of abortion. However, since laws vary from state to state and between countries, it is important to be aware of local legal requirements, such as a waiting period between signing the consent form and undergoing the procedure or gestational age restrictions.

- **Chorioamnionicity**

Chorioamnionitis is best diagnosed by ultrasound in the first trimester.

This information is vital because of the potential consequences for the twin, including neurological injury and death, when placental vascular anastomoses are present in monochorionic multiple pregnancies. Cardioplegia with intracardiac injection of potassium chloride, which is commonly used for MPR in multichorionic multiples, is not appropriate in monochorionic multiples, which requires a different technique.

- **Programming**

MPR is usually performed between 10^{+0} and 13^{+6} weeks of gestation, although it can be performed at any gestational age at which legal termination of pregnancy is possible. Reduction at this early gestational age allows parents to undergo the procedure while the pregnancy is relatively private, allows time for most spontaneous fetal losses to occur, and allows at least some assessment of fetal health. Options for fetal assessment prior to MPR, as discussed below, should be reviewed and MPR planned accordingly.

The risk of pregnancy loss associated with the procedure is considered to be low at this gestational age. There may be a slight increase in the risk of loss at 6 to 8 weeks (Haas *et al.,* 2016) and after 16 to 18 weeks of gestation (Evans *et al.,* 1999) , but data are inconsistent.

- **Fetal evaluation**

A study of fetal anatomy is performed prior to MPR to look for structural abnormalities and markers of aneuploidy, such as increased nuchal translucency or absence of a nasal bone. A detailed first-trimester anatomical assessment at 12^{+0} and 13^{+6} weeks will maximize assessment, but even before 12 weeks, many fetal abnormalities will be detected (' AIUM Practice Parameters for the Performance of Detailed Diagnostic Obstetric Ultrasound Examinations Between 12 Weeks 0 Days and 13 Weeks 6 Days ', 2021) . 40% of fatal abnormalities can be detected by the end of the first trimester. However, this early assessment should not replace a comprehensive anatomical survey at 18 to 22 weeks' gestation, which will detect more abnormalities (Bromley *et al.,* 2014) . As evaluation of first-trimester fetuses is limited, patients should be clearly advised that the continued health of unreduced fetuses cannot be guaranteed. Although rare, there are cases in which unreduced fetuses are diagnosed with congenital or acquired abnormalities later in gestation.

Chorionic villus sampling (CVS) can be performed on one or more fetuses prior to MPR. Performing CVS prior to MPR does not appear to increase the postoperative pregnancy loss rate above that of MPR and may reduce losses (Eddleman *et al.,* 2000; Bromley *et al.,* 2014) . CVS can be performed on all fetuses or only on fetuses not scheduled for reduction.

The increasing use of preimplantation genetic testing for aneuploidy (PGT-A) has caused controversy regarding the usefulness of performing CVS before or after MPR, but PGT-A may not be definitive, so it is still recommended the confirmatory test with CVS (Brezina *et al.,* 2016) .

At the time of CVS, an accurate description, as well as a diagram of the absolute and relative positions of the gestational sacs and placenta, should be carefully recorded so that if an abnormal karyotype is identified, it can be correctly matched to the affected fetus, as many karyotypically abnormal fetuses will be indistinguishable from normal fetuses at this gestational age. Attention must also be paid to the relative fullness of the maternal bladder, as filling and emptying of the bladder can alter the apparent position of the sacs/placentas. Diagnostic error due to mismatching of genetic test results to the fetus or sampling error has been reported in 0.6 to 0.8% of twins and up to 1.2% of higher order multiple pregnancies (Pergament *et al.,* 1992; Wapner *et al.al.,* 1993; De Catte, Liebaers and Foulon, 2000; Eddleman *et al.,* 2000; Agarwal and Alfirevic, 2012) .

- **Final number of fetuses for triplets and higher order multiples**

Most higher order multiple pregnancies are reduced to twins, as many patients desire the birth of twins rather than a singleton after years of infertility (Gleicher *et al.,* 1995; Pinborg *et al.,* 2003; Child, Henderson and Tan, 2004; Ryan *et al., 2004). al.,* 2004) . However, the reduction of triplet and higher order multiple pregnancies in singletons is becoming more common and associated with good outcomes (Stone *et al.,* 2002, 2008; Brambati *et al.,* 2004) . More data are needed to determine whether reducing these pregnancies to singletons significantly improves pregnancy outcome over twinning, which usually has good pregnancy outcomes compared with higher order multiple pregnancies.

Technique

Fetuses selected for MPR are generally closer to the anterior uterine wall and/or fundus, as these locations are more accessible for needle insertion. However, if a fetus has delayed cephalocaudal length, a significantly smaller sac, markers suggestive of aneuploidy, or an obvious abnormality, then that fetus is

preferentially selected for MPR, as these findings are associated with adverse pregnancy outcome (e.g., miscarriage, fetal aneuploidy).

The most common technique uses a transabdominal (TA) approach. A transcervical or transvaginal approach can be used, but these have been associated with high rates of pregnancy loss after surgery compared with the TA approach. Therefore, these approaches are usually reserved for situations in which the TA approach is not technically feasible (Evans *et al.*, 1994) . The majority of MPR can be done with the TA approach.

Antibiotic prophylaxis is not routinely recommended as no benefit has been established.

The procedure is usually performed by injecting approximately 2 to 3 mL of potassium chloride (concentration 2 mEq KCl/mL) into the fetal thoracic cavity using a 22-gauge spinal needle under ultrasound guidance. Cardiac asystole usually occurs within one minute of injection, and the total procedure time is usually less than five minutes. Additional fetuses can be reduced with the same needle puncture or, more commonly, with a separate needle puncture. Lidocaine, digoxin, hyperosmotic urea, and saline cardiac tamponade have also been used successfully to induce asystole, although they are more commonly used at later gestational ages (Chen *et al.*, 2009) .

An ultrasound examination is usually performed one hour after the procedure to confirm asystole in reduced fetuses and cardiac activity in non-reduced fetuses. If fetal heart activity has resumed in reduced fetuses, which is rare, the procedure is repeated.

Post-interventional assessment factors and follow-up

A small amount of contractions or leakage of amniotic fluid from the sac or sacs of the reduced fetus or fetuses may occur. Vaginal bleeding is uncommon, so patients with bleeding should be evaluated for possible causes.

An ultrasound examination is performed to confirm the fetal well-being of the remaining fetuses one to two weeks after the procedure. The reduced fetus(es) are typically dried and compressed over time and embedded in the fetal membranes/placentas of the unreduced fetus(es).

Laboratory changes after MPR and ST are described below.

Monthly ultrasounds are recommended for fetal development in the third trimester. Lower birth weights have been observed in singleton fetuses reduced by triplets or higher order multiples than in singleton fetuses reduced by twins (2489-2897 grams [in a singleton fetus from triplets or more] vs. 3122 grams [in a singleton from twins]) (Stone *et al.*, 2008) .

Prenatal care is otherwise routine care and depends on the number of fetuses remaining.

Prenatal evaluation of fetal well-being (e.g., NST) is not indicated for otherwise uncomplicated pregnancies. It should be reserved for routine obstetric indications.

MPR does not affect decision-making about mode of delivery. However, whenever possible, obstetricians should know the history of MPR to minimize the risk of retention of gestational material. Although reduced fetuses/placentas are usually born with the placenta of non-reduced fetuses, there is a small risk of retained gestational material. The placenta should be carefully examined for the presence of a reduced fetus/sac, which can be identified in most cases.

Psychosocial outcomes

The decision to undergo MPR, usually after many agonizing years of infertility, is difficult for most patients. Being selective about sharing information about fertility and infertility treatments, pregnancy, and MPR with family, friends, and acquaintances can help reduce the stress associated with these issues (Britt and Evans, 2007; Evans and Britt, 2008) .

Long-term psychosocial outcomes were illustrated in a prospective study comparing patients who underwent MPR over a two-year period with those who did not reduce their triplet pregnancy (Garel *et al.*, 1997) . Although many women in the MPR group expressed regret and guilt a year after the birth of the remaining fetuses, the majority overcame the pain associated with the reduction at two years. Furthermore, compared to mothers of nonreduced triplets, mothers who had undergone MPR had less anxiety and depression and a more satisfying relationship with their children (Garel *et al.*, 1997) .

Pregnancy outcome

No randomized trials have been performed for MPR, as randomization in this setting would not be acceptable to most couples and may not be ethically appropriate (Dodd, Dowswell and Crowther, 2015) .

Data from observational studies consistently show that pregnancy outcomes after MPR, particularly preterm birth rates, are significantly improved. Results also improve with increased operator experience (Evans *et al.*, 2001; Stone *et al.*, 2002) .

- **Downsizing from triplets to twins**

MPR from triplet to twin pregnancy is associated with later gestational age at birth and a reduction in obstetric complications (Zipori *et al.*, 2017; Karamustafaoglu Balci *et al.*, 2022) .

- A 2017 meta-analysis including 24 studies comparing twin-reduced versus unreduced (conservatively managed) triplet pregnancies provided useful data for counseling triplet patients about the pregnancy outcomes of MPR (Zipori *et al.,* 2017) :
  - Preterm birth- Decrease in twins was associated with the following:
    - ✓ Delivery at a later gestational age (mean difference 2.61 weeks, 95% CI 2.09-3.12)
    - ✓ 60 to 70% reduction in preterm birth (<32 weeks' gestation: OR 0.30, 95% CI 0.22-0.41, <28 weeks' gestation: OR 0.40, 95% CI 0.22-0.71)
    - ✓ Reduction in neonatal mortality (OR 0.36, 95% CI 0.15-0.83)
    - ✓ Greater birth weight (mean difference 500 g, 95% CI 439.95-560.04)
  - Other adverse pregnancy outcomes also improved in the reduction group:
    - ✓ Gestational diabetes (OR 0.35, 95% CI 0.19-0.67)
    - ✓ Hypertensive disorder of pregnancy (OR 0.47, 95% CI 0.31-0.72)
    - ✓ Need for prenatal care (OR -10.46, 95% CI -17.12 to -3.81)
    - ✓ Cesarean delivery (OR 0.18, 95% CI 0.10-0.33)
  - Pregnancy loss - The risk of pregnancy loss before 24 weeks' gestation was similar in both groups (7.4 vs. 8.1 %, OR 0.87, 95% CI 0.52-1.42).
- Another 2017 meta-analysis separately assessed the outcomes of continued trichorionic triamniotic pregnancies (TCTA) and dichorionic triamniotic triplet pregnancies (DCTA) versus those electively reduced to twins (Anthoulakis *et al.,* 2017) .
  - In TCTA pregnancies, the reduction was associated with a significant reduction in preterm delivery <34 weeks (17.3 vs 50.2 %, OR 0.36, 95% CI 0.28-0.48), without a significant increase in miscarriage rate (8.1 vs. 7.4 %, OR 1.08, 95% CI 0.58-1.98).
  - In DCTA pregnancies, continuing pregnancies had a high rate of preterm delivery <34 weeks (51.9 %), which was only modestly reduced (to 46.2 %) by selective reduction of triplets with separate placenta, but these cases were very few to allow safe conclusions about the utility of the procedure in DCTA pregnancies.

➢ **Reduction from twins to singletons**

A reduction in singletons from twins has been associated with improved pregnancy outcomes. Supporting data include the following:

- A 2020 systematic review and meta-analysis of six studies involving 7398 participants showed that MPR of dichorionic twins in singletons was associated with a 30% lower risk of preterm delivery (five studies, RR 0.30, 95% CI 0.22 -0.40, p<0.001) and higher birth weight (four studies, mean differences 548.1 grams, 95% CI 424.04-672.15, p<0.001) than wait-and-see management (Jin *et al.*, 2020) . They also found no difference in miscarriages between reduced and non-reduced pregnancies.
- In a retrospective review comparing pregnancy outcomes of twin pregnancies reduced to singletons (number = 250) with continued (unreduced) twin pregnancies (number = 605) (Vieira *et al.*, 2019) , MPR was associated with:
  - Higher average gestational age at delivery (39 vs. 36.7 weeks)
  - Reduction in preterm birth <37 weeks (18 vs 54 %) and <34 weeks (7 vs 17 %)
  - Birth weight reduction <10th percentile (15 vs 38%)
  - Birth weight reduction <5th percentile (9 vs. 22%)
  - Reduction in cesarean delivery (47 vs. 79%)
  - Reduction in pre-eclampsia (4 vs 17 %)
  - Reduction in pre-term premature rupture of membranes (6 vs 19 %)
  - Reduction in gestational diabetes (5 vs. 9%)
  - No significant increase in unintended pregnancy loss <24 weeks (2.4 vs 2.3%)

➢ **Higher order pregnancies reduced to twins versus to singletons**

In a single-center observational series of 841 MPRs with known outcome, the pregnancy loss rate for patients reducing from a multiple gestation (2 to 5+) to twins was higher than for reduction to singleton (5.3 vs. 3 .8 %) (Stone *et al.*, 2008) . Specifically, the loss rates for quintuplets, quadruplets and triplets in twins were 12.1, 5.8 and 4.5%, respectively. Loss rates for quintuplets, quadruplets, triplets and twins in singletons were 0.4, 6.1 and 2.1%, respectively.

The mean gestational age at delivery was inversely proportional to the final numbers: the mean gestational age at delivery of singletons, twins and triplets was 38.0, 35.2 and 30.3 weeks.

5.2. Selective termination in multiple pregnancies

Definition

The selective termination (ST, selective termination) refers to a procedure in which one or more specific fetuses of a multiple pregnancy are terminated due to a known or suspected fetal abnormality, including a chromosomal, structural, genetic or developmental abnormality, which has been detected by ultrasound examination or by definitive fetal diagnosis after amniocentesis or chorionic villus sampling. This is in contrast to MPR, in which fetuses are selected randomly, but taking into account technical factors.

Reasoning

ST was initially offered as an option to parents of fetuses with significant non-fatal abnormalities that could result in the birth of a live newborn and the long-term survival of a severely disabled child. ST is now also offered to parents of fetuses with fatal abnormalities because, for some parents, it is emotionally preferable to undergo ST rather than continue to carry a fetus that will die before or shortly after birth. In addition, it is thought that, in some cases, termination of the abnormal fetus may optimize the outcome of the other normal fetus or fetuses. For example, anencephaly, a fatal anomaly, is often complicated by severe polyhydramnios due to impaired fetal swallowing, which increases the risk for preterm birth. Termination of the anencephalic fetus and subsequent resolution of polyhydramnios can theoretically reduce the risk of preterm delivery and improve the outcome for the other twin with extended gestation. Another example is when a twin is dropsy. ST of one hydropic twin has been reported to reverse preeclampsia when the other twin is normal (Heyborne and Porreco, 2004) .

Pre-interventional assessment factors

- **Local regulations**

In many states in America, ST is considered a form of abortion and, as with MPR, it is important to know the law in the state/country where the ST is performed as well as any special legal arrangements, such as a waiting period between signing of the consent form and the performance of the operation and restrictions on gestational age. Third-trimester abortion is legal in some states in the United States and in many countries.

- **Evaluation of fetuses**

The first step is to correctly identify the fetus to be terminated. Previously diagnosed fetal abnormalities, particularly genetic disorders in which the fetus may appear sonographically normal, are not always apparent at the time of ST. Correct identification of the affected fetus can be made by ultrasonographic detection of a structural abnormality (if present), by sex (if different between fetuses), or by previously documented location of fetuses, gestational sac, and/or placenta. Using dye at the time of a previously performed invasive diagnostic test is typically not useful at the time of ST, as the dye may not remain in the amniotic fluid long enough. Therefore, accurate intrauterine mapping of fetal and placental location at the time of prenatal diagnosis is critical. A description and recording of the image of the sacs/placenta is performed in three planes (axial, sagittal and coronal).

If there is any doubt as to the correct identification of the affected fetus at the time of ST, rapid fetal karyotyping by fluorescence in situ hybridization (FISH) can be performed before the procedure (assuming the abnormality is detected by FISH). FISH results are usually available within 48 hours. Although the fetuses will move, the relationship of each sac to the other sac(s) and the position/appearance of the placenta will not change much in these 48 hours. Performing FISH prior to ST is particularly useful if the initial diagnostic genetic procedure was performed at another institution.

- **Chorioamnionicity**

As with MPR, accurate determination of chorionicity is crucial before performing ST, as termination techniques differ for dichorionic versus monochorionic pairs (intrathoracic potassium chloride infusion versus umbilical cord occlusion).

Dichorionic fetuses

- **Gestational age**

In experienced hands, ST is safe and effective at any gestational age, but should occur soon after the decision to terminate has been made.

- **Technique**

Potassium chloride is injected into the thoracic cavity (ideally intracardially) of the affected fetus under ultrasound guidance until asystole is confirmed, similar to the technique used for MPR. Digoxin or lidocaine may also be used, although the time to asystole may be longer.

- **Follow-up after surgery**

An ultrasound is performed one hour after the procedure to ensure asystole of the terminated fetus and normal cardiac activity of the remaining fetuses. In addition, ultrasound examinations are performed to confirm the well-being of the remaining fetuses one to two weeks after the operation, and monthly ultrasounds are performed to monitor fetal development in the third trimester.

Since ST is usually performed at a later gestational age than MPR and with a larger fetus, the terminated fetus is generally not absorbed. Over a period of weeks to months, however, the amniotic fluid around the fetus will disappear and the fetal tissue will be significantly compressed. The dead fetus is usually born together with the placenta, without the patient perceiving its delivery as separate from the expulsion of the placenta. It can be sent for histological examination, but is usually too soaked for any meaningful evaluation. Care should be taken to ensure that there is no retained gestational material in the uterus.

- **Pregnancy outcome**

In ongoing pregnancies, the outcome after ST is generally favorable, with low rates of prematurity and few maternal complications (Eddleman *et al.,* 2002; Bigelow *et al.,* 2014) . In two large series, the median gestational age at delivery after ST for ongoing pregnancies (some multiple pregnancies) was 35.7 and 37.1 weeks (Evans *et al.,* 1999; Eddleman *et al.,* 2002) .

The overall rate of pregnancy loss before 24 weeks' gestation after first or second trimester ST was 4.0% in the largest single-center series of 200 patients (Eddleman *et al.,* 2002) and 7.5% in the largest collaborative experience of 402 patients (Evans *et al.,* 1999) . The lowest rate of loss (2.4 %) after ST is observed with an initial number of two fetuses (Eddleman *et al.,* 2002) . This rate increased significantly to 11.1% when the pregnancy started with three or more fetuses. The most striking increase in postoperative loss rates was observed when more than one fetus was terminated: 42.9 versus 2.6% when only one fetus was terminated. The reason for the higher rate of multifetal loss with ST than with MPR is unclear, but may be a result of small numbers in these series or later gestational age at the time of surgery. The effect of gestational age on the loss rate after surgery is unclear, as the data were inconsistent. Some studies have reported a trend toward higher pregnancy loss and preterm birth rates for ST after 20 weeks (including third-trimester ST) than for ST ≤20 weeks (Lynch *et al.,* 1996; Evans *et al.,* 1999; Bigelow *et al.,* 2014) , while others observed a trend towards a higher rate of pregnancy loss with ST ≤20 weeks compared to ST performed later (Eddleman *et al.,* 2002) .

Monochorionic fetuses

- **Gestational age**

The results seem to be better if the procedure is done after 18 weeks of pregnancy. However, surgery is usually performed once the decision for ST is made.

- **Technique**

The conventional technique of potassium chloride injection assumes multichorionic placentas, which do not contain vascular anastomoses between the fetuses. If two fetuses are monochorionic and therefore share a circulation, and if one is reduced by an injection of toxin, then there is a possibility that the toxin will also enter the circulation of the other twin and cause fetal death (Benson *et al.,* 1998) . In addition, acute adverse hemodynamic changes could occur in the surviving fetus, due to blood loss in the vasculature of the terminated fetus, and could lead to neurological damage. Therefore, if a fetus in a monochorionic pregnancy needs to be terminated, an alternative technique should be used (De Catte, Camus and Foulon, 2002; Lewi *et al.,* 2003; Athanasiadis *et al.,* 2005) .

Possible approaches to ST in monochorionic twins include open surgical procedures (via hysterotomy), endoscopic procedures (febroscopy), and ultrasound-guided needle techniques. Regardless of the approach, the most common method for ST is umbilical cord occlusion because it reduces the risk to the other twin by separating the fetal vascular systems.

Cord occlusion can be performed with a variety of techniques, including bipolar coagulation, laser ablation, photocoagulation, radiofrequency ablation, or suture ligation. Radiofrequency ablation has become the preferred cord occlusion technique (Ville *et al.,* 1994; Dommergues *et al.,* 1995; Deprest *et al.,* 1996, 2000; Quintero *et al.,* 1996; Rodeck, Deans and Jauniaux, 1998 ; Denbow *et al.,* 1999; Nicolini *et al.,* 2001; Taylor, Shalev, *et al.,* 2002; Tsao *et al.,* 2002; Shevell *et al.,* 2004; Robyr *et al.,* 2005; Rustico *et al.,* 2005; Lewi *et al.,* 2006; Moise *et al.,* 2008; Paramasivam *et al.,* 2010; Wimalasundera, 2010) . However, the optimal technique has not been established, as most studies consist of single case reports or small case series, and technical factors (e.g., umbilical cord diameter and length) may influence the choice of procedure.

Using thinner instruments and minimizing operating time can reduce the rate of preterm birth and pregnancy loss (Lanna *et al.,* 2012) . Complication rates have decreased over time as the size of surgical needles and trocars has decreased (Roman *et al.,* 2010) .

- **Follow-up after surgery**

Follow-up after surgery is the same as for dichorionic fetuses.

- **Pregnancy outcome**

A systematic review of studies of umbilical cord occlusion for selective feticide in monochorionic twins included 345 cases performed at 14 to 35 weeks' gestation between 2000 and 2008 (Rossi and D' Addario, 2009). The main findings were:

- Survival of the other twin was higher if the procedure was performed after 18 weeks' gestation (89 vs. 69%).
- Survival after radiofrequency ablation, bipolar cord coagulation, laser cord coagulation, and cord ligation was 86, 82, 72, and 70%, respectively. The majority of unterminated fetal deaths occurred within two weeks of surgery. The overall neonatal death rate was 4%.
- 3% of procedures failed due to technical difficulties or complications such as bleeding.
- Preterm rupture of membranes complicated 22 % of pregnancies and preterm delivery ≤34 weeks occurred in 33 %.
- 7% of surviving fetuses experienced neonatal morbidity related to neurological damage or secondary to prematurity.

A more recent prospective observational study of 100 consecutive cases of ST between 12.1 and 27.6 weeks' gestation using radiofrequency ablation reported the following findings (Kumar *et al.*, 2014) :

- 78% of patients had at least one live birth.
- Median gestational age at delivery was 35.2 weeks (range 24 to 41 weeks) and median birth weight was 2494 g (range 694 to 4480 g).
- The spontaneous loss rate <24 weeks was 6%. Half of the fetuses from this percentage regressed within two weeks of the operation.
- There was no difference in survival if the operation was performed before or after the 20th week of gestation.
- The death rate of unterminated twins was 12% and, overall, there were three cases (3%) of brain damage on post-procedure MRI.

- **Maternal complications**

In a systematic review of 1239 ST procedures performed with fetoscopic radiofrequency ablation, the overall incidence of maternal complications was 5.2 % (95% CI 3.00-7.96), and consisted mainly of chorioamnionitis (19/54), detachment (14/54) and intraoperative bleeding (10/54) (Sacco *et al.,* 2019) . In this review, preterm premature rupture of membranes, separation of the chorionic membranes, preterm onset of labor and preterm delivery were considered obstetric rather than maternal complications and were therefore not reported.

5.3. Laboratory changes after multifetal pregnancy reduction or selective termination

The concentration of maternal serum alpha-fetoprotein (MSAFP) is usually elevated for several weeks after any fetal reduction procedure and is not necessarily indicative of fetal defects (Grau *et al.,* 1990) . The increase is probably caused by the release of tissue or serum from the reduced fetus or fetuses. Since MSAFP is always elevated, it should not be used to screen for neural tube defects. Instead, a detailed ultrasound should be done.

If fetal genetic studies were not performed prior to MPR or ST, then maternal serum tests for Down syndrome, such as the quadruple test, should not be performed after such procedures, as the presence of reduced fetuses will result in a high abnormal results. Noninvasive prenatal diagnostic tests that assess free fetal DNA in the maternal circulation should also generally be avoided because DNA from reduced fetuses may be present in the maternal circulation. Given the reduced reliability of maternal serum/blood screening tests after MPR and ST, detailed assessment of fetal development by ultrasound remains the preferred means of screening unreduced fetuses for neural tube defects and markers associated with aneuploidy. Diagnostic testing performed on amniotic fluid or villi can also be used, as it is not affected by a history of MPR or ST.

Laboratory evidence of coagulation disorders has been observed, but no cases of clinically apparent disseminated intravascular coagulation have been reported (Berkowitz, Stone and Eddleman, 1997) .

One study reported that MPR did not affect the validity of the fetal fibronectin test, performed later in pregnancy (Roman *et al.,* 2004) .

6. Prenatal care in multiple pregnancies

6.1. Education and promotion of the health of pregnant women with multiple pregnancies

6.1.1. Weight gain in multiple pregnancies

Twin pregnancy

The National Academy of Medicine in the US (formerly the Institute of Medicine) made the following recommendation for total weight gain for women carrying twins to term pregnancy ") (Institute of Medicine (US) and National Research Council (US) Committee that Reexamine IOM Pregnancy Weight Guidelines . Rasmussen KM, Yaktine AL, editors, 2009) :

- Body mass index (BMI) <18.5 kg/m ^{2} (underweight subjects) - No recommendations due to insufficient data.
- BMI 18.5 to 24.9 kg/m ^{2} (normal weight) - Weight gain 37 to 54 lb (16.8 to 24.5 kg).
- BMI 25.0 to 29.9 kg/m ^{2} (overweight people) - Weight gain 31 to 50 lb (14.1 to 22.7 kg).
- BMI ≥30.0 kg/m ^{2} (obese subjects) – Weight gain 25 to 42 lb (11.4 to 19.1 kg).

These limits represent weight gain from the 25th ^{to} the 75th percentile in women who gave birth to twins weighing at least 2500 g. Women who met these guidelines generally had fewer preterm deliveries and higher birth weights compared to those who did not meet the minimum guideline-recommended weight gain, while exceeding the guideline generally increased maternal risks of gestational hypertension/preeclampsia, of eclampsia and caesarean section (Lin *et al.*, 2021, Lipworth *et al.*, 2022) . Poor gestational weight gain after 20 weeks appears to have a greater impact than poor first trimester weight gain (Pettit *et al.*, 2015) . Thus, reassurance is suggested in early pregnancy of women who cannot meet caloric intake or weight gain recommendations due to nausea and vomiting or other reasons.

To achieve adequate gestational weight gain, a woman entering pregnancy with a BMI in the normal range must increase her dietary intake by approximately 300 kcal/day above that for a singleton pregnancy or 600 kcal/day above that of a nonpregnant woman. After 20 weeks of gestation, weight gain should be about 1.75 lb (0.8 kg)/week for underweight pregnant women and about 1.5 lb (0.7 kg)/week for normal-weight pregnant women, with same or slightly lower weekly weight gain in pregnant women who are overweight or obese.

Triplet pregnancy

There are no documented weight gain and dietary guidelines for triplet pregnancies. Weight gain goals, which reflect the US National Academy of Medicine (formerly the Institute of Medicine [IOM]) gestational weight gain guidelines for late-gestation twin pregnancies, are commonly used.

However, almost no triplet pregnancies make it to term (>37 weeks of gestation). A more practical clinical recommendation is for maternal weight gain of approximately 0.7 kg (1.5 lb) per week and >16.2 kg (36 lb) by 24 weeks' gestation, as weight gain below limit has been associated with lower birth weight in triplets (Flidel - Rimon *et al.*, 2005) .

Some authorities believe that these pregnancy weight gain targets are too high. The target described above for pregnant women with obesity is particularly controversial. For pregnant patients with obesity and singleton gestation, gestational weight gain less than that recommended by the National Academy of Medicine may be associated with better maternal and perinatal outcomes, and this may also be true for pregnant women with obesity and triplet gestation.

6.1.2. Nutrition and supplements in multiple pregnancies

Twin pregnancy

The Society for Maternal-Fetal Medicine has provided caloric requirements and supplementation recommendations for twin pregnancy (Goodnight, Newman, and Society of Maternal–Fetal Medicine, 2009).

Triplet pregnancy

Recommendations for daily intake of micronutrients are based on existing data for twin pregnancies, as outlined by the Society for Maternal-Fetal Medicine (Goodnight, Newman, and Society of Maternal – Fetal Medicine, 2009) . One or two multivitamins or a prenatal vitamin may be taken daily. The vitamin content varies depending on the product selected.

6.1.3. Physical activity and exercise in multiple pregnancies

Twin pregnancy

In early pregnancy, women with uncomplicated twin pregnancies can generally follow the same exercise/physical activity recommendations as singleton pregnancies. The physician should assess

individual risk factors for preterm birth and advise the pregnant woman accordingly. As pregnancy progresses, physical changes generally limit the duration and type of exercise performed. Although case reports describe elite athletes who trained until delivery despite a twin pregnancy, some limitation of activity is generally desirable and prudent. Recommendations for individual women may depend on factors such as overall health status, recommended exercise regimen, and musculoskeletal factors.

Women often ask about work and sexual activity during pregnancy. Guidance is the same as for women with singleton pregnancies, with no restrictions for uncomplicated pregnancies. For patients with complications such as vaginal bleeding, short cervix, placenta previa, or vas deferens, restrictions on sexual activity are prudent and reasonable.

Triplet pregnancy

There is no consensus on physical activity for pregnant women carrying triplets due to a lack of definitive data. Most activity recommendations are, in general, similar to those for singleton pregnancies, especially before 20 weeks' gestation.

After about 20 weeks of pregnancy, many pregnant women with triplets want to limit physical activity due to fatigue and physical discomfort. In the mid to late second trimester, the uterus enlarges to a size comparable to that of a singleton pregnancy at term. These women can rest and reduce activity inside and outside the home as needed.

Sexual intercourse does not appear to increase the risk of preterm birth (Yost *et al.*, 2006) . Abstinence is not necessary.

6.2. Screening in multiple pregnancies

6.2.1. Screening for chromosomal abnormalities of fetuses

6.2.1.a. Screening for fetal chromosomal abnormalities

Twin pregnancy

For dizygotic twin pregnancies, the risk of at least one affected fetus is considered to be twice the risk of a singleton pregnancy for the corresponding maternal age (eg at age 35: 2 x 1/350 at delivery) and the risk of two affected of fetuses is assumed to be the product of the mother's singleton pregnancy risk (eg at age 35: 1/350 x 1/350 at delivery).

Although at least one study reported that observed rates of Down syndrome in twin pregnancies were lower than expected, possibly due to an increased incidence of early fetal loss (Sparks *et al.,* 2016) , more data are needed before risk estimates for Down syndrome can be adjusted.

A monozygotic twin pregnancy is thought to have the same risk of Down syndrome as a singleton pregnancy. Both fetuses will be affected or both fetuses will be unaffected. Rarely, however, these twins have different genotypes due to postzygotic events, including nonsegregation and mosaicism (Nieuwint *et al.,* 1999; Edlow *et al.,* 2011) . It may also be discordant for X-inactivation (in females), differential gene imprinting, and smaller-scale genetic abnormalities such as microdeletions (Peng *et al.,* 2016) .

For women who choose to be screened for Down syndrome, either the combined first-trimester test or free fetal DNA (cffDNA) in maternal blood is recommended. While the combined test provides early, fetus-specific risk assessment, cffDNA has higher detection rates.

- **Non-invasive prenatal testing using free fetal DNA**

Non-invasive prenatal screening for Down syndrome using cffDNA is difficult. Because cffDNA in the maternal circulation originates from each fetus, the mean fetal fraction for each twin is lower than that for singleton fetuses (although the total fetal fraction is higher in twin pregnancies), and the fetal fraction may differ between twins by at least 1.5 times in 10% of cases (Palomaki *et al.,* 2021) . Testing is commercially available for trisomies 13, 18, and 21, although fewer validation data are available from twin pregnancies than from singleton pregnancies (Lau *et al.,* 2013; Leung *et al.,* 2013; Huang *et al.,* 2014) . Increasing data indicate that the sensitivity of cffDNA for Down syndrome in twins is similar to that in singleton pregnancies. Studies also generally report a higher failure rate of the test in twins (Galeva *et al.,* 2019; Gil *et al.,* 2019; van Riel *et al.,* 2021) , but there are exceptions (Khalil *et al.,* 2021) .

A bulletin from the American College of Obstetricians and Gynecologists states that cffDNA testing for Down syndrome can be done in twin pregnancies, and the available performance data are encouraging, but the total number of reported affected pregnancies is small, thus preventing an accurate evaluation of performance. (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics, Committee on Genetics, and Society for Maternal-Fetal Medicine, 2020) . The International Society for Prenatal Diagnosis position statement on population-based cffDNA screening for Down syndrome in multiple pregnancies concluded that cffDNA screening for common trisomies in twins provides higher positive predictive values compared to serum screening and nuchal translucency testing

(Palomaki *et al.,* 2021) . Test failures occur at a median of 3.6% of cases (range 1.6 to 13.2%), which is higher than the rate in singleton pregnancies and is usually due to low fetal fraction.

- **First trimester combined test**

Increased nuchal translucency (NT) is a marker for Down syndrome, other aneuploidies, congenital malformations, and the development of TTTS. Combined first-trimester testing, consisting of ultrasound measurement of NT plus serum markers (beta human chorionic gonadotropin [β-hCG] and pregnancy-associated plasma protein [PAPP-A]) may provide a specific fetal risk assessment for SCI Down in twin pregnancies.

Interpretation of maternal serum markers alone is problematic in twin pregnancies, as both fetuses contribute to marker concentration, and because marker levels may be affected by the early loss of one or more multiple fetuses (Chasen, Perni, *et al.,* 2006; Spencer, Staboulidou and Nicolaides, 2010) . Measuring NT can improve the detection rate and, importantly, help identify the affected fetus (Spencer and Nicolaides, 2003; Chasen *et al.,* 2007) . In a systematic review of combined first-trimester risk assessment (NT and maternal serum markers) in twin pregnancies, the sensitivity of the tests in dichorionic twin pregnancies was 86 % (95% CI 73-94) and the sensitivity of the test in monochorionic twins was 87 % (95% CI 53-98) (Prats *et al.,* 2014) .

It is worth noting that the false-positive rate of population control is higher in monochorionic than in dichorionic twins, because elevated NT can be an early manifestation of TTTS syndrome as well as an indicator of aneuploidy (Stagnati *et al.,* 2017) . Also, in vitro fertilization (IVF) affects the levels of serum markers used in screening for Down syndrome and may be taken into account by some laboratories when calculating screening results in twins conceived by this method (Maymon *et al.,* 2005) .

In particular, for monoamniotic twins, due to the complexity of aneuploidy screening, referral to a genetic counselor is recommended if possible. Standard methods for screening for Down syndrome can be used (e.g., cffDNA testing, maternal serum biomarkers, and ultrasound markers). For population-based screening tests that include nuchal translucency (NT, combined first-trimester test), the formula for determining pregnancy-specific risk of aneuploidy uses the mean nuchal translucency at 11 $^{+0}$ to 13 $^{+6}$ weeks of gestation for the two fetuses (Prats *et al.,* 2012) .

It is also worth emphasizing that fetuses with the same genotype may have different phenotypes. For example, only one twin fetus with Down syndrome may have elevated NT. In a series of eight monochorionic twin pairs discordant for NT that were karyotyped, discordance was a marker for

concordant chromosomal abnormalities in one twin pair and for discordant chromosomal abnormalities in two twin pairs (Edlow *et al.*, 2011) .

Triplet pregnancy

Genetic counseling is recommended for all pregnant women with triplet pregnancies to discuss the risk of aneuploidy in one or more fetuses. The risk of aneuploidy in a trizygotic triplet pregnancy is higher than in a singleton or dizygotic twin pregnancy, since there are three independent risks for aneuploidy in the fetus. The risk of trisomy 21 of a fetus of a 28-year-old woman carrying a trizygotic triplet pregnancy is similar to the risk of trisomy 21 of a fetus of a 35-year-old woman carrying a singleton pregnancy (Malone FD and D ' Alton ME, 2005) . Thus, the conventional application of advanced maternal age as applied to the risk of aneuploidy can be considered as maternal age ≥28 years at the estimated date of delivery.

The distribution of nuchal translucency measurements is the same in triplets as in singletons, so NT can be used to screen for trisomy 21 and other anomalies (Maslovitz *et al.*, 2004) . Elevated NT (defined as greater than the 95th percentile for gestational age) has been validated as a screening test for trisomy 21 and trisomy 18 in triplets based on one study (Sepulveda, Wong and Casasbuenas, 2009) . In this study, five of six aneuploid fetuses had increased NT (three cases of trisomy 21, one case of trisomy 18, and one case of X chromosome monosomy, one 45,X/46,XX mosaic omitted).

No serum marker or free fetal DNA (cffDNA) test for aneuploidy has been validated in triplet and higher order multiple pregnancies, and no study has published observed detection rates for Down syndrome and other common trisomies in triplet pregnancies. Given the rarity of triplet pregnancies and the reluctance of clinicians to offer serum or c f fDNA-based testing in this group, it is unlikely that the type of data set now available for twins will ever be available for triplet pregnancies. However, with the limited data available and acknowledging a test failure rate of up to 20%, the International Society for Prenatal Diagnosis position statement on cfDNA testing for Down syndrome in triplet pregnancies states that cfDNA testing may be a possible option, but screening should always be offered and the limitations of screening tests in triplet pregnancies should be emphasized (Palomaki *et al.*, 2021) .

6.2.1.b. Diagnostic testing for chromosomal abnormalities of fetuses

Twin pregnancy

Both fetuses should be karyotyped when karyotyping, as even monozygotic twins can be discordant. Issues related to twin diagnostic genetic testing by chorionic villus sampling (CVS) and amniocentesis are discussed separately. According to the NICE Institute, CVS is preferred in dichorionic twin pregnancies because it can be performed earlier than amniocentesis (National Guidelines Alliance (UK), 2019) . Early detection of aneuploidy is very important in twin pregnancies, given the lower risk of elective termination in the first trimester compared to the second trimester (7% risk of whole pregnancy loss and 14% risk of delivery before 32 weeks) (Evans et al ., 1999) .

- **Chorionic villus sampling**

Ultrasonographic determination of chorionicity of multiple pregnancies is essential prior to CVS, as chorionicity determines the number of samples to be obtained. Furthermore, an accurate map of the fetal to placental relationship in multiple pregnancies is critical for the accurate performance of selective termination later in pregnancy.

CVS in twins can be performed using a transabdominal (TA), transcervical (TC) or combined approach (transabdominal for one twin, transcervical for the other). One or two samplings are required, regardless of the technique.

- Only one specimen is required in the presence of monochorionic twins (i.e., only one distinct placental mass and either an absent septal membrane, or a common membrane with a placental rebound site without a peak and thin septal membranes). However, case reports have reported discordant karyotypes in monozygotic twins. Therefore, some clinicians sample both fetuses when an abnormality is present.
- If separate placentas are present, the procedure is similar to CVS for a singleton pregnancy (but with two separate needle insertions). The combination of TA-CVS and TC-CVS may be necessary in some cases to prevent contamination between twins: a typical example is when one placenta is anterior and the other is posterior. If access to the posterior placenta with a TA approach requires crossing the anterior placenta, TC-CVS should be used in the posterior placenta. Cytogenetic results (if the sex of the fetuses is discordant) and DNA polymorphisms, if requested, will confirm the separate origin of the chorionic tissue from each twin.

- If the placentas are fused and either dichorionic or of uncertain chorionicity, the tip of the aspirator should be inserted either close to the umbilical cord bulge or at the placental margin, away from the area of fusion, to minimize the possibility of sampling twice from the same fetus. The device must not pass through the placenta of one twin to reach the placenta of the other twin. Cytogenetic results and DNA polymorphism may allow differentiation between samples. However, if the results are identical and chorionicity remains uncertain, it is recommended to confirm that each fetus has been sampled. This can be achieved by amniocentesis later in pregnancy. Subsequent amniocentesis is required in up to 6% of cases (Pergament *et al.*, 1992; Wapner *et al.*, 1993) .

Uncertain results that require further investigation (such as sampling one fetus twice, cross-contamination due to mixed sampling, and contamination with maternal cells) are more common in multiple pregnancies evaluated by CVS than by amniocentesis. The risk of sampling error in twin pregnancy is small 0.6 to 0.8 %) (Pergament *et al.*, 1992; Wapner *et al.*, 1993; De Catte, Liebaers and Foulon, 2000; Agarwal and Alfirevic, 2012) and lower than in triplets and higher order pregnancies (1.2 %) (Eddleman *et al.*, 2000) . Despite these limitations, CVS offers the advantage of early selective fetal reduction if requested due to abnormal results.

➢ Amniocentesis

• Multi-needle technique

Most operators perform separate procedures on each sac for genetic studies of multiple pregnancies, using a separate and sequential insertion of a new needle for each amniotic cavity. The multi-needle technique does not appear to increase the risk of adverse outcome compared with the single-needle technique (Simonazzi *et al.*, 2010) .

Sampling of only one sac will usually be sufficient in monochorionic twins without sonographic evidence of abnormalities and with concordant growth (Weisz and Rodeck, 2005) , but discordant karyotyping and microarray reports have been described in monozygotic twins, so the one-sample approach is flawed (Rustico *et al.*, 2005; Weisz and Rodeck, 2005) .

With the multi-needle technique, amniotic fluid is aspirated from a bag and indigo blue dye is injected carmine (2 to 3 mL) before removing the needle. If indigo carmine is not available, methylene blue should not be used because it can cause methemoglobinemia in the neonate, increase the risk of small bowel atresia, and stain the skin. Alternative agents, including indocyanine green (dose unknown) and fluorescein (2 to 5 mL of 10% solution), have been suggested, but there is no published information

on their use and safety in obstetrics (Ireland *et al.,* 2017) . If dye is available, amniocentesis is then performed on the other sac by inserting a new needle and aspirating amniotic fluid, which should be free of dye, thus confirming that a different sac has been sampled. Experienced operators are often comfortable performing the multi-needle technique without dye injection, particularly when the separating membranes are visible. However, misdiagnosis using such a technique has been reported in up to 3.5% of samples (Weisz and Rodeck, 2005) .

- **Single needle technique**

Aspiration of both sacs in a twin pregnancy by inserting a needle into the uterus is an alternative technique. This technique reduces maternal distress.

The needle is inserted into the more anterior sac, selecting a pool of fluid that is contiguous with the deeper sac of the other twin. After aspirating fluid from the first bag, the needle is advanced under ultrasound guidance through the septum into the second bag. No dye is used to confirm the origin of the liquid.

Theoretical concerns with this procedure include the potential for mixing of the two fluids, leading to inaccurate interpretation of genetic tests and shearing of the septal membrane, resulting in a functionally monoamniotic pregnancy with the attendant risks. The position of the placenta or the position of the fetuses can make this procedure either very difficult or very dangerous. Data on single needle insertion are too limited to allow adequate assessment of the relative risks and safety of this approach (Jeanty, Shah and Roussis, 1990; Buscaglia *et al.,* 1995; Sebire *et al.,* 1996; Nieuwint *et al.,* 1999) .

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- **Loss rate**

The risk of loss associated with amniocentesis in twin pregnancies is probably increased by about 1% above the baseline risk of loss among twin pregnancies, but the exact risk is uncertain (Agarwal and Alfirevic, 2012; Vink, Fuchs and D'Alton , 2012; Di Mascio, Khalil, Rizzo, *et al.,* 2020) . The American College of Obstetricians and Gynecologists estimates a procedure-related loss rate of 1% in twins (' Practice Bulletin No. _ 162: Prenatal Diagnostic Testing for Genetic Disorders ', 2016) .

In two systematic reviews, the total pregnancy loss rate in twin pregnancies undergoing amniocentesis was higher than in those not undergoing amniocentesis (one review: 3.9 vs 3.1%, pooled OR 1.5, 95 % CI 1.0-2.1 (Vink, Fuchs and D'Alton, 2012; Di Mascio, Khalil, Rizzo, *et al.,* 2020) . While the pooled rate of loss for one or both fetuses before 24 weeks of gestation after amniocentesis was similar

to the natural loss rate in twin pregnancies in both reviews, these results are difficult to interpret due to variations in the definition of pregnancy loss (fetal death or miscarriage/delivery), if one or both the two fetuses and the time lost after the procedure.

There are insufficient data from large, well-controlled studies to conclude whether the risk of early procedure-related fetal loss is higher in twin than singleton pregnancies undergoing amniocentesis. Confounding factors to be addressed include maternal age, chorionicity, ultrasound findings, and maternal analyzer test results. Other important factors include completeness of pregnancy outcome ascertainment and how fetal loss is defined (all losses up to termination vs. losses up to 24 weeks vs. losses within 4 weeks of the procedure).

The only two observational studies comparing amniocentesis with CVS in twin pregnancies found no significant difference between the techniques in pregnancy loss rate (Wapner *et al.*, 1993; Antsaklis *et al.*, 2002) .

- **Amniocentesis for signs of infection**

Only the lower (presenting) sac needs to be sampled in late second or early third trimester procedures to evaluate for infection in preterm premature rupture of membranes or preterm labor, as infection generally follows an ascending pathway from the bay.

Triplet pregnancy

Chorionic villus sampling (CVS) is an option for prenatal diagnosis of aneuploidy in triplet pregnancies. This technique is particularly useful for pregnant women at high risk of age-related fetal aneuploidy and planning multiple pregnancy reduction. Because karyotype results are generally available before the reduction procedure, it is possible to identify and selectively reduce an aneuploid fetus. However, CVS is more difficult in triplets than in singleton pregnancies and the woman must understand that it may be difficult to be sure that all 3 placentas have been sampled and not just one placenta twice while another placenta is completely missed.The risk of sampling error in triplets and higher order pregnancies was 1.2% in one study (Eddleman *et al.*, 2000) .

Genetic amniocentesis is another option for prenatal diagnosis. The pregnancy loss rate associated with the procedure is probably similar to that after genetic amniocentesis in singleton pregnancies. In the multi-needle technique, indigo carmine dye is usually injected into the second sac after the amniotic fluid sample is taken from that sac, and then a third needle is inserted into the third sac (and so on until each sac has

been sampled). Effusion of clear fluid confirms that the needle has been successfully inserted into a new sac, while aspiration of blue-tinged fluid indicates that the needle has been reinserted into a sac that has already been punctured.

6.2.2. Extensions of crown-rump length and nuchal translucency discordance in the first trimester

Crown-rump length discordance

CRL discordance is a predictor of adverse twin pregnancy outcome, but the use of different discordance thresholds and different exclusion criteria (e.g., anomalous twins, aneuploid twins, monochorionic [MC] twins) between studies made a meta- analysis of published data (D ' Antonio *et al.*, 2014) . A study of dichorionic (DC), monochorionic diamniotic (MCDA), and monochorionic monoamniotic (MCMA) twin pregnancies with two live fetuses at 11 to 13 weeks' gestation, no anatomical or chromosomal abnormalities and known pregnancy outcome provides more reliable data, although the findings will should be interpreted with caution, as the absolute number of cases with CRL discordance was small (Litwinska, Syngelaki, Cimpoca, Sapantzoglou, *et al.*, 2020) . In DC twin pregnancies, the overall fetal loss rate <24 weeks' gestation was 2.8%, but in the subgroup with a CRL difference ≥15% (94 of 4896 [1.9%]), the fetal loss rate was 9.6% (9 out of 94). In MCDA twin pregnancies, the overall fetal loss rate <24 weeks was 9%, but in the subgroup with a CRL difference ≥15% (35 of 1274 [2.7%]), the fetal loss rate was 37.1% (13 of 35). CRL discordance was also associated with increased risks for preterm delivery <32 and <37 weeks, birth of at least one small for gestational age (<5th percentile) neonate, birth weight discordance ≥20% and ≥25%, and in MCDA pregnancies development of twin-twin transfusion syndrome (TTTS) and/or selective fetal growth restriction (sFGR) requiring endoscopic laser surgery. However, the predictive value of CRL discordance for any adverse pregnancy outcome was poor, and therefore not a good screening test.

CRL discordance at 11 to 14 weeks is associated with increased adverse pregnancy outcomes but has low prognostic value, this finding does not warrant a significant change in routine close monitoring of twin pregnancies, but an increased awareness of the above pregnancy complications is suggested. If the CRL-based gestational age differs from the calendar gestational age by more than seven days in a well-dated first-trimester pregnancy (early ultrasound, assisted reproductive technology), use the CRL of the older twin for gestational age and repeat the ultrasound assessment in two weeks. If growth restriction continues

into the second trimester and is unexplained, growth ultrasounds at three-to-four-week intervals are recommended. MCDA twins are monitored for TTTS and sFGR.

There is little information on the difference in first-trimester CRL in twins and the risk for aneuploidy. In a study of 182 twin pregnancies, a 17 mm difference in CRL was associated with trisomy 18 in one twin pair, and a 16 mm difference was associated with triploidy in another pair (Salomon *et al.,* 2005) . The difference in CRL in these two pregnancies was above the 90th percentile (8 mm). Of the remaining 18 twin pairs with CRL ≥8 mm discordance, 11 had a normal outcome, 5 delivered preterm at 29 to 36 weeks, and 1 underwent termination of pregnancy for cystic fibrosis.

The risk of fetal malformations was found to be 25% in pregnancies with CRL ≥10% discordance, compared to 4% in pregnancies with CRL discordance <10% (Kalish *et al.,* 2004) .

Discordance of nuchal translucency

Meta-analyses evaluating the role of first-trimester and early second-trimester markers in predicting TTTS syndrome in MC twin pregnancies found that NT discordance >20%, NT >95th percentile in at least one fetus, CRL discordance between them >10% or abnormal ductus venosus flow on first-trimester ultrasound were separately associated with the development of TTTS, but with low sensitivity (Stagnati *et al.,* 2017; Mackie *et al.,* 2018) . NT discordance and abnormal ductus venosus flow had the highest sensitivities at 53 and 50%, respectively (Stagnati *et al.,* 2017) . Discordance in NT≥20% is found in 25% of monochorionic twins and the risk of early intrauterine death or severe TTTS in this population is more than 30%. The risk of complications is less than 10% if NT discordance is <20% (Kagan *et al.,* 2007) . On the other hand, ductus venosus Doppler in the first trimester is not recommended for predicting TTTS, because Doppler in early pregnancy exposes twins to higher ultrasound power with no clear benefit in predicting or reducing complications from TTTS. According to the NICE Institute, the management of twin pregnancies with CRL discordance ≥10% or NT discordance ≥20% should be discussed with a specialist in fetal medicine (National Guidelines Alliance (UK), 2019) .

6.2.3. Screening for congenital anomalies

During the **first trimester ultrasound** (between 11^{+0} and 13^{+6} weeks of gestation) fetuses should be evaluated for the presence of any significant abnormalities (A . Khalil *et al.,* 2016) .

Anatomy ultrasound is usually performed at 18 to 22 weeks' gestation in all twin pregnancies (Emery *et al.,* 2015) .

In addition to anatomic ultrasound at 18 to 22 weeks' gestation, a **fetal heart ultrasound** is performed at 18 to 22 weeks for monochorionic but not dichorionic twins because 2 to 10% of monochorionic twins referred for routine fetal heart ultrasound have congenital heart disease in at least one twin. (Donofrio *et al.*, 2014; Bahtiyar *et al.*, 2015) , and fetal heart ultrasound is important in the diagnosis and management of TTTS. Furthermore, while twin pregnancies are generally not referred for fetal echocardiography with the sole indication of IVF conception, some authorities consider IVF an indication for echocardiography in all twin pregnancies (' AIUM Practice Parameters for the Performance of Fetal Echocardiography ', 2020) .

According to NICE, screening for structural abnormalities (such as heart defects) is recommended in twin and triplet pregnancies, as in routine prenatal care. It also recommends scheduling ultrasound in twin and triplet pregnancies at a slightly later gestational age than in singleton pregnancies (National Guidelines Alliance (UK), 2019) .

Regarding screening for **neural tube defects,** the α-fetal protein (AFP) maternal serum (MSAFP) is proportional to the number of fetuses. Thus, the upper limit for a twin pregnancy is twice (e.g., 4 to 5 MoMs) that of a singleton pregnancy. Triplets should undergo a focused anatomic investigation of the neural tube in the second trimester, since MSAFP testing has not been validated in triplets.

6.2.4. Screening for risk of preterm birth-Short cervical length

Twin pregnancy

On the fetal anatomy ultrasound at 18 to 22 weeks' gestation, one approach is to assess the length of the cervix with a transabdominal ultrasound and then perform a transvaginal ultrasound if the cervix is poorly visualized or appears short. The ISUOG Society recommends a different approach: cervical length measurement by transvaginal ultrasound every two weeks in twin pregnancies between 16 and 24 weeks, as in singleton pregnancies. 25 mm is the limit most often used in the second trimester (A . Khalil *et al.*, 2016) . Practice patterns regarding cervical length measurement in twin pregnancies vary among clinicians, given the lack of high-quality evidence favoring one approach over another.

According to NICE guidelines, evidence suggests that cervical length is a moderate predictor of spontaneous preterm delivery in twin pregnancies. Although there were some inconsistencies between studies, the panel agreed that it still supports the use of cervical length measurements to predict preterm birth in twin pregnancies. Finding that a woman is at risk of preterm birth allows intervention to be offered,

and there is some evidence that vaginal progesterone may reduce this risk in women with twin pregnancies. However, the committee was also aware that new evidence would emerge about the use of vaginal progesterone in subgroups of women with a short cervix that could change their conclusions about its effectiveness. This uncertainty meant that the panel could not recommend vaginal progesterone for the prevention of preterm birth. Because of this, the committee also decided that it could not recommend cervical length screening in the absence of an effective intervention for women at higher risk of preterm birth (National Guidelines Alliance (UK), 2019) .

For women with a short cervix, options include cervical cerclage or treatment with daily vaginal progesterone.

Triplet pregnancy

Preterm birth is the most common cause of death and morbidity in triplet pregnancies. Educating pregnant women about the signs and symptoms of preterm labor is recommended, but cervical digital examination, fetal fibronectin testing, or home monitoring of uterine activity by the pregnant woman is not routinely recommended, as these interventions have no proven benefit on pregnancy outcome.

Regarding the role of ultrasound cervical length measurement, cervical length measurement is not recommended in triplet pregnancies. Although this is a common screening test for predicting preterm delivery in singleton and twin pregnancies, short cervical length was not a sensitive screening test for predicting preterm delivery in triplets in the three retrospective studies that evaluated this issue (Pils *et al.,* 2017; Fichera *et al.,* 2018; Rosen *et al.,* 2018) . In all these studies, the median cervical length was greater than 30 mm until about 24 weeks and then decreased, but neither cutoff was useful for predicting preterm delivery. Furthermore, in contrast to singleton and twin pregnancies, the limited data on the effectiveness of intervention (e.g., progesterone supplementation, cervical cerclage) to prevent preterm birth in women with triplets and short cervical length suggest no benefit (Caritis *et al.,* 2009; Combs *et al.,* 2010; Rafael, Berghella and Alfirevic, 2014) .

6.2.5. Screening for fetal growth restriction and discordance

Repeat ultrasound examinations are performed in the second and third trimesters to screen for fetal growth restriction and developmental discordance, given the risk of adverse outcome associated with these conditions and the insensitivity of measuring the distance between the superior lip of the pubic symphysis

to the uterine fundus to identify fetal growth abnormalities in twins (Hill *et al.,* 1994) . Although growth monitoring is usually performed in the second and third trimesters, cephalo-caudal length (CRL) discordance can be observed as early as the first trimester and is predictive of later weight discordance.

According to the American College of Obstetricians and Gynecologists, discordant fetal growth in women with multiple pregnancies is usually defined as a 20% difference in estimated fetal weight between the largest and smallest fetus. This growth discordance ratio is calculated by determining the difference in estimated fetal weight between the two fetuses, divided by the weight of the larger fetus (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, Society for Maternal - Fetal Medicine, 2021) . According to the ISUOG company, a combination of head, abdomen and femur measurements is the best for calculating fetal weight (A. Khalil *et al.,* 2016) .

The NICE Institute of the United Kingdom gives the following guidelines (National Guidelines Alliance (UK), 2019) :

- In women with **dichorionic twin** and **trichorionic triplet pregnancy:**

  At every ultrasound from the 24th week, diagnostic monitoring is done for fetal weight difference using 2 or more biometric parameters and the amount of amniotic fluid. To assess the amount of amniotic fluid, the deepest pool of amniotic fluid (DVP) is measured on both sides of the amniotic membrane.

Monitoring for weight difference between fetuses continues at intervals not exceeding:

  - 28 days for women with dichorionic twin pregnancies
  - 14 days for women with a trichorionic triplet pregnancy.

- In women with **a monochorionic twin** and **dichorionic or monochorionic triplet pregnancy:**

  Diagnostic monitoring for weight difference between fetuses using 2 or more biometric parameters (in addition to assessment of amniotic fluid quantity) is offered at every ultrasound from week 16 onwards.

Monitoring for weight difference between fetuses continues at intervals not to exceed 14 days.

- To all women with **a twin or triplet pregnancy:**

  Increased diagnostic monitoring during the **second and third trimesters** to at least a weekly basis and doppler assessment of umbilical artery flow for each fetus is recommended if:

  - there is ≥20% discordance in EFW and/or
  - the EFW of any of the fetuses is below the 10th percentile for gestational age.

Referral of women with twin or triplet pregnancies to a tertiary fetal medicine center is also recommended if there is a ≥25% EFW discordance and the EFW of either fetus is below the 10th percentile for gestational age, because this is a clinically important marker for selective fetal growth restriction (sFGR)

Despite the routine use of ultrasound to monitor fetal development, its ability to accurately identify discordant twins and adverse perinatal outcome is limited. In a systematic review, estimated fetal weight difference ≥20% had a sensitivity and specificity of 65% and 91%, respectively, for predicting birth weight difference ≥20% (Leombroni *et al.,* 2017) .

There is no convincing evidence that Doppler measurement has a benefit in detecting growth restriction over the use of ultrasound alone. Therefore, the routine use of Doppler measurement in twin pregnancies is not recommended (Giles *et al.,* 2003) . However, Doppler ultrasound is useful for monitoring pregnancies in which growth restriction, discordance, or fetal anemia have been diagnosed.

6.2.6. Screening for placental abnormalities

Ultrasound assessment of the placenta is particularly important in twin pregnancies because they are at increased risk for placental findings associated with adverse outcome. Identification and appropriate management of affected pregnancies can improve pregnancy outcome.

Placenta previa

The incidence of placenta previa in twin pregnancies is higher than in singleton pregnancies (3.9 per 1000 live births versus 2.8 per 1000 live births). This has been attributed to the larger total surface area of twin placentas, particularly dichorionic twin placentas (Ananth *et al.,* 2003) .

Vasia previa

A systematic review of cohort studies and patient controls identified 438 cases of vasia previa and reported that 11% were in twin pregnancies, suggesting a higher risk in twins compared to the general obstetric population. Transvaginal ultrasound examination with color Doppler measurement will detect vasia previa (Jauniaux, Melcer and Maymon, 2017) .

Velamentous cord insertion

Membranous umbilical cord prolapse, which is associated with an increased risk for fetal growth restriction and cord compression, has been reported in 12% of monochorionic twin pregnancies, 7% of dichorionic twin pregnancies, and 2% of singleton pregnancies (Kalafat *et al.*, 2018) .

6.3. Algorithms for ultrasound monitoring of multiple pregnancies

6.3.1. Twin pregnancy

6.3.1.a. Dichorionic twins

Dichorionic twins are at risk for growth restriction but not at risk for TTTS and TAPS. A common practice is to perform an ultrasound examination every four to six weeks after 20 weeks of gestation to monitor fetal growth, as fetal growth restriction leading to discordance is optimally detected between 20 and 28 weeks of gestation (Gonz á lez - Quintero *et al.*, 2003) . Many twin fetuses with developmental abnormalities can be identified between 20 and 24 weeks, so if there is no evidence of a developmental abnormality at that time, then scanning may not be necessary (Grobman and Parilla, 1999) . However, repeated ultrasound evaluation is continued until delivery. Regular scanning every two to four weeks detected more abnormalities leading to preterm birth in one study, but whether this resulted in better perinatal outcomes was not determined (Corcoran *et al.*, 2015) .

According to the International Society for Ultrasound in Obstetrics and Gynecology NICE, women with an uncomplicated dichorionic twin pregnancy should have a first trimester ultrasound scan, a detailed second trimester scan and scans every 4 weeks thereafter. Complicated dichorionic twins should be examined sonographically more frequently, depending on the condition and its severity.

More specifically, in an uncomplicated dichorionic twin pregnancy, ultrasound imaging should be performed in the first trimester, again at approximately 20 weeks of gestation (second trimester anatomy ultrasound), and every 4 weeks thereafter (unless a complication is detected that may require more frequent scans).

At each ultrasound the following should be assessed: fetal biometry, amniotic fluid volume and umbilical artery Doppler (from 20 weeks' gestation) for both twins. The difference in estimated fetal weight (EFW) should be calculated and documented at each scan from 20 weeks.

Cervical length assessment is ideally performed at the same visit as the second-trimester anomaly scan to identify women at risk of extreme preterm labor (A . Khalil *et al.*, 2016) .

6.3.1.b. Monochorionic diamniotic twins

Monochorionic diamniotic twins are at risk of developing TTTS, TAPS and/or selective growth restriction (sFGR). Early detection can improve perinatal outcome (Sueters *et al.*, 2006; de Villiers *et al.*, 2013) .

The diagnosis of TTTS is based on the ultrasonographic finding of oligohydramnios (maximum vertical pool <2 cm) and polyhydramnios (maximum vertical pool >8 cm).

The diagnosis of TAPS is based on MCA - PSV >1.5 times the median value (MoM) in one twin and <0.8 MoM in the other twin.

The diagnosis of sFGR in the second trimester is based on the following:

- Estimated Fetal Weight (EFW) < 3rd percentile of a fetus or
- At least two of the following four criteria:
  - EFW <10th percentile for a twin
  - Abdominal circumference <10th percentile for a twin
  - Weight Discordance ≥25%
  - UA pulsatility index >95th percentile for the younger twin

Monochorionic placenta is a major risk factor for asymmetric fetal growth due to uneven placental distribution or TTTS (González - Quintero *et al.*, 2003; Fick *et al.*, 2006; Russell, Quintero and Kontopoulos, 2007) , although monochorionic placenta also appears to have a small independent adverse effect on intrauterine growth (Papageorghiou *et al.*, 2008) . sFGR differs from the inadequate uteroplacental perfusion that occurs in dichorionic twins and singleton fetuses.

A specific protocol for the follow-up of monochorionic twin pregnancies is shown in table 1. According to the International Society for Ultrasound in Obstetrics and Gynecology NICE, unconjoined monochorionic twins should undergo a first-trimester ultrasound and then every 2 weeks after 16 weeks, in order to detect TTTS and TAPS early. Their early detection has been shown to improve perinatal outcome. Complicated monochorionic twins should be scanned more frequently, depending on the condition and its severity.

In particular, middle cerebral artery peak systolic velocity (MCA- PSV) should be recorded from 20 weeks in order to screen for TAPS. In MCDA twins, amniotic fluid volume (maximum vertical pocket) should be assessed and documented at each ultrasound to screen for TTTS (A . Khalil *et al.,* 2016) .

6.3.1.c Monochorionic monoamniotic twins

A **specific protocol** for monitoring monochorionic twin pregnancies is presented in table 1. According to the International Society of Ultrasound in Obstetrics and Gynecology ISUOG, unconjoined monochorionic twins should undergo a first-trimester ultrasound and then every 2 weeks after 16 weeks, in order to detect TTTS and TAPS early. Their early detection has been shown to improve perinatal outcome. Complicated monochorionic twins should be scanned more frequently, depending on the condition and its severity.

Fetal weight is monitored for growth restriction and discordance, although weight discordance >20% had low predictive accuracy for mortality in a study of 242 monoamniotic twin pregnancies by three twin research partners (Saccone *et al.,* 2020) . Therefore, there is insufficient evidence to suggest that monoamniotic twins have a different frequency of growth monitoring compared to monochorionic diamniotic twins (table 1).

Doppler examination to detect altered flow has been suggested as an indication of compression of the umbilical cord vessels. The high velocity of flow in the umbilical vein (Belfort *et al.,* 1993; Gembruch and Baschat, 1996) , a notch in the waveform of the umbilical artery (Abuhamad *et al.,* 1995) or the persistent absence of end-diastolic flow (Rosemond and Hinds, 1998) were reported to suggest that the fetoplacental circulation is compromised. However, the presence of umbilical artery notch and cord entanglement, without other signs of fetal distress, is not indicative of adverse twin perinatal outcome (Aurioles - Garibay *et al.,* 2014) , and therefore Doppler examination of the vessels of the umbilical cord is not recommended for the routine monitoring of monoamniotic twins.

It is common practice to **hospitalize** patients with monoamniotic twin pregnancies in the early third trimester for intensive fetal heart rate monitoring, but patterns vary between institutions. These patients are admitted at 26 to 28 weeks of gestation.

A survey of maternal-fetal medicine experts noted that 84% of respondents recommended in-hospital fetal monitoring, with 54% initiating in-hospital monitoring at 26 to 28 weeks (Desai *et al.,* 2012) . The authors also noted that 75% of respondents recommended daily intermittent fetal monitoring, with 81% performing fetal testing two to three times daily.

Reviews have generally reported better pregnancy outcomes with inpatient care compared with outpatient care (Post and Heyborne, 2015; D' Antonio _ *et al.*, 2019) . In a meta-analysis of monoamniotic twin pregnancies (25 studies, 1628 non-abnormal twins ≥ 24 weeks' gestation), fetal death occurred in 3% (95% CI 1–5) of monoamniotic twin pregnancies treated as inpatients versus 7% (95% CI 4-11) from those treated as outpatients (D ' Antonio *et al.,* 2019) . However, a review of data from three cohort studies found that deaths among fetuses with different degrees of birth weight difference were similar in women treated as inpatients or outpatients (Saccone *et al.,* 2020) . All studies were small and none were randomized trials. Importantly, in some studies, inpatients had more intensive fetal monitoring than outpatients, which may account for the observed benefit rather than other hospital characteristics. On the other hand, inpatients sometimes had more pregnancy complications than outpatients and thus were at a higher baseline risk for an adverse outcome. Given these limitations, it is unclear whether the risk of fetal death is clearly increased with routine management of pregnant women outside the hospital. A prudent approach until better data is available is to admit these patients at 26 to 28 weeks' gestation for inpatient monitoring.

6.3.2. Triplet pregnancy

In the first half of pregnancy, office visits can be scheduled according to the usual obstetrical standards for singleton pregnancy. Pregnant women visit the doctor weekly starting at 24 weeks of pregnancy to be closely monitored for signs or symptoms of preeclampsia and preterm labor. However, there is limited evidence that weekly visits improve outcomes. The timing and frequency of second and third trimester ultrasounds is based on chorionicity and amnionicity. Others recommend visits at 20, 24, 28, 32 and 34 weeks for trichorionic triamniotic triplets and at 20, 22, 24, 26, 28, 30, 32 and 34 weeks for monochorionic triamniotic and dichorionic triamniotic triplets (Bricker , 2014) . Weekly visits are suitable from week 34 until birth, which is usually scheduled at 35^{+6} weeks.

6.3.2.a. Monochorionic triamniotic and dichorionic triamniotic triplets

Any multiple pregnancy with a common chorionic sac puts the affected fetuses at risk for TTTS, selective growth restriction, and TAPS. An ultrasound protocol similar to that commonly used to monitor monochorionic twin pregnancies is followed (table 1) (Society for Maternal - Fetal Medicine and Simpson, 2013) .

6.3.2.b. Monochorionic monoamniotic or dichorionic diamniotic triplets

Any multiple pregnancy with a common amniotic sac puts the fetuses involved at high risk of umbilical cord entanglement and death from cord compression. Experts recommend admitting patients with this type of placenta to the hospital at 26 weeks' gestation to facilitate an hour of continuous fetal heart rate monitoring every eight hours.

It is recommended that Doppler examination of the umbilical cord vessels not be used in the routine monitoring of monoamniotic polydymas to detect altered flow suggestive of cord entanglement and compression (Aurioles - Garibay *et al.,* 2014) . Although the high flow velocity in the umbilical vein (Belfort *et al.,* 1993; Gembruch and Baschat, 1996) , a notch in the waveform of the umbilical artery (Abuhamad *et al.,* 1995) or the persistent absence of end-diastolic flow (Rosemond and Hinds, 1998) may indicate compromised fetoplacental circulation, these findings have low specificity.

Multiple pregnancies with a common amniotic sac are also at risk for TTTS, selective growth restriction and TAPS. Ultrasound follow-up for these conditions is the same as described above for triplets with a common chorionic sac (monochorionic triamniotic and dichorionic triamniotic triplets).

6.3.2.c. Trichorionic triamniotic triplets

Trichorionic triamniotic placenta is associated with more favorable perinatal outcomes than triplet pregnancies, in which the fetuses share an amniotic sac or placenta/chorion (Kawaguchi *et al.,* 2013; Peress, Peaceman and Yee, 2017) . Growth restriction is still a major concern, so starting at 20 weeks, an ultrasound scan is generally performed every three to four weeks to monitor fetal growth.

Monitoring for TTTS and TAPS is not necessary as the placenta is not common.

6.4. Antepartum fetal assessment in multiple pregnancies

6.4.1. Twin pregnancy

Routine use of prenatal fetal testing (resting cardiotocography [NST], biophysical profile [BPP], amniotic fluid volume determination, or Doppler examination) has no proven benefit in uncomplicated twin pregnancies. However, antepartum fetal monitoring in twins is widely practiced starting around 32 weeks of gestation because of the increased risk of stillbirth in twins, particularly monochorionic twins (Barigye

et al., 2005) . The exact time to start testing varies between centers, depending on factors such as chorionicity and amnionicity and underlying complications.

Weekly check-up starts from the 32nd ^{to} the 36th week in dichorionic twins, while in monochorionic diamniotic twins from the 28th to the 32nd week of pregnancy. If complications such as growth restriction develop, then screening is started earlier and/or performed more frequently. Either NST or BPP can be used (Lodeiro *et al.*, 1986; Patkos *et al.*, 1986; Booker *et al.*, 2015) . The best technique for estimating amniotic fluid volume in diamniotic twin pregnancies is uncertain. Subjective estimation of the volume of amniotic fluid in each sac appears to be as accurate as quantitative estimation. However, the maximum vertical pool in each bag is usually used.

The American College of Obstetricians and Gynecologists recommends considering weekly prenatal assessment of fetal well-being beginning at 36 $^{+0}$ weeks' gestation for uncomplicated dichorionic twin pregnancies and individualized monitoring of complicated dichorionic twin pregnancies (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, Society for Maternal - Fetal Medicine, 2021) . For monochorionic twins, prenatal evaluation of fetal well-being typically begins at 32 $^{+0}$ weeks' gestation because of the increased risk of fetal death in these pregnancies. Monochorionic monoamniotic twins are monitored more closely. Prenatal fetal monitoring is indicated because monoamniotic twins are at increased risk of death, which has been attributed, at least in part, to umbilical cord involvement. Monitoring and early intervention can prevent some of these deaths. The best approach to monitoring is unclear, as no high-quality data are available to guide decision-making. No single approach can prevent all fetal deaths.

When the pregnancy reaches a gestational age at which delivery could be considered due to a nonreassuring fetal heart rate (generally 24 to 28 weeks), extended fetal heart rate readings are taken twice a week for about an hour to detect possible multiple deep variable decelerations, suggesting compression of umbilical cords by entrapment. When fetuses are sufficiently mature to demonstrate heart rate reactivity, the NST test can be performed. Other physicians may reasonably choose a different gestational age to begin monitoring and a different frequency and duration of monitoring.

For hospitalized patients ≥ 28 weeks' gestation, fetal heart rate is monitored three times daily until a reassuring NST is obtained. After reviewing the literature, one group concluded that fetal death due to umbilical cord involvement was not a sudden acute event in the majority of cases, but rather secondary to a subacute event, which can be prevented with fairly frequent monitoring in the vast majority of cases. (Post and Heyborne, 2015) . For hospital inpatients, they suggested that a reasonable fetal monitoring

regimen based on the available literature is an NST or an hourly fetal heart rate recording at least three times daily. For out-of-hospital outpatients, they suggested NST three to four times per week, with the understanding that out-of-hospital follow-up is not ideal.

6.4.2. Triplet pregnancy

There are no evidence-based guidelines regarding the timing and frequency of prenatal assessment of fetal well-being in triplets. Fetal screening is based on chorioamnionicity.

Monochorionic triamniotic and dichorionic triamniotic triplets

A weekly biophysical profile score is obtained starting at 28 weeks ' gestation because all these pregnancies are at high risk for fetal complications due to the common chorionic sac. Ultrasound allows the identification of each fetus and thus avoids the technical difficulties encountered when performing NST in higher order multiples (Elliott and Finberg, 1995) . However, NST is an acceptable alternative.

Monochorionic monoamniotic or dichorionic diamniotic triplets

It is recommended that these triplets be monitored three times a day with one hour of continuous heart rate monitoring of each fetus when the mother is hospitalized at approximately 26 weeks ' gestation. The aim is to detect decelerations, which indicate umbilical cord involvement by compression of the common amniotic sac, and this is most easily achieved by prolonged fetal heart rate monitoring with biophysical profiling.

Trichorionic triamniotic triplets

A weekly biophysical profile score is obtained beginning at 32 weeks, based on evidence that dichorionic twins are at increased risk of death with advanced gestational age (Cheong - See *et al.*, 2016) .

When the results of the fetal well-being assessment of a singleton preterm fetus are not reassuring, the decision to intervene is determined by whether the risk of the fetus remaining in the uterus outweighs that of preterm delivery. Conversely, in multiple pregnancies an ethical dilemma arises when one fetus is at risk but the others are not. These decisions are complex and should be made jointly with, at a minimum, the parents, a maternal-fetal medicine specialist, and a neonatologist.

7. Time of delivery in multiple pregnancies

7.1. Time of delivery in twin pregnancies

7.1.1. Uncomplicated twin pregnancies

The optimal time of delivery in uncomplicated twin pregnancies depends on chorionicity and amnionicity. However, timing of delivery is not at the discretion of the obstetrician in most cases, because spontaneous or medically indicated preterm labor complicates over 50% of twin pregnancies (Kogan *et al.*, 2000) .

Dichorionic twins

For uncomplicated dichorionic diamniotic twin pregnancies, planned delivery is recommended from 38 $^{+0}$ to 38 $^{+6}$ weeks of gestation, according to the recommendations of the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, Society for Maternal - Fetal Medicine, 2021) . This gestational age is optimal for delivery, based on a review of the available data on the increased risk of unexpected stillbirth with expectant management and the low risk of neonatal mortality and morbidity with delivery. In contrast, in the UK, the National Institute for Health and Care Excellence recommends planning delivery at 37 weeks for uncomplicated dichorionic diamniotic pregnancies (National Guidelines Alliance (UK), 2019) .

There are no high-quality data from randomized trials on which to base a recommendation on the optimal timing for delivery of dichorionic diamniotic twins. Although the authors of a 2016 meta-analysis of cohort studies assessing the potential risk of stillbirth and neonatal complications in uncomplicated twin pregnancies recommended delivery at 37 $^{+0}$ to 37 $^{+6}$ weeks, their data do not warrant a strong recommendation. In dichorionic diamniotic twins, they found that the relative risks of stillbirth and neonatal death were similar for pregnancies between 37 $^{+0}$ and 37 $^{+6}$ weeks (risk difference 1.2 deaths/1000 pregnancies, 95% CI -1.3 to 3.6), while the future risk for stillbirth exceeded that for neonatal death at 38 $^{+0}$ to 38 $^{+6}$ weeks (risk difference 8.8 deaths/1000 pregnancies, 95% CI 3.6-14.0) (Cheong - See *et al.*, 2016) . However, neonatal morbidity, including respiratory distress syndrome, sepsis, assisted ventilation, and neonatal intensive care unit admission, was lower at 38 $^{+0}$ to 38 $^{+6}$ weeks than at 37 $^{+0}$ to 37 $^{+6}$ weeks. The findings of the meta-analysis are limited by the absence of data on the quality of ultrasound examination, prenatal fetal monitoring, method of delivery and level of neonatal care. Without this

information, it is difficult to assess the impact of a policy to deliver all dichorionic diamniotic twins at 37 $^{+0}$ to 37 $^{+6}$ weeks' gestation.

Monochorionic diamniotic twins

NICE Institute recommends delivery of monochorionic diamniotic twins at 36 weeks' gestation (National Guidelines Alliance (UK), 2019) . This approach is narrower than the ACOG and SMFM guideline, which recommends delivery at 34 $^{+0}$ to 37 $^{+6}$ weeks (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, Society for Maternal - Fetal Medicine, 2021) and from that to the guideline of the North American Fetal Treatment Network, which recommends delivery at 36 $^{+0}$ to 37 $^{+6}$ weeks (Emery *et al.*, 2015) . Some authorities have supported delivery as early as 32 weeks of gestation (Barigye *et al.*, 2005; Cleary-Goldman and D'Alton, 2005; Simões *et al.*, 2006; Hack, Derks, *et al.*, 2008) .

No randomized trials have evaluated the optimal time for delivery of monochorionic diamniotic twin pregnancies. The authors of the 2016 systematic review of the potential risk of stillbirth and neonatal complications in twin pregnancies, discussed above (dichorionic twins), also evaluated the time to delivery in uncomplicated monochorionic diamniotic twin pregnancies (Cheong - See *et al.*, 2016) and recommended delivery at 36 $^{+0}$ to 36 $^{+6}$ weeks in these pregnancies because they observed a trend toward a higher potential risk for stillbirth than for neonatal death beyond this gestational age (risk difference at ^{37} week of gestation: 2.5 deaths/1000 pregnancies, 95% CI -12.4 to 17.4). The number of deaths at each gestational age was small, precluding precise estimates of risk. In addition, as discussed above, the analysis was limited by the absence of data on the quality of ultrasound examination, prenatal fetal monitoring, mode of delivery, and level of neonatal care.

7.1.2. Complicated twin pregnancies

Monochorionic monoamniotic twins

The American ACOG college (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics, Society for Maternal-Fetal Medicine, 2021) , the NICE Institute of United Kingdom Basilio (National Guideline Alliance (UK), 2019) and others experts (Beasley *et al.*, 1999; Allen *et al.*, 2001; Ezra *et al.*, 2005; Spong *et al.*, 2011; Raju *et al.*, 2014; Van Mieghem *et al.*, 2014) plan to deliver these pregnancies between 32 $^{+0}$ and 34 $^{+0}$ weeks of gestation due to the increased risk of perinatal

mortality in the third trimester, estimated to be at least 5% in pregnancies that continue beyond this gestational age range (Roque et _ *al* ., 2003; Van Mieghem *et al.*, 2014; Ishii, 2015) . If only one death occurs, this puts the other twin at risk because of the risk of neurological damage. Although several studies have observed that healthy fetuses that reach 35 weeks of gestation have a low rate of fetal death, there were only 150 cases in this age range in a meta-analysis of monochorionic monoamniotic twin pregnancies and they were shared between different institutions with different protocols for assessing well-being. fetal state (D ' Antonio *et al.*, 2019) .

Neonatal outcomes are quite good at 32 weeks for neonates treated in well-equipped neonatal intensive care units. In a large study, the rate of neonatal death after delivery at 32 and 34 weeks was 0.2% (1 in 451) and 0 (0 in 1058) respectively (Doyle *et al.*, 1999; Manuck *et al.*, 2016) . Thus, the risk of death associated with preterm delivery appears to be lower than that associated with continued pregnancy, although delivery places the fetus at risk of major and minor morbidity. The available evidence is insufficient to allow a strong recommendation regarding the optimal gestational age for planned delivery of these pregnancies, as no randomized trials have been performed (Shub and Walker, 2015) . The results of a questionnaire sent to maternal-fetal medicine specialists showed that the mean gestational age for planned delivery was 34 weeks (Desai *et al.*, 2012) .

The timing of unplanned delivery is dictated by the clinical scenario (e.g., non-reassuring results on prenatal fetal monitoring).

Other complicated twin pregnancies

Twin pregnancies can be complicated by a variety of disorders, which may or may not be unique to the twin pregnancy. The timing of delivery in these pregnancies is based on the type and severity of the disorder (e.g., feto-fetal transfusion syndrome, growth restriction, preeclampsia). The timing of delivery in complicated twin pregnancies has already been described according to the resulting complications in the individual sections of Chapter 4.

7.2. Time of delivery in triplet pregnancies

Monoamniotic or diamniotic triplets

These triplets are delivered by caesarean section at approximately 32 $^{+4}$ weeks' gestation (i.e., between 32 $^{+0}$ and 32 $^{+6}$ weeks) based on the extension of the finding that the risk of fetal death in a monoamniotic multiple pregnancy exceeds the risk for a postnatal non-respiratory complication at this gestational age

(Van Mieghem *et al.,* 2014) . The NICE Institute recommends an individual assessment for the timing of planned delivery in any triplet pregnancy with a shared amniotic sac between the fetuses (National Guidelines Alliance (UK), 2019) .

Triamniotic triplets

The National Institute for Health and Clinical Excellence NICE concluded that continuation of an uncomplicated trichorionic triamniotic or dichorionic triamniotic triplet pregnancy beyond 35 $^{+6}$ weeks' gestation would lead to an increased risk of fetal death. For this reason, he suggests planned delivery at 35 weeks of pregnancy.

Regarding the monochorionic triamniotic triplet pregnancy, the NICE Institute recommends that the time of delivery depends on the individual clinical scenario and individual assessment (National Guidelines Alliance (UK), 2019) .

8. Mode of delivery in multiple pregnancies

8.1. Mode of delivery in twin pregnancies

Both amnionicity and fetal presentation at the onset of labor influence the choice of delivery route in twin pregnancies. Vaginal delivery is preferred for diamniotic twins in which the superior twin is cephalic at the onset of labor, if appropriate expertise in internal and external transformation and/or breech delivery is available, and there are no typical indications for cesarean section (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, Society for Maternal - Fetal Medicine, 2021) . Cesarean delivery is preferred for diamniotic twins with a presenting noncephalic twin, monoamniotic twins, and pregnancies with typical obstetric indications for cesarean section (e.g., placenta previa).

At the onset of labor, approximately 80% of first twins are cephalic (42% cephalic/cephalic, 38% cephalic/noncephalic) and 20% are noncephalic (7% noncephalic/cephalic, 13% noncephalic/noncephalic) (Chasen *et al.,* 2005) . However, the position of the second twin can change after delivery: in one study, 11% of second twins with cephalic presentation on admission to the delivery unit were noncephalic at delivery and 30 % of second twins that were noncephalic at admission they were cephalic at delivery (Easter, Lieberman and Carusi, 2016) .

8.1.1. Diamniotic twins with cephalic presentation of the first fetus

An attempt at vaginal delivery can be made in diamniotic twins with the first twin in cephalic presentation. With appropriate intrapartum monitoring and management, the second twin is not at increased risk of neonatal mortality or morbidity with planned vaginal delivery versus planned caesarean section, even in cases where there is a time gap from term (from 37 $^{+0/7}$ weeks of gestation) or the second twin is in noncephalic presentation (Hogle *et al.*, 2003; Sibony *et al.*, 2003; Rossi, Mullin and Chmait, 2011; Vendittelli *et al.*, 2011; Sentilhes *et al.*, 2015) . However, the clinician should be comfortable with possible internal or external transformation or breech extraction. In a series that included nearly 20,000 twin pregnancies over 32 weeks' gestation and the first cephalic twin, 80% of women achieved planned vaginal delivery of both twins, 14.6% delivered both twins by unplanned caesarean section, and 5,13% gave birth by combined vaginal delivery with caesarean section (Goossens *et al.*, 2021) . About 30% of second twins were noncephalic at baseline and 72% of these pregnancies achieved planned vaginal delivery compared with 84% of twins cephalic-cephalic at baseline.

The Twin Birth Study is the best available evidence that planned cesarean delivery does not significantly improve neonatal or early childhood outcome compared with planned vaginal delivery (with cesarean section if medically indicated) for diamniotic twins, when the first twin is in cephalic presentation. This trial randomized 1398 pregnant women with diamniotic twin pregnancies and the first cephalic twin (the second twin could be cephalic or noncephalic) to planned cesarean or planned vaginal delivery between 37 $^{+5}$ and 38 $^{+6}$ weeks ' gestation (Barrett *et al.*, 2013) . The composite outcome (fetal or neonatal death or severe neonatal morbidity) was similar for both groups (planned caesarean section: 2.2%, planned vaginal delivery: 1.9%, RR 1.16, 95% CI 0.77-1.74). Findings were similar when the analysis was restricted to monochorionic diamniotic twins (Aviram *et al.*, 2020) . At two years of age, both groups continued to have similar rates of death or neurodevelopmental delay (Asztalos *et al.*, 2016) . Of note, the cesarean delivery rate was 90.7% in the planned cesarean group and 43.8% in the planned vaginal delivery group, which shows the high incidence of cesarean delivery even when vaginal delivery is planned.

Approach in the case of cephalic presentation of the first and noncephalic presentation of the second twin

Most patients with cephalic/noncephalic twins are offered a trial of vaginal delivery with an attempt to deliver the second twin in breech presentation (assuming no contraindications) and planning to have a caesarean delivery if breech delivery is unsuccessful, based on absence of high-quality data favoring one

approach over the other. If the patient rejects the plan for breech extraction, she is given the option of intrapartum external cephalic transformation of the second twin or planned cesarean delivery of both twins.

However, the following patients with twins in cephalic/noncephalic presentation are not offered a trial of vaginal delivery and instead are offered a planned caesarean section of both twins:

- Gestational age <28 weeks
- Estimated fetal weight of the second twin <1500 grams.

In cephalic/noncephalic twin patients who choose a trial of vaginal delivery, sciatic presentation would not be

performed in the following cases due to concerns about head entrapment:

- Estimated fetal weight of the second twin 20% greater than that of the presenting twin (this limit is not based on specific data). In these cases, it would be planned to perform external cephalic transformation of the noncephalic second twin after the birth of the first twin.
- Prolonged second stage of labor or marked "shaping" and forehead formation of the first twin suggests that the pelvis may not be adequate for breech extraction. In these cases, external transformation or caesarean section is offered for the birth of the second twin.

When discussing the options of breech extraction or internal versus external transformation with patients, the physician should include information about his or her experience and comfort level with these procedures. Many obstetricians (43 % in one study (Asztalos *et al.*, 2016)), based on training and experience, may feel more comfortable performing a caesarean section. Under these circumstances, delivery of both twins by caesarean section is recommended. This approach is consistent with that of the American College of Obstetricians and Gynecologists, which considers vaginal delivery a reasonable option in diamniotic twin pregnancies of more than 32 weeks' gestation with a cephalically presenting fetus, regardless of presentation of the second fetus, provided that it is available an obstetrician experienced in the management of a noncephalic second twin (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, Society for Maternal - Fetal Medicine, 2021) .

The safety of this approach is supported by the Twin Birth Study, in which planned caesarean section in the subgroup of cephalic/noncephalic twin pregnancies, which accounted for more than one-third of the fetuses, did not reduce the risk of fetal or neonatal death, or severe neonatal morbidity compared with planned vaginal delivery (with caesarean section if medically indicated) (Barrett *et al.*, 2013) . In addition,

several observational studies have reported successful vaginal delivery of both twins using internal or external transformation or breech extraction (Acker *et al.,* 1982; Chervenak *et al.,* 1983, 1985; Blickstein *et al.,* 1987; Rabinovici *et al.,* 1988; Gocke *et al.,* 1989; Morales *et al.,* 1989; Adam, Allen and Baskett, 1991; Wells, Thorp and Bowes, 1991; Davison *et al.,* 1992; Fishman, Grubb and Kovacs, 1993; Chauhan *et al.,* 1995; Kaplan *et al.,* 1995; Mauldin, Newman and Mauldin, 1998; Winn *et al.,* 2001; Peaceman, Kuo and Feinglass, 2009; Fox *et al.,* 2010; Easter, Lieberman and Carusi, 2016; Schmitz *et al.,* 2018) . The second twins of cephalic/noncephalic and cephalic/cephalic pairs had generally similar neonatal outcomes regardless of mode of birth or interventions performed during delivery. However, successful vaginal delivery appeared to be less likely when external transformation was attempted than when breech extraction was performed immediately after delivery of the presenting twin (Gocke et al., 1989; Wells, Thorp and Bowes, 1991; Chauhan *et al.,* 1995; Mauldin, Newman and Mauldin, 1998) . External transformation was completed in 40 to 50% of cases (in the remainder a cesarean section was performed), while breech extraction was successful in 96 to 100% of patients (Chauhan *et al.,* 1995; Mauldin, Newman and Mauldin, 1998) . Of note, the average gestational age was 34 to 37 weeks and the average birth weight was 2100 to 2500 grams in these studies.

8.1.2. Diamniotic twins with noncephalic presentation of the first fetus

Cesarean delivery is recommended when the first twin is in noncephalic presentation, which occurs in about 20% of twin pregnancies. A unique potential complication of breech extraction with a second cephalic twin is conjoined twins, but this is rare. In this case, one twin's umbilical cord locks with the other twin's umbilical cord, making vaginal delivery impossible.

There is general consensus in the obstetric community against vaginal delivery of the iliacally presenting fetus in a twin pregnancy (Dodd and Crowther, 2005; Arabin and Kyvernitakis, 2011) . However, some physicians believe that planned vaginal delivery in carefully selected patients by obstetricians experienced in vaginal delivery is not associated with a higher risk of neonatal mortality and morbidity for the first or second twin than planned caesarean section and should be an option which is seriously considered. No randomized trials have been performed to assess the safety of vaginal delivery in this setting, but limited data from observational studies are available.

For example, in a secondary analysis of data from a prospective study (JUMODA) of 298 planned vaginal deliveries of first twins with iliac presentation in 176 French hospitals, 185 women (62 %) delivered both twins vaginally (Korb *et al.,* 2020) . In all pregnancies, twins were ≥ 32 weeks, without significant

anomalies, with a birth weight between 1500 and 4000 grams and a second twin that was not significantly larger than the first twin. The cephalic presentation of the second twin was not an exclusion factor. The composite rate of neonatal mortality/major morbidity for first twins was similar in the planned vaginal delivery and planned caesarean section groups (1.7 % [5/298] and 1.9 % [22/1169], respectively; gross relative risk 0 .90, 95% CI 0.34-2.34, which remained statistically non-significant in propensity score matching analysis).

Although these data may be reassuring for patients who desire vaginal delivery and meet the study inclusion criteria, there are important limitations to this study. The study of planned vaginal deliveries accounted for only 20.3% of twins with iliac presentation. The confidence intervals around the primary outcome are large and the study was not powered to exclude a small increase in neonatal mortality and morbidity associated with planned vaginal delivery of a noncephalic first twin. No information was provided on outcomes for cephalic versus noncephalic second twins, and the occurrence of conjoined twins. Importantly, these findings can only be generalized to centers where obstetricians are trained and accustomed to vaginal delivery for breech presentation. In conclusion, although cesarean delivery is recommended for twin pregnancies with a noncephalic presenting fetus, it is recognized that planned vaginal delivery may play a role in certain limited circumstances.

8.1.3. Special populations

8.1.3.a. Trial of vaginal delivery after previous caesarean section

A previous caesarean section

A trial of vaginal delivery is offered to women with an amniotic twin pregnancy with a cephalically presenting fetus and one previous caesarean delivery, provided they proceed to spontaneous labour. Because the most common initial sign of uterine rupture is changes in fetal heart rate, both fetuses are monitored continuously. If this is not technically possible, then a caesarean section is performed.

A meta-analysis of 11 cohort studies including nearly 2500 twin pregnancies undergoing a trial of labor after a prior cesarean (TOLAC, trial of labor after a prior cesarean) provided reassuring data (Kabiri *et al.*, 2019) . Twins undergoing TOLAC had similar rates of successful vaginal delivery and uterine rupture as singletons undergoing TOLAC (vaginal delivery: 71 vs 74 %, CI 0.85, 95% CI 0.61-1.18, uterine rupture: 4/407 [0.98 %] vs 253/31,630 [0.80 %], SD 1.34, 95% CI 0.54-3.31). Although twins who

underwent TOLAC had higher rates of uterine rupture than twins who underwent planned repeat caesarean section (OR 10.09, 95% CI 4.30-23.69), the rates of uterine scar rupture, bleeding, blood transfusion and neonatal morbidity and mortality were similar in the 2 groups.

Two previous C-sections

A repeat cesarean section is recommended for these women, but some physicians may make this decision on a case-by-case basis, allowing a trial of vaginal delivery electively and with very close maternal and fetal monitoring. There are few data evaluating the safety of TOLAC with twins and ≥2 previous cesarean deliveries.

8.1.3.c. Monochorionic monoamniotic twins

Monochorionic monoamniotic twins are delivered by caesarean section, with rare exceptions, to avoid complications during delivery from cord entanglement (Lee, 2012; Van Mieghem *et al.*, 2014) .

8.1.3.b. Very low birth weight twins

Very early gestational age or very low birth weight alone are not considered as sole factors when choosing the route of birth. A trial of vaginal delivery is recommended in this group, unless there is a standard indication for caesarean section (e.g., breech presentation, previous caesarean section).

Although no randomized trials have evaluated the optimal route of delivery for these pregnancies, the body of evidence from observational studies suggests that cesarean section performed for very early gestational age in twins does not improve neonatal morbidity and mortality compared with vaginal delivery. childbirth (Mol *et al.*, 2020? Hiersch *et al.*, 2021? Korb *et al.*, 2022) . In cohort studies of twins born at 24 $^{+0}$ to 27 $^{+6}$ weeks (541 twin pairs (Hiersch *et al.*, 2021) and 26 $^{+0}$ to 31 $^{+6}$ weeks (424 twin pairs) (Korb *et al.*, 2022) , rates of adverse neonatal outcome and survival to discharge without major morbidity were similar for planned vaginal delivery versus planned cesarean delivery. In a third cohort study, planned caesarean section was associated with higher perinatal morbidity and mortality than planned vaginal delivery (Mol *et al.*, 2020) .

8.2. Mode of delivery in triplet pregnancies

Cesarean delivery is the preferred route for all triplet pregnancies. A review of data from a United States national database found that vaginal delivery of triplets was associated with an increased risk of stillbirth and neonatal and infant deaths compared with cesarean delivery (Vintzileos *et al.,* 2005) . This finding was supported by a multicenter retrospective cohort study, which reported that the rate of successful attempted vaginal delivery was only 16.7% (four pairs of triplets) and that vaginal delivery was associated with a higher risk of maternal transfusion and neonatal mechanical ventilation, as and with a tendency for increased complex neonatal morbidity (Lappen, Hackney and Bailit, 2016) . However, obstetricians experienced in vaginal delivery of multiple pregnancies may consider offering patients a planned vaginal delivery of triplets using a shared decision-making approach (American College of Obstetricians and Gynecologists ' Committee on Practice Bulletins — Obstetrics, Society for Maternal - Fetal Medicine, 2021) .

Multiple pregnancies are at increased risk for uterine atony, postpartum hemorrhage, and emergency hysterectomy (Francois *et al.,* 2005) . Therefore, preparation for these potential complications is important.

Conclusions-Discussion

The main purpose of prenatal care is to help ensure the birth of a healthy newborn while minimizing risk to the mother. This requires identifying pregnancies at high risk for complications, predicting potential problems, intervening if possible to prevent or minimize morbidity and promote health, and education, support and shared decision-making with the pregnant woman. This is accomplished, in part, by obtaining a comprehensive medical, obstetric, psychosocial, and family history, establishing a probable date of delivery, and performing appropriate laboratory tests. Prenatal care should begin in the first trimester, ideally by 10 weeks of gestation.

Early (before 20 weeks' gestation) routine ultrasound examination provides a better estimate of gestational age than LMP-based estimation, resulting in a reduced incidence of induction of labor due to gestation beyond 42 weeks or use of tocolysis for suspected preterm labor. Early ultrasound examination can lead to early detection of clinically non-apparent fetal malformations as well as multiple pregnancy. In women with risk factors for ectopic pregnancy, early recognition of the location of the pregnancy is important.

A detailed history includes obstetric history, review of medications taken, but also screening for substance use, depression and anxiety, and abuse or assault. Calculation of body mass index facilitates advice on appropriate weight gain during pregnancy.

The following tests are performed on all pregnant women during the initial prenatal visit:

- Blood group, RhD type and indirect Coombs test.
- Hematocrit/hemoglobin and mean corpuscular volume (MCV).
- Evidence of immunity to rubella and varicella.
- Qualitative assessment of urine protein.
- Evaluation for asymptomatic bacteriuria. A urine culture is recommended.
- Screening for cervical cancer according to guidelines.
- Testing for syphilis, chlamydia, hepatitis B antigen, hepatitis C antibody and HIV.

All pregnant women should be offered prenatal genetic testing (serum testing with or without cervical smear or non -invasive testing by examining free ¬fetal DNA in maternal plasma [cell-free fetal DNA - cffDNA]) and should have the option of having a diagnostic invasive procedure instead of screening (regardless of maternal age). Diagnostic testing involves performing genetic studies on samples (e.g., chorionic villi or amnion cells), obtained through the invasive procedure of chorionic villus sampling or amniocentesis, to identify fetuses with aneuploidy.

For genetically inherited disorders, physicians may choose to take a national or nationwide approach. Alternatively, they can offer all women an expanded carrier screening panel. In the United States, population-based carrier genetic screening for cystic fibrosis and spinal muscular atrophy is routinely offered. To identify carriers of hemoglobinopathy, a simple screening test is the assessment of MCV. However, CBC and MCV may not detect carriers of hemoglobin S, C, or E. Analysis of maternal hemoglobin can be performed by either high-performance liquid chromatography (HPLC) or isoelectric focusing (IEF) to identify these abnormal hemoglobins. To check for sickle cell anemia, women should undergo a sickle-cell test.

Women at increased risk for thyroid disorders (hypo- or hyperthyroidism) or type 2 diabetes mellitus, as well as for certain infectious diseases are screened for these disorders.

Data on the optimal number and frequency of prenatal visits, as well as the optimal content of these visits, are limited.

Pregnant women should be advised about signs and symptoms that should be reported to a doctor immediately, such as:

- Vaginal bleeding
- Discharge of fluid from the vagina
- Decreased fetal activity
- Signs and symptoms of preterm labor
- Signs and symptoms of preeclampsia
- Signs and symptoms suggestive of medical or surgical disorder

Regarding singleton pregnancies, the assessments that are done on a continuous basis at each prenatal visit are the following:

- Blood pressure measurement
- Weight measurement
- Overview of signs and symptoms of possible pregnancy problems
- Documenting fetal heartbeats
- Assessment of maternal perception of fetal activity in the second and third trimesters
- Assessment of fetal growth in the second and third trimesters either by measurement of fundus height or by ultrasound assessment for women with risk factors for intrauterine growth restriction.
- Assessment of fetal presentation in the third trimester.
- Assessment of significant events from a previous visit, such as recent travel, illness, stressors, or exposure to infection (e.g., Zika virus or severe acute respiratory syndrome, coronavirus 2 [SARS-CoV-2]), etc.

Periodic evaluations and procedures performed from 15 to 24 weeks of singleton pregnancy concern the following:

- Gestational age-appropriate screening for neural tube defects and other congenital anomalies and trisomy 21 screening or testing are offered.
- A short cervical length (≤25 mm) on transvaginal ultrasound between 16- and 24-weeks' gestation is associated with an increased risk of spontaneous preterm delivery. The length of the cervix can be measured when a pregnant woman has an ultrasound scan for fetal abnormalities. There is

insufficient evidence to mandate a policy of population-based screening of cervical length between 16 and 24 weeks as routine for all pregnancies, but it is usually performed in pregnancies at high risk for spontaneous preterm delivery.

From 24 to 28 weeks of singleton pregnancy, the following are recommended:

- Screening for gestational diabetes and anemia at 24 to 28 weeks' gestation.
- In RhD negative women, antibody testing is performed at 28 weeks of gestation and anti-D immunoglobulin is administered.

Finally, from 28 to 36 weeks of singleton pregnancy, the following are recommended:

- Screening for sexually transmitted infections in women at increased risk.
- Prenatal evaluation of fetal well-being is indicated in pregnancies in which there is an increased risk of fetal death before delivery. It usually starts at 32 weeks or later but may start earlier if the doctor thinks the fetus is at increased risk of death and delivery or other intervention is an option.
- For breech pregnancies, external transformation is offered at 36 weeks of gestation.
- Screening for group B β-hemolytic streptococcus at 36 +0 to 37 +6 weeks of gestation.
- Educating women about childbirth preparation, the birth process and the postpartum period.

Regarding twin pregnancies, routine ultrasound examination in the first or early second trimester is the best method to ensure early diagnosis of a twin pregnancy, determine the exact gestational age and determine chorionicity. Regarding the latter, the most reliable indicators of dichorionic twins are the identification of two separate placentas and discordant fetal sex. If there is a single placental mass, chorionicity and amnionicity are determined by identifying a common membrane and examining that membrane for a twin peak or lambda sign (dichorionic twins), a T sign (monochorionic/diamniotic twins), thickness (thick for dichorionic twins), and the number of layers (four layers for dichorionic twins).
Regarding maternal complications, multiple pregnancy is considered a high-risk factor for preeclampsia and is therefore an indication for prophylactic administration of low-dose aspirin. The dose for multiple pregnancies is the same as for singleton pregnancies. On the other hand, whether gestational diabetes is more common in twin pregnancies is unclear. Screening, diagnosis and management are similar to singleton pregnancy.

Morbidity and mortality in twins are significantly higher than in singletons.

Additionally, all twin pregnancies are at increased risk of preterm birth, congenital anomalies, and growth restriction compared with singleton pregnancies, although twins are associated with lower rates of prolonged pregnancy and macrosomia. Monochorionic twins in particular are at significantly higher risk of adverse perinatal outcome than dichorionic twins. They are also at risk for unique complications of pregnancy, such as twin-twin transfusion syndrome (TTTS), twin anemia-polycythemia sequence (TAPS), twin reversed arterial perfusion sequence (TRAP), and selective fetal growth restriction (sFGR). Monoamniotic twins are also at risk of entanglement of the umbilical cords, as well as the possibility of being conjoined.

In particular, the main source of perinatal morbidity and mortality in twin pregnancies is preterm birth. A brief administration of tocolysis in patients with acute preterm labor is reasonable to allow the administration of antenatal corticosteroids. There is no convincing evidence that routine prophylactic use of tocolytic drugs, pessary, cervical cerclage, or supplemental progesterone (vaginal or intramuscular) in twin pregnancies in which the cervix is normal (i.e., not dilated or short in length) in the second trimester reduces chances of premature birth. However, the selective use of each of the interventions may be indicated in specific clinical scenarios. For women with twin pregnancies with asymptomatic cervical dilatation before 24 weeks, clinically indicated cervical cerclage after amniocentesis in the sac of the presenting twin is recommended, rather than conservative management, to rule out subclinical infection. Alternatively, the woman may be observed for several hours for clinical signs of infection. Women who refuse cerclage are offered vaginal progesterone therapy, as are women with a short cervix. For women with a twin pregnancy and a short, closed cervix on second-trimester transvaginal ultrasound, vaginal progesterone therapy is recommended to reduce the risk of preterm birth, especially in women with no prior history of preterm birth, rather than simply monitoring, cerclage, or pessary. Practice variability for this clinical scenario is common. Some investigators use a cervical length <20 mm as a threshold to define a short cervix in the second trimester in women without prior spontaneous labor, while other investigators use a cervical length ≤25 mm for all pregnant women. Cervical cerclage is also an option on a case-by-case basis when the cervix is too short and the physician believes that the suture can be placed safely. Some investigators use a threshold of ≤15 mm to consider cerclage, and others use a threshold of <20 mm, taking into account the woman's obstetric history. Cerclage is more likely to be considered in a pregnant woman with a prior history of preterm labor and vaginal progesterone in a woman without a prior history, as cervical insufficiency is more likely in a patient with a prior history of preterm labor. Premature rupture

of membranes (PROM) typically occurs in the sac of the presenting twin. However, PROM can also develop in the sac of the non-presenting twin, especially after invasive procedures (e.g., amniocentesis, fetoscopy). The management of PPROM and PROM is generally similar in twin and singleton pregnancies. There may rarely be a role for delayed labor in carefully selected twin pregnancies at early gestational age (<24 weeks), in which only the first (presenting) fetus is spontaneously delivered vaginally due to PPROM.

Management of fetal growth restriction and/or discordance depends on chorionicity. Growth restriction in dichorionic twins is generally treated as in singleton pregnancies: determination of cause, repeated ultrasound assessment of fetal growth, continuous assessment of fetal well-being (biophysical profile [BPP] or cardiotocography [NST] with amniotic fluid volume estimation and Doppler velocimetry), and timing of delivery based on a combination of factors (gestational age, umbilical artery Doppler, BPP score, ductus venosus Doppler, and presence or absence of risk factors or signs for uteroplacental insufficiency). Regarding discordant congenital anomalies of fetuses, their management depends on chorionicity. In monochorionic twins, elective termination of the fetus can be performed, but the technique is different from that in dichorionic twins and is more demanding. Umbilical cord occlusion (e.g., radiofrequency or laser ablation, bipolar coagulation, ligation) is required instead of intravenous potassium chloride or digoxin to reduce risk to the other fetus due to shared circulations. In dichorionic twins, selective termination of the abnormal fetus using intravascular injection (e.g., intracardiac injection of potassium chloride) is a safe and effective option in expert hands, although there is a risk of miscarriage or preterm delivery of the co-twin.

Monochorionic twin pregnancies should be monitored with serial ultrasound for the development of TTTS, TAPS, and selective intrauterine growth restriction (sFGR) (Table 1). However, diagnosis of TTTS, TAPS, and sFGR can be difficult because these disorders have overlapping findings and can present in any combination.

TTTS syndrome is characterized by relative hypovolemia of one twin and hypervolemia of the other as a result of an imbalance in the direction of flow through the placental anastomoses. The key prenatal finding is monochorionic placentation with discordant amounts of amniotic fluid (maximum pocket <2 cm in one amniotic sac and >8 cm in the other amniotic sac). TTTS is usually first detected in ultrasound examinations performed in the early to mid-second trimester. In a minority of cases, acute intrapartum TTTS occurs at birth from a rapid and large blood transfusion from the donor to the recipient. This leads to immediate anemia and possibly hypovolemic shock in the donor twin and immediate polycythemia in

the recipient twin. The five classic stages of TTTS are based on findings from two-dimensional ultrasound and Doppler measurements of the umbilical artery, umbilical vein, and ductus venosus. Higher stages, characterized by Doppler abnormalities with or without ascites, are generally associated with a worse perinatal prognosis, but the clinical picture of a particular case does not always follow a smooth progression of stages. The three main approaches to the management of TTTS are conservative management, ligation of placental anastomoses via amnioscopy and laser, and amnioablation. The choice of approach depends on the stage, maternal symptoms and signs, gestational age, and the availability of the required technical expertise.

Twin anemia-polycythemia sequence (TAPS) can occur spontaneously or after laser ablation for TTTS syndrome. It is characterized by a highly discordant hemoglobin difference between the fetuses, and, unlike TTTS, the amniotic fluid volume of each twin is normal in the classic, pure form of the syndrome. It may be considered an atypical chronic form of TTTS caused by unbalanced slow transfusion of red blood cells through a few very small placental arteriovenous anastomoses, leading to large hemoglobin differences between the twins, resulting in anemia in one twin and polycythemia in the other twin. To screen for TAPS, serial middle cerebral artery peak systolic velocity (MCA-PSV) measurements are performed beginning at 16 weeks looking for supportive findings such as discordant placental echogenicity, cardiomegaly of the donor twin, or a starry sky liver of the recipient twin. Although there is some overlap between the findings for TAPS sequence and TTTS, key features that aid in the differential diagnosis are that MCA-PSV discordance is diagnostic of TAPS sequence and is not found in pure TTTS, and amniotic fluid discordance (oligohydramnios and polyhydramnios sequence) is essential in pure TTTS and is not observed in pure TAPS sequence. After the diagnosis of TAPS, Doppler flow studies of the umbilical artery, umbilical vein, and ductus venosus should be performed to classify the severity of the disease, which is the basis for further monitoring and management. In the absence of fetal therapy, the TAPS sequence may result in the birth of two healthy neonates, the need for a neonatal blood transfusion or partial exchange transfusion, or even the death of one or both twins. Its management is similar for both automatic and post-treatment laser sequence TAPS. Management is usually conservative with intervention offered for persistent and worsening stage 2 or higher TAPS sequence. The choice of intervention is based on the gestational age, the stage of the disease and the experience of the physician. There is no consensus on the optimal treatment. Conservative management, laser surgery, intrauterine transfusion, selective fetal reduction and preterm delivery have been used. The appearance or persistence of stage 2, 3 or 4 TAPS beyond 32 +0 weeks' gestation is an indication for delivery.

Selective fetal growth restriction (sFGR) refers to the restriction of growth of a fetus of a monochorionic twin pair due to discordant distribution of the placenta. It affects 10 to 15% of these pregnancies. Beginning in the early second trimester, monochorionic twin pregnancies should undergo regular serial ultrasound examinations to monitor the development of sFGR as well as TTTS syndrome or TAPS sequence. The umbilical artery waveform pattern and end-diastolic flow of the smaller fetus are used to classify sFGR into three types that are predictive of the expected clinical course and risk profile. sFGR type 2 has the worst prognosis because of the high risk of death of one fetus and preterm delivery. The goal in managing monochorionic twins with sFGR is to identify those who can be safely managed conservatively versus those who could benefit from fetal intervention, either selective fetal reduction or fetoscopic laser ablation, or delivery.

Twin reversed arterial perfusion sequence (TRAP) or acardiac twin refers to a rare complication unique to monochorionic twin pregnancies in which one severely abnormal twin with an absent or atypical heart ("acardiac twin") is passively and reversibly supplied with blood from the other twin ("twin-pump") through anomalous arterioarterial anastomoses. TRAP sequence is diagnosed prenatally based on three main ultrasound findings:

- Monochorionic multiple pregnancy
- A fetus with either absent cardiac activity or a rudimentary pump structure
- Doppler study demonstrating retrograde arterial flow to the acardiac fetus (pathologic finding).

The phenotype of the acardiac fetus ranges from well-developed lower limbs, pelvis, and abdomen to a mass of tissue that is not easily recognizable as a fetus. The skull may be absent or present with major defects such as anencephaly, holoprosencephaly, or other major neuroanatomical malformations. Other possible abnormalities include limb defects, anterior abdominal wall defects, and absence of lungs, kidneys, spleen, or liver. The pump fetus may have signs of high-output heart failure, including polyhydramnios, cardiomegaly, pericardial and pleural effusions, ascites, and tricuspid valve regurgitation. These findings are poor prognostic factors. The ratio of the weight of the acardiac twin to that of the on-pump twin can also be used to assess prognosis. Among TRAP sequence cases with poor prognostic features treated conservatively, perinatal twin mortality rates of ≥50% were reported in two series. However, one series had older data and the other a small number of cases. As pregnancies complicated by the TRAP sequence appear to have an increased risk of birth defects, an invasive procedure (e.g., amniocentesis, chorionic villus sampling) to obtain fetal cells for genetic testing is recommended. Pregnant women with a TRAP sequence should be referred to fetal treatment centers for further evaluation

and counseling regarding treatment options. Women with clinical manifestations indicative of a poor prognosis are candidates for intervention through umbilical cord occlusion therapy. Intrauterine therapy improves survival rates to 80% or higher. Three current methods of umbilical cord occlusion therapy for the management of TRAP sequence are radiofrequency ablation (RFA), bipolar cord coagulation, and intrafetal or interstitial laser coagulation.

In monoamniotic twin pregnancies, fetal mortality occurs in approximately 20% and is the most serious complication in multiple pregnancies with a monoamniotic placenta. Umbilical cord entanglement is a major cause of fetal death in these pregnancies. Finding umbilical cord entanglement (M-mode with two different heartbeats in adjacent cord loops) is diagnostic for monoamniotic twins, but umbilical cord entanglement is not always detected. Another finding diagnostic of monoamniotic twins is the absence of a membrane between the fetuses as well as a yolk sac with two fetal poles. In the second and third trimesters, the diagnosis is excluded if two placentas, a common membrane or fetuses of different sexes are detected. Furthermore, the risk for trisomy 21 in each fetus of monozygotic twin pregnancies is similar to or lower than the risk in singleton pregnancies of matched maternal age. Both twins of a monozygotic pair are either affected or unaffected, with rare exceptions. Standard methods for screening for Down syndrome can be used (e.g., cell free fetal DNA [cffDNA], maternal serum markers). Major anomalies have been reported in 7 to 28% of monoamniotic twin pregnancies. Also, congenital heart defects are more common in monoamniotic twins than in singletons. Of note, monoamniotic twins have a lower rate of TTTS syndrome than diamniotic twins (2 to 6% vs. 9 to 15%), but the risk is sufficient to warrant screening.

Early spontaneous reduction of a sac ("vanishing twin") has been reported in 15 to 36% of IVF pregnancies. Death of a single fetus after 20 weeks of gestation occurs in approximately 5% of twin pregnancies. Because of placental vascular anastomoses between monochorionic twins, intrauterine death of one twin in a monochorionic twin pregnancy can cause acute hypotension, anemia, and ischemia in the other co-twin, resulting in co-twin morbidity or death. For this reason, in monochorionic twins, if fetal evaluation after 26 weeks' gestation suggests imminent death of one twin, early delivery of both twins is recommended rather than conservative management. On the other hand, when the death of one twin has already occurred, early delivery of the other twin is unlikely to benefit and puts the surviving fetus at risk of morbidity and/or mortality from preterm birth.

Multifetal pregnancy reduction (MPR) refers to a procedure in which the total number of fetuses in a multiple pregnancy is reduced by terminating one or more fetuses, chosen mostly at random, but

considering technical factors. The main rationale for the MPR is that the "take home" baby rate per pregnancy increases with increasing gestational age at birth as well as birth weight, thereby reducing morbidity and mortality from preterm birth. The risks of certain maternal complications, such as preeclampsia, are also reduced. The financial and psychological effects of multiple pregnancy on families also play a role. MPR should be offered for any pregnancy with three or more fetuses, as there is good evidence from meta-analyses of observational studies that it improves neonatal survival rates and outcome in surviving fetuses. MPR can also be applied for dichorionic twin pregnancies, particularly if there is a medical or obstetrical indication, such as maternal medical disease (e.g., heart disease, kidney disease) or a history of preterm birth or cervical insufficiency. Reduction to singleton pregnancy may also be considered in women of very advanced maternal age (≥45 years), as they are at high risk for pregnancy complications with a twin pregnancy, compared to a singleton pregnancy. In addition, reduction may be considered for monochorionic diamniotic twins with radiofrequency ablation (RFA). MPR is usually performed between 10 +0 and 13 +6 weeks of gestation but can be performed later in pregnancy. Local laws and regulations, chorioamnionicity, and the results of prenatal fetal screening with both invasive tests and ultrasound influence the timing and choice of procedure. Pre-procedure chorionic villus sampling can be performed in fetuses not scheduled for reduction and does not increase the post-procedural pregnancy loss rate, while offering the certainty that a chromosomally normal fetus will be left behind. Preoperative ultrasound assessment of fetal growth and anatomy is also recommended. Fetuses selected for MPR are generally closer to the anterior uterine wall and/or fundus, as these locations are more accessible for needle insertion. Potassium chloride is injected into the fetal chest cavity, which causes asystole, but other drugs can be used. Most triplet and higher order multiple pregnancies are reduced to twin pregnancies. However, reduction to singleton pregnancy is becoming more common and is associated with good outcomes. More data are needed to determine whether reduction to a singleton significantly improves pregnancy outcome over reduction to twins, which usually has acceptable pregnancy outcomes, particularly compared to higher order multiple pregnancies. The main benefit of MPR is the reduction of preterm birth. MPR loss rates are approximately 5%, but are affected by operator experience, initial number of fetuses (highest risk of loss at six or more fetuses), and final number of fetuses (highest risk of loss at three or more fetuses). Maternal serum alpha-fetoprotein (MSAFP) concentration is usually elevated for several weeks after any fetal reduction procedure and is not necessarily indicative of fetal defects. Laboratory evidence of coagulation disorders has been observed, but no cases of clinically apparent disseminated intravascular coagulation have been reported.

Selective termination (ST) refers to a procedure in which one or more specific fetuses of a multiple pregnancy are terminated because of a known or suspected fetal abnormality, including a chromosomal, structural, genetic or developmental abnormality, which has been identified by ultrasound examination or with definitive fetal diagnostic testing after amniocentesis or chorionic villus sampling. ST was initially offered as an option to parents of fetuses with significant non-fatal abnormalities that could result in the birth of a live newborn and the long-term survival of a severely disabled child. ST is now also offered to parents of fetuses with fatal abnormalities because, for some parents, it is emotionally preferable to undergo ST rather than continue to carry a fetus that will die before or shortly after birth. In addition, it is considered that, in some cases, the termination of the abnormal fetus may optimize the outcome of the other normal fetus or fetuses. Loss rates after ST termination depend on starting and ending fetal number. In monochorionic fetuses, the most common method for termination is cord occlusion because it reduces the risk to the other fetus.

Therefore, the routine prenatal care of women with twin pregnancies has some differences from the usual prenatal care of singleton pregnancies in several aspects, such as recommendations for weight gain and micronutrient intake, universal prophylactic administration of low-dose aspirin to prevent of preeclampsia, the choice of an appropriate method for screening for chromosomal abnormalities, and the frequency and purpose of ultrasound monitoring. For women who choose to be screened for Down syndrome, either combined first-trimester testing or non-invasive prenatal testing using cell-free fetal DNA (cffDNA) is recommended. While the combined test provides an early, fetus-specific risk assessment due to the inclusion of nuchal translucency measurement, cffDNA has higher detection rates. Both fetuses should be karyotyped, when performed, as even monozygotic twins may be discordant. On fetal anatomy ultrasound at 18 to 22 weeks' gestation, one approach is to routinely assess cervical length with transabdominal ultrasound and then perform transvaginal ultrasound if the cervix is poorly imaged or short. The ISUOG Society recommends a different approach: cervical length measurement by transvaginal ultrasound every two weeks in twin pregnancies between 16 and 24 weeks, as in singleton pregnancies at increased risk for preterm birth. In terms of congenital anomalies, each fetus of a dizygotic twin pair has a similar congenital anomaly rate to singleton fetuses, and the anomalies, if present, have a low concordance rate. The concordance rate of major congenital malformations in monozygotic twins is approximately 20%. In addition to anatomic ultrasound at 18 to 22 weeks' gestation, fetal heart ultrasound is performed at 18 to 22 weeks for monochorionic but not dichorionic twins, because 2 to 10% of monochorionic twins referred

for routine fetal heart ultrasound have congenital heart disease in at least one twin, and fetal heart ultrasound is important in the diagnosis and management of TTTS.

With regard to fetal growth, growth restriction is more common in twin than singleton pregnancies and can manifest in three ways:

- One twin may be small for gestational age (called selective fetal growth restriction)
- Both twins may be small for gestational age, or
- One twin may be significantly smaller than the other twin (i.e., growth discordance), although neither is small for gestational age. In nearly two-thirds of discordant twin pairs, the younger twin has a birth weight <10th percentile.

According to the International Society of Ultrasound in Obstetrics and Gynecology ISUOG, women with an uncomplicated dichorionic twin pregnancy should have a first-trimester ultrasound, a second-trimester anatomical ultrasound (including measurement of cervical length) and scans every 4 weeks thereafter. Complicated dichorionic twins should be examined sonographically more frequently, depending on the condition and its severity. At each ultrasound the following should be assessed: fetal biometry, amniotic fluid volume and umbilical artery Doppler (from 20 weeks' gestation) for both twins. The difference in estimated fetal weight (EFW) should be calculated and documented at each scan from 20 weeks. On the other hand, uncomplicated monochorionic twins, according to the ISUOG Society, should undergo a first-trimester ultrasound and then every 2 weeks after 16 weeks, in order to detect early TTTS syndrome, TAPS sequence or selective growth restriction sFGR (table 1). Their early detection has been shown to improve perinatal outcome. Complicated monochorionic twins should be scanned more frequently, depending on the condition and its severity. In particular, middle cerebral artery peak systolic velocity (MCA- PSV) should be recorded from 20 weeks to screen for TAPS. In monochorionic diamniotic twins (MCDA), amniotic fluid volume (maximum vertical pocket) should be assessed and documented at each ultrasound to screen for TTTS. Regarding monochorionic monoamniotic twins, there is insufficient evidence to suggest a different frequency of growth monitoring compared to monochorionic diamniotic twins. Doppler examination to detect altered flow has been suggested as an indication of umbilical cord vascular compression but is not recommended for routine monitoring.

For antepartum fetal assessment, weekly NST and amniotic fluid volume determination or biophysical profile are performed starting at 32 weeks in dichorionic twins and from 28 weeks in monochorionic diamniotic twins. If complications such as growth restriction develop, then screening is started earlier and/or performed more frequently. Monochorionic monoamniotic twins are monitored more closely. It is common practice to hospitalize patients with monoamniotic twin pregnancies in the early third trimester for intensive fetal heart rate monitoring, but patterns vary between institutions. These patients are admitted at 26 to 28 weeks of gestation.

Decision making regarding the timing and route of delivery in uncomplicated twin pregnancies is based on chorionicity, amnionicity, and presentations of both twins. In complicated twin pregnancies, decision-making takes the specific complication into account, as is the case with singleton pregnancies.

Spontaneous or medically indicated preterm labor complicates more than 50% of twin pregnancies. Thus, timing of delivery is not at the physician's discretion in most cases. For uncomplicated dichorionic twin pregnancies, planned delivery is recommended from 38 +0 to 38 +6 weeks of gestation, according to the recommendations of the American College of Obstetricians and Gynecologists (ACOG). In contrast, in the UK, the National Institute for Health and Care Excellence (NICE) recommends planning delivery at 37 weeks. Delivery of monochorionic diamniotic twins based on the UK NICE Institute is recommended at 36 weeks of gestation. This approach has narrower limits than that of ACOG, which recommends delivery at 34 +0 to 37 +6 weeks. In contrast, for monochorionic monoamniotic pregnancies, ACOG and NICE recommend delivery between 32 +0 and 34 +0 weeks of gestation, due to the increased risk of perinatal mortality in the third trimester.

Both amnionicity and fetal presentation at the onset of labor influence the choice of delivery route in twin pregnancies. For diamniotic twins with cephalic presentation of both fetuses, vaginal delivery is recommended in the absence of established indications for caesarean section. For diamniotic twins with the first fetus cephalic and the other noncephalic, a trial of vaginal delivery with an attempt for breech extraction of the second twin is offered only if the obstetrician has the required experience and the patient gives informed consent. When the first twin is not in cephalic presentation, caesarean section is recommended. While a trial of vaginal delivery after prior caesarean section (TOLAC) is offered to women with twins and one prior caesarean section, there are few data evaluating the safety of TOLAC in twins and two or more prior cesarean deliveries.

A repeat cesarean delivery is recommended for these women, but some physicians may make this decision on a case-by-case basis, allowing a trial of vaginal delivery electively and with very close maternal and fetal monitoring. Monochorionic monoamniotic twins are born by caesarean section, to avoid complications during delivery from entanglement of the umbilical cords.

On the other hand, pregnant women with triplet pregnancies should receive counseling regarding the specific issues and risks associated with these pregnancies, management of complications, and the recommendation for cesarean delivery. Follow-up of triplet pregnancies involves more frequent ultrasound examinations and office visits, particularly after 20 weeks' gestation, because of the increased risk of maternal morbidity and perinatal morbidity and mortality. In the second half of pregnancy, these pregnancies are at increased risk for preterm birth, preeclampsia, or fetal growth discordance compared to singleton pregnancies.

In terms of ultrasound monitoring, an ultrasound is performed in the first or early second trimester to determine whether a triplet pregnancy is trichorionic, fully monochorionic, or has a monochorionic pair of twins to guide pregnancy counseling and management. Regarding the role of ultrasound cervical length measurement, cervical length measurement is not recommended in triplet pregnancies. Although this is a common screening test for predicting preterm delivery in singleton and twin pregnancies, short cervical length is not a sensitive screening test for predicting preterm delivery in triplets. Furthermore, in contrast to singleton and twin pregnancies, the limited data on the effectiveness of intervention (e.g., progesterone supplementation, cervical cerclage) to prevent preterm birth in women with triplets and short cervical length suggest no avail. Also, triplet pregnancies should undergo focused anatomic screening for neural tube defects in the second trimester, since α-fetal protein (AFP) testing has not been validated in triplets. The development of the fetuses is monitored by ultrasound examination. Onset and frequency are driven by the type of placenta. Fetal growth restriction is diagnosed using the same criteria used for singleton pregnancies. Discrepant growth is usually defined as a 20 to 25% difference in sonographically estimated fetal weight (EFW) of the smallest compared to the largest fetus (EFW of larger fetus - EFW of smaller fetus) / (EFW of larger fetus × 100). The discordance may be an indicator of structural or genetic abnormalities, infection, TTTS syndrome, or disease caused by the placenta.

In particular, any multiple pregnancy with a common chorionic sac puts the involved fetuses at risk for TTTS, TAPS and sFGR. For this reason, monochorionic triamniotic and dichorionic triamniotic triplets follow an ultrasound protocol similar to that commonly used to monitor monochorionic twin pregnancies. Also, any multiple pregnancy with a common amniotic sac puts the fetuses involved at high risk of

umbilical cord entanglement and death from cord compression. Thus, experts recommend that patients with monochorionic monoamniotic or dichorionic diamniotic triplets be admitted to the hospital at 26 weeks of gestation to facilitate the performance of one hour of continuous fetal heart rate monitoring every eight hours. Multiple pregnancies with a common amniotic sac are also at risk for TTTS, selective growth restriction and TAPS. Ultrasound follow-up for these conditions is the same as described above for triplets with a common chorionic sac (monochorionic triamniotic and dichorionic triamniotic). Finally, trichorionic triamniotic placentation is associated with more favorable perinatal outcomes than triplet pregnancies in which the fetuses share an amniotic sac or placenta/chorion. However, growth restriction is still a major concern, so starting at 20 weeks, an ultrasound scan is generally performed every three to four weeks to monitor fetal growth. Monitoring for TTTS and TAPS is not necessary as the placenta is not common.

It is also important to offer genetic counseling to women with triplet pregnancies to discuss the risk of aneuploidy in one or more fetuses. No serum marker or free fetal DNA (cffDNA) test for aneuploidy has been validated in triplet pregnancies, and no study has published observed detection rates for Down syndrome and other common trisomies in triplet pregnancies. Increased nuchal translucency (defined as greater than the 95th percentile for gestational age) has been validated as a screening test for trisomy 21 and trisomy 18 in triplets, but not for trisomy 13.

Regarding the prophylaxis of preeclampsia in triplet pregnancies, it is recommended, as in twin pregnancies, daily administration of low-dose aspirin after 12 weeks of gestation to reduce the occurrence of preeclampsia and related complications (premature delivery and growth restriction). Screening for diabetes is done at the first antenatal visit and, if negative, again at 24 weeks ' gestation. Multiple interventions have been investigated to reduce the risk of preterm birth, none of which have been shown to be effective for triplet pregnancies. However, administration of corticosteroids and magnesium sulfate may reduce neonatal morbidity from preterm birth.

Timing of delivery in triplet pregnancies is based on the type of amnionicity, regardless of lung maturity. Monoamniotic and diamniotic triplets are born between 32 +0 and 32 +6 weeks. For an uncomplicated trichorionic triamniotic or dichorionic triamniotic triplet pregnancy, NICE recommends planned delivery at 35 weeks' gestation. Regarding the monochorionic triamniotic triplet pregnancy, NICE recommends that the time of delivery depends on the individual clinical scenario and the individual assessment of the physician. Preterm delivery is indicated in complicated pregnancies and the timing depends on the individual clinical scenario. In all triplet pregnancies, cesarean delivery is recommended.

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