A STUDY OF COMPLICATIONS IN INFANTS OF DIABETIC MOTHER

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ACRONYMS

AGA : Appropriate for gestational age

ASD : Atrial septal defect

DM : Diabetes Mellitus

GCT : Glucose Challenge Test

GDM . : Gestational Diabetes Mellitus

HbAlc : Hemoglobin Ale

IDM : Infant of Diabetic Mother

IDDM : Insulin Dependent Diabetic Mother

LGA : Large for Gestational Age

MODY : Maturity Onset Diabetes of the Young

NDDG : National Diabetes Data Group

NEC : Necrotizing Enterocolitis

OGTT : Oral Glucose Tolerance Test

PDA : Patent Ductus Arteriosus

PGDM : Pregestational Diabetes Mellitus

PPH : Persistent Pulmonary Hypertension

PTH : Parathyroid Hormone

RDS : Respiratory Distress Syndrome

RVT : Renal Vein Thrombosis

SGA : Small for Gestational Age

VSD : Ventricular Septal Defect

INTRODUCTION

Diabetic mellitus is a group of metabolic disease characterized by chronic hyperglycemia associated with disturbance of carbohydrates, fat and protein metabolism due to absolute or relative deficiency in insulin secretion and or action.

Historically, infants of diabetic mothers (IDM) have been at significantly greater risk for spontaneous abortion, stillbirth, congenital malformations and perinatal morbidity and mortality. Subsequently, advances in maternal and fetal care have improved the outcome of the infant of a diabetic mother.

The IDMs are at an increased risk for periconceptional, fetal, neonatal and long term morbidities. They have double the risk of serious birth injury, triple the likelihood of caesarean section and quadruple the incidence of admission to a newborn intensive care unit. The causes of the fetal and neonatal sequelae of maternal diabetes are likely multifactorial, however, many of the perinatal complications can be traced to the effect of maternal glycemic control on the fetus and can be prevented or at least reduced through meticulous perinatal and intra-partum care.

The present study was conducted in infants born to a diabetic woman at Manipal Hospital, Bangalore. The complications and perinatal outcome in infants of diabetic mothers were studied.

Aims and Objectives

- To know the metabolic complications in infants of diabetic mother.
- To know the incidence of major and minor congenital anomalies in infants of diabetic mother.
- To know the perinatal outcome in infants of diabetic mothers.

Review of Literature

DIABETES MELLITUS: It is defined as a group of metabolic diseases that are characterized by hyperglycemia resulting from defects in insulin secretion or action or both1.

CRITERIA FOR DIAGNOSIS OF DIABETES MELLITUS:

- Fasting plasma glucose > 126 Mg/dl
- 2 hour post prandial glucose > 200 Mg/dl

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS1:

1) Type 1 Diabetes (Beta -cell destruction usually leading to absolute insulin deficiency)

A) Autoimmune

B) Idiopathic

2) Type 2 diabetes (Insulin Resistance with relative insulin deficiency)

3) Other specific types

A) Genetic defects of Beta cell function

Mitochondrial DNA defect

Wolfram's syndrome

Maturity - onset Diabetes of the young (MODY)

-Chr 20 q (MODY-1)

-Chr 7 P (MODY-2)

- Chr 12 q (MODY -3)

B) Genetic defects in insulin action

- Type A insulin resistance
- Leprechaunism
- Rabson - Mendehall syndrome
- Lipodystrophy
- Others

C) Diseases of the exocrine pancreas

- Pancreatitis (including fibrocalculous Pancreatopathy)
- Pancreatectomy
- Trauma (severe)
- Neoplasia
- Cystic fibrosis
- Haemochromatosis
- Others

D) Endocrinopathies

- Cushing syndrome
- Acromegaly
- Pheochromocytoma
- Glucagonoma
- Aldosteronoma

Hyperthyroidism

- Somatostatinoma
- Others

E) Drug or Chemical induced (Impairing insulin secretion or enhancing insulin resistance nicotinic Acid)

- Nicotinic Acid
- Glucocorticoids
- Thyroid hormone
- Beta adrenergic agonists
- Thiazides
- Phenytoin (Dilantin)
- Pentamidine
- Diazoxide
- Vecor
- Interferon(alpha)

F) Infections

- Congenital rubella
- Cytomegalovirus
- Coxsackie B Virus
- Mumps
- Adenovirus

G) Uncommon forms of immune mediated DM

- Anti - Insulin receptor antibodies
- Stiff - Man syndrome

H) Other genetic syndromes sometimes associated with DM

- Down syndrome
- Klinefelter syndrome
- Turner syndrome
- Prader - Willi syndrome
- Lawrence - Moon - Biedl syndrome
- Myotonic dystrophy
- Friedrich's Ataxia

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- Huntington's Chores
- Porphyria
- Others

4) Gestational Diabetes Mellitus

PREGNANCY IN WOMEN WITH DIABETES MELLITUS

HISTORY:

The doctoral thesis of Heinrich Gottleib Bennewitz of Berlin published in 1824 presents the first case of what was probably insulin dependent diabetes in pregnancy[2]. Bennewitz describes Frederica pape, a 22-year-old woman, who after several successful MD Thesis. pregnancies,

was admitted to the Berlin infirmary at 36 weeks gestation with polydypsia and polyuria, classic symptoms of Diabetes. This pregnancy ended with intra-partum death of 12 lb fetus 2.

In an article published in 1882 J.Mathews Duncan reported 22 pregnancies in 15 women with diabetes complicating pregnancy. 13 fetal deaths occurred in 19 pregnancies and 9 of the women died within 1 year of the pregnancy .Duncan identified the two important causes of perinatal loss, stillbirths and macrosomia.

In 1915, Elliott Joslin reported 4 maternal deaths in 7 cases between 1905 and 1915. 2 women died from ketoacidosis and coma and one from tuberculosis. Joslin stressed that fatal ketoacidosis and coma were more likely to occur in pregnancy. Only one surviving infant was observed in these 7 cases. The other six resulted in 4 stillbirths, one neonatal death and one pregnancy termination 2.

In 1909 J. Whitridge Williams Summarized the world literature that now included 66 pregnancies in 43 patients. The maternal mortality was 50 %. Approximately half of these women died during the pregnancy and half over the next 2 years. The rate of pregnancy loss was more than 40 %.2

In 1913, De Lee stressed that pregnancy should be terminated if complicated by diabetes as the maternal and fetal risks were too great 2.

DISCOVERY OF INSULIN:

In 1921, Frederick Banting and his collaborators, physiologist J.J.R.Macleod, biochemist James Collip and medical student Charles Best isolated insulin. With insulin

most women with Diabetes Mellitus could survive pregnancy. In 1928 De Lee who warned against the continuation of pregnancy before discovery of insulin now advised, owing to the introduction insulin and to advances in our knowledge of diabetes the treatment of diabetes complicating pregnancy has undergone a complete revolution .2

In 1923, William Reveno, one of the founders of the American Diabetes Association reported successful therapy of diabetic ketoacidosis in pregnancy .2

In 1928, Dr. Priscilla white of the Joslin clinic noted that excellent glucose control was essential to fetal welfare and suggested that the high glucose content of placental blood was probably associated with excessive fetal growth. White added that a team approach with "Close and constant supervision" of the patient was key part of the treatment programme. 2

PREVALENCE:

Diabetes Mellitus complicates 3 - 5 % of all pregnancies. TYPE 2 DM the most common form of DM is characterized by onset late in life, peripheral insulin resistance, relative insulin deficiency obesity and the development of vascular renal and neuropathic complications. More than half of the women who develop GDM which represents approximately 90 % of all cases of diabetes complicating pregnancy will develop type 2 DM later in life. Type 1 DM occurs

early in life is characterized by an autoimmune process that destroys the insulin producing (beta) cells of the pancreas and therefore must be treated with insulin replacement. 3

Diabetes is the most common medical complication of pregnancy. Women can be separated into those who were known to have diabetes before pregnancy Pre- gestational or overt and those diagnosed during pregnancy - gestational 4.

CLASSIFICATION OF DIABETES MELLITUS COMPLICATING PREGNANCY

Dr Priscilla White was a diabetologist interested in the outcome of pregnancy in relation to the duration of disease, the age at diagnosis and the presence of end organ effects of diabetes. These variables in her analysis were prognostically significant and were incorporated initially in a more complex form into the classification system still widespread use today 5.

Table 1: Classification of Diabetes in Pregnancy'

Gestational Diabetes Class	Fasting Glucose Level	Postprandial glucose Level
A-l	< 105 mg/ dl &	< 120 mg / dl
A-2	> 105 mg/ dl & or	>120 mg / dl

GESTATIONAL DIABETES MELLITUS

Definition: Gestational diabetes mellitus is defined as glucose intolerance that begins or is first defected during pregnancy1,6.

Prevalence: GDM affects nearly 7 % of all pregnancies resulting in > 2, 00,000 cases per year 7. Depending on the population sample and diagnostic criteria the prevalence may range from 1 - 14 % .' GDM represents nearly 90 % of all pregnancies complicated by diabetes.

Screening: Screening strategy for detecting Gestational DM6

GDM risk Assessment should be ascertained at the first prenatal visit.

• Low Risk: Blood glucose testing not routinely required if all of the following charactestics are present.

> Member of an ethnic group with a low prevalence of GDM

> No known Diabetes Mellitus in first degree relative

> Age <25 Years

> Weight normal before pregnancy

> Weight Normal at birth

> No History of abnormal glucose metabolism

> No History of poor obstetric outcome

• Average Risk: Perform blood glucose testing at 24 - 28 weeks using either.

> 2 step procedure : 50 g Glucose challenge test followed by diagnostic oral Glucose tolerance Test (OGTT) in those meeting threshold values I Glucose Challenge Test(GCT)

> One step procedure: Diagnostic oral glucose tolerance test performed on all subjects.

High Risk: Perform blood glucose testing as soon as feasible using the procedures described above, if one or more of these are present.

> Severe obesity

> Strong family history of type 2 DM

> Previous history of GDM, impaired glucose metabolism or glucosuria.

If GDM is not diagnosed blood glucose testing should be repeated at 24 -28 weeks or at any time a patient has symptoms or signs that are suggestive of hyperglycaemia.

SCREENING TEST:

For most women glucose screening should be conducted at 24 -28 weeks gestation with use of a 50 g oral load without regard to the time of day or the time of last meal. A venous plasma glucose is measured 1 hour later, and a value of 140 mg/dl or greater necessitates a full diagnostic 100 g oral GTT3. Using a cut off of 140 mg / dl will detect 80-90 % of women with GDM and will require that a GTT be performed in 15 % of patients. Lowering the cut off to 130 mg I dl will increase the sensitivity to nearly 100 % But will require GTT‘s in nearly 25 % of all patients.

DIAGNOSIS OF GDM:

Diagnosis of GDM with use of a 100 gram oral glucose load.3,4,5

	National Diabetes Data group (NDDG) (mg / dl)	Carpenter and couston (mg/dl)
Fasting	105	95
1 Hour	190	180
2 Hours	165	155
3 Hours	145	140

If two or more values are met or exceeded the diagnosis of GDM is established .3

INFANT OF DIABETIC MOTHER:

Farquhar et al in 1959 described infants of diabetic mothers as follows "they emerge at least alive from within the fiery metabolic furnace of diabetes mellitus that they resemble one another so closely that they might well be related. They are plump, liberally coated with vernix caseosa, full faced and plethoric. During their first two or more extra-uterine hours they lie on their back bloated and flushed their legs flexed and abducted, their lightly closed hands on each side of the head the abdomen prominent and their respiration sighing. They convey a distinct impression of having such a surfeit of both food and fluid pressed upon them by an insistent hostess that they desire only peace so that they may recover from their excesses.8

The infant of the diabetic mother (IDM) is an excellent example of the morbidities that may exist in the neonate because of maternal diseases.9

Potential morbidities in the infant of a diabetic mother .9

- Congenital anomalies
- Macrosomia
- Birth Injury
- Asphyxia
- Hypoglycaemia
- Hypocalcaemia
- Hypomagnesaemia
- Hyperbilirubinemia
- Increased blood volume

Heart failure
Neurological instability
Organomegaly
Polycythemia & Hyperviscocity
Respiratory distress
Respiratory Distress Syndrome
Small Left colon syndrome
Transient haematuria

DIABETIC EMBRYOPATHY

More than a hundred years ago the association between maternal diabetes mellitus and congenital anomalies was first made .Prior to the discovery of insulin the outlook for a

successful pregnancy outcome in women with diabetes was extremely bleak. Following the introduction of insulin therapy, both maternal as well as fetal morbidity and mortality began to decline .Despite the numerous therapeutic advancements achieved over the past 50 years, congenital malformations remain an unresolved problem .

Diabetes mellitus is one of the most common maternal illnesses that results in anomalous offspring. The frequency of major congenital anomalies has been estimated at 6 % to 10 % which represents a two to three fold increase over the frequency in the general population. Congenital malformations in the offspring of diabetic mothers account for approximately 40 % of perinatal deaths among this group of infants .'1

Congenital anomalies in infants of diabetic mothers11'12

1) Skeletal and central nervous system

- Caudal Regression Syndrome
- Neural tube defects excluding anencephaly
- Anencephaly with or without herniation of neural elements
- Microcephaly

2) Cardiac

- Transposition of the great vessels with or without ventricular septal defect
- Ventricular septal defects
- Coarctation of the aorta with or without VSD or PDA
- Atrial septal defects
- Cardiomegaly

3) Renal anomalies

- Hydronephrosis
- Renal agenesis
- Ureteral duplication

4) Gastrointestinal

- Duodenal atresia
- Anorectal atresia
- Small left colon syndrome

5) Others

- Single umbilical artery

Khoury et al evaluated the patterns of birth defects associated with diabetic embryopathy by analyzing 4929 infants with major defects. The predictive value was greatest for the combination of vertebral and cardiovascular anomalies.13

Minor congenital anomalies

A. Bhattacharyya et al have reported hypospadias, polydactyly, webbed fingers, and congenital dislocation of hip joints, undescended testis and tongue-tie and cleft lip in children of GDM mothers56.

ETIOLOGIC FACTORS ASSOCIATED WITH DIABETIC EMBRYOPATHY

Altered Metabolic Fuels

• Maternal hyperglycaemia: In vivo and in vitro animal studies have demonstrated that hyperglycaemia has a teratogenic effect during organogenesis. The defects in yolk sac structure seen in embryos exposed to hyperglycaemia suggest that hyperglycaemia during organogenesis has a primary deleterious effect on yolk sac function with resultant embryopathy. In addition various other possible consequences of hyperglycaemia have been suggested to play a role in diabetes -

related malformations, such as arachidonic acid deficiency accumulation of sorbitol and a deficiency of myoinositol. 11

• Maternal hyperketonemia: Hyperketonemia contributes to the development of diabetes related malformations. 11

• Maternal hypoglycaemia : The role of hypoglycaemia in the genesis of birth defects remains controversial at the present time.11

Free oxygen radicals

Fetal hyperglycemia may promote excessive formation of oxygen radicals in the mitochondria of susceptible tissues leading, to formation of hydro peroxides which inhibit prostacyclin. The resultant over abundance of thromboxanes and other prostaglandins may then disrupt vascularization of developing tissues.14

Somatomedin Inhibitors

Impairments of glucose metabolism have been shown to result in the appearance of Somatomedin inhibitors in the serum of diabetic animals. To date however there are no data in humans linking Somatomedin inhibitors to congenital malformations in the offspring of diabetic mothers.11

Other Maternal Factors

The exact role of zinc deficiency in diabetes related embryopathy has yet to be elucidated.11

Other factors like vitamin A may be altered in poorly controlled diabetes and proved to have teratogenic potential.11

Fetal Malformations in Maternal Diabetes

Several well done epidemiologic studies have demonstrated a strong association between maternal glycemic control at the time of conception and during early gestation and the incidence of congenital anomalies .10

The rate of congenital anomalies for IDM can be predicted from maternal hemoglobin Al C values at 14 weeks gestation. Mothers with values of less than 7 % have no great risk of having an infant with congenital anomalies than mothers without diabetes. For mothers with values between 7 % and 8.5 %, the risk is 5 %, the risk raises to 22 % for mothers with hemoglobin Al c values more than 10 % .10

Molested Pederson et al examined 835 consecutive infants of diabetic mothers and compared them with 1212 infants of non-diabetic mothers. Fetal malformations and malformations involving more than one organ system were six times more frequent in the IDM. Poor glucose control during the critical weeks of organogenesis, 5-8 weeks after the last menstrual period is thought to be the key etiologic factor.3

Miller et al demonstrated a linear relationship between glycated hemoglobin values and malformations rates ,15 Developmental morphologic data shows that significantly more common congenital malformations in infants of diabetic mothers occur before the seventh week of gestation. This suggests that any therapeutic intervention aimed at decreasing the incidence of congenital malformations should be instituted during the critical early period ,16

Schafer et al showed that in women without a diagnosis of diabetes before pregnancy the maternal fasting serum glucose concentration at diagnosis was a useful predictor of the risk of major but not minor anomalies. The rate of major anomalies doubled with a fasting glucose level > 120 mg/ dl. A fasting glucose level below that of overt diabetes outside of pregnancy carries an important risk of major anomalies that must be considered in the counseling and management of this patients.17

Sheffield et al, in their study concluded that women with pregestational diabetes or gestational diabetes plus fasting hyperglycemia have a three to four fold increased risk of infant malformations, whereas women with mild gestational diabetes have malformation rates no different than the general non diabetic obstetric population.18

Rates of adverse neonatal outcomes are 3-9 times greater in infants of diabetic mothers compared with those of non - diabetic mothers. There were no significant improvements in congenital anomaly in IDM in 1996- 2002 compared with 1988 -95.19

Guerin et al conducted a study among 1977 pregnant women to assess the use of maternal Glycosylated Hemoglobin (HbAlC) concentration to estimate the risk of congenital anomalies in the offspring of women with pre-pregnancy diabetes. They concluded that at a periconceptional HbAlC concentration 2SD above normal, the absolute risk of pregnancy affected by a congenital anomaly was 2 % .At 2 SD above normal, the risk was 3 % and at 8 SD it was nearly 10 %. For each 1 SD unit increase in HbAlC the associated risk of a congenital malformation increased by an odds ratio of 1.2. The risk in relation to A1C followed the same pattern.20

Well controlled diabetic women still have an increased risk of major malformation above that for the non - Diabetic population. However dia'betic patients risk for major malformation can be kept to a minimum by achieving good control around the time of conception.21

Maternal Diabetes and fetal Heart

Maternal diabetes mellitus significantly affects the fetal heart and fetal placental circulation in both structure and function. The influence of pre conceptional diabetes begins during embryonic development in the first trimester, with altered cardiac morphogenesis and placental development. It continues to have an influence on the fetal circulation through the second and third trimesters and into the perinatal and neonatal period ,22

Hypertrophic cardiomyopathy observed in the infant of the diabetic mother is characterized by thickening of the interventricularr septum and to a lesser extent the ventricular free walls 22. Most affected infants are clinically asymptomatic and have resolution of hypertrophy within months, presumably as there is no further exposure to the abnormal intrauterine milieu.22

The development of hypertrophic cardiomyopathy is believed to occur as a consequence of both fetal hyperinsulinemia and the normally increased expression and affinity of insulin receptors which leads to the proliferation and hypertrophy of cardiac myocytes.22

Fluctuations in glucose values rather than basal state may be more important determinants of fetal cardiac and general somatic growth in maternal diabetes.22

Congenital heart defects occur in up to 8.5 per 100 live births of infants of diabetic mothers. High maternal hemoglobin Al c values during early pregnancy are associated with increased risk of malformations. Hyperglycemia has a direct influence on proliferation and migration of neural crest cells which are critical in the development of the heart and brain.22

The study by Wren et al showed that pre - existing maternal diabetes is associated with a five fold increase in risk of cardiovascular malformations. Transposition of the great arteries,

truncus arteriosus and tricuspid atresia are over represented to produce a substantial excess of these malformations.23

It is important to monitor fetal heart function in macrosomic infants of diabetic mothers. Hypertrophic cardiomyopathy might explain otherwise unexplained fetal deaths in women with diabetes.24

Poor maternal diabetes control and maternal systemic hypertension are closely correlated with evidence of myocardial hypertrophy in the infants of diabetic mothers.25

In the infants of mothers with well controlled pregestational or gestational diabetes a prolonged deceleration time of early left ventricular diastolic filling probably reflecting an impaired left ventricular relaxation rather than compliance was found in comparison with normal term neonates in a study done in Finland.26

Caudal Regression syndrome and Maternal Diabetes:

Caudal regression syndrome occurs 600 times more commonly in the offspring of diabetic women as compared with non - Diabetic women. It is not believed to be pathognomonic for DM as it does occur in the offspring of non - diabetic women as well.11,12

LARGE FOR GESTATIONAL AGE INFANTS

Macrosomia is defined as either birth weight greater than the 90 centile for gestational age or > 4000g , independent of gestational age or sex.27,14 The incidence of infants with birth weight >= 4000 g is approximately 8 % in non - diabetic women and about 26 % in women with diabetes.28

The classic appearance of the macrosomic IDM is that of large, ruddy puffy fat and often limp infant with legs held in flexed and abducted position .In addition prominent fat pads are present over the upper back and around the lower jaw to produce the image of a round cherubic face.12

The Pederson hypothesis proposes that cause for macrosomia in diabetic pregnancies is hyperglycemia -heperinsulinism. In the first half of pregnancy, the fetus is exposed primarily to hyperglycemia, which without secondary hyperinsulinemia results in slowing of fetal growth and during the second half of pregnancy hypertrophic is-let cells respond to hyperglycemia with an increase insulin production. This potent combination of hyperinsulinemia a major anabolic hormone and hyperglycemia a major anabolic fuel results in a cascade of third trimesters events that culminate in striking increase in fat stores and a modest 12 % increase in protein stores. Much of the consequent weight accretion occurs after 32 weeks gestation. Hepatomegaly, splenomegaly and Cardiomegaly (caused by interventricular septal hypertrophy) are particularly prominent. Head circumferences are not typically increased. Control of maternal hyperglycemia alone however may not be sufficient to avoid fetal overgrowth or fetal hyperinsulinemia.30

Maternal hyperglycemia, although the most well recognized factor related to fetal macrosomia is not the only maternal metabolic fuel associated with fetal growth .There is a significant

correlation between maternal plasma amino acid levels (serine, proline, lysine, threonine, arginine) and birth weight.30

The neonatal birth weight has also been positively correlated with triglyceride and FFA concentrations both of which readily cross the placenta in late pregnancy. Insulin and insulin like growth factors (IGFI & II) play a role in regulation of fetal growth. These growth factors which structurally are proinsulin like polypeptides are produced by virtually all fetal organs and are potent stimulators of cell differentiation and division. LGA had significantly increased levels of these factors. Other factors implicated in macrosomia include growth factor and leptin.14

Macrosomia places the IDM at greater risk for birth trauma because of cephalopelvic disproportion. Difficult vaginal delivery secondary to shoulder dystocia predisposes to the development of cephalhaematoma, subdural haemorrhage, facial palsy brachial plexus injury and clavicular fractures. An infant that has undergone significant traumatic stress during delivery is also at greater risk for fetal distress lower apgar scores poor transition to extra uterine life and birth asphyxia. Caesarean section rates for macrosomic IDMs may be as high as 47 %.12

Hyperglycemia is known to occur in 47 % of macrosomic and in about 20 % of non-macrosomic IDMs. Hypocalcaemia, hypomagnesaemia, hyperbilirubinemia and polycythemia also affect macrosomic infants but at rates comparable with that of non - macrosomic IDMs.

Ballard et al, in their study concluded that the rates of complications like hyperbilirubinemia, hypoglycemia and acidosis were greatest in infants with disproportionate macrosomia and least in non macrosomic infants. Disproportionate macrosomia (excessive weight characterized by a high wt / length ratio) in the IDM is associated with an increased likelihood of neonatal complications.31

Prevention of macrosomia

Because macrosomic fetuses are at an increased risk for immediate complications related to birth injury as well as for potential long term consequences such as late childhood obesity and insulin resistance measures for prevention of macrosomia have been recommended.4

Aggressive Management of gestational diabetic women with insulin and diet therapy as compared with diet alone has been shown to produce offspring with lower birth weight and a lower birth weight and a lower incidence of macrosomia. Diabetic women with additional risk factors for macrosomia such as obesity and post maturity have the highest risk of delivering macrosomic fetus and should be monitored closely for this occurrence.12

Although utilization of obstetric ultrasound to assess both abdominal circumferences (greater than 90th percentile for the gestational age) and shoulder width (> 12 mm) have been shown to improve the accuracy of diagnosis of the macrosomic fetus, no techniques or formulas have been shown to be correct all of the time.12

In a study done by Langer et al the severity of glucose intolerance (hyperglycemia) was found to be associated with both maternal and neonatal morbidity in terms of infant size and caesarean section rate. Appropriately monitored toward stability with a narrow range to achieve tight metabolic control, ambulatory glycemia in pregnancy is associated with a decreased risk of maternal and fetal complications.32

Donald coustan and Joseph Imarah in their study showed that gestational diabetics treated with prophylactic insulin had a reduced incidence of not only macrosomia but also its sequel of traumatic delivery.33

Intensive home glucose monitoring will allow for the early identification of gestational diabetic patients needing insulin and thus reduces the incidence of macrosomia and large for gestational age infants.34

Lapolla et al, in a study done Italy showed that fasting plasma glucose at GCT could predict fetal overgrowth and plasma glucose > 85 mg/ dl doubles the risk of LGA infants HbAl c at 24 -27 gestational weeks does not predict fetal overgrowth . Mild alterations in glucose tolerance correlated with fetal overgrowth needs monitoring and treatment.35

Raed Salim et al, demonstrated that anthropometric measurements of infants mothers with well controlled gestational diabetes do not differ from infants of non TZ diabetic mothers.

Third trimester glycemic parameters are more powerful predictors of fetal growth than glycemic parameters earlier in pregnancy or during preconception. Hyperglycemic excursions are the strongest predictor of LGA infants.37

Schwartz et al, in their study concluded that macrosomia in the fetus of the diabetic mother remains inadequately explained. Nevertheless fetal hyperinsulinism remains the driving force for excessive fetal growth. The stimulus for fetal insulin excess in humans remains to be defined.

Studies have been done to know the growth patterns of LGA babies. Vohr et al, demonstrated that macrosomic infants of GDM mothers have unique patterns of adiposity that are present at birth and persist at age 1 year.39

SHOULDER DYSTOCIA

The incidence of shoulder dystocia ranges from 0.2 - 2.8 % in the general population in infants of women with GDM the incidence can be as great as 3 - 9 %30. Large fetal size as is seen in the infant of the woman with GDM relative to the pelvic outlet is the most common risk factor for the development of a shoulder dystocia.

In infants of mothers with normal glucose tolerance, the risk of shoulder dystocia in an infant who weighs less than 4000 g is only 1 % but the risk increase to 14 -25 % if the weight is more than 4500 g . In the infant of a woman with GDM when the birth weight exceeds 4000 g the incidence of shoulder dystocia is 18 - 23 % and may approach 50% if the infant is more than 4500 g.30 In addition the growth of these infants tends to be asymmetric with larger chest /

head and shoulder I head ratios when compared with infants born to women with normal glucose tolerance. When shoulder dystocia does occur birth traumas in the form of Erb's palsy, clavicular fracture fetal distress low Apgar scores and birth asphyxia are cited as the most common birth related injuries.30 For this reason elective caesarean section often is recommended when the estimated fetal weight exceeds 4000 - 4500 g in the infant of a diabetic mother.

Elective induction of labour in the macrosomic infant of the woman with GDM has been proposed as a way to decrease the incidence of shoulder dystocia in this population.30

Conway et al, in their study demonstrated that an ultrasonographically estimated weight threshold as an indication for elective delivery in diabetic women reduces the rate of shoulder dystocia without a clinically meaningful increase in caesarean section rate. This practice in conjunction with an intensified management approach to diabetes, improves the outcome of these high risk women and their infants.40

The diabetic fetus, even when glycemic control is adequate has a 2 to 3 fold higher risk for the development of shoulder dystocia. The risk increases as neonatal size increases.41

SMALL FOR GESTATIONAL AGE INFANTS

Small for gestational age infant is defined as two standard deviations below the mean for gestational age or as below the tenth percentile for gestational age.42

Poor intrauterine growth can be seen in 3 % to 7 % of non diabetic pregnancies and upto 20 % of diabetic pregnancies.12' 28 similar rates of small for gestational age infants have been observed among off springs of GDM and IDDM mothers.28

Multiple mechanisms may lead to intrauterine growth retardation in the offspring of diabetic women. Non Chromosomal malformations are often associated with fetal growth retardation. Abnormalities in replication and reduction in the number of cells result in a pattern of impaired fetal growth that is early in onset and symmetric in distribution. Pederson and Molested observed that fetuses of IDDM mothers found to the growth retarded between 7 to 10 weeks of gestation tend to have more malformations at birth.28

Langer et al divided 334 GDM patients who experienced tight metabolic control into three groups according to their fasting mean blood glucose. Twenty percent of 79 patients who had average blood glucose < 86 mg/dl delivered small for gestational age infants which was twice as common as in those women in the 87 to 104 mg/ dl and 105 mg/ dl serum glucose categories ,43 Furthermore, in small for gestational age fetuses levels of total amino acids, branched chain amino acids, lysine and serine were below normal values28

Preeclampsia or toxaemia conditions to which the pregnant woman is predisposed can decrease uterine blood flow leading to decreased oxygen I nutrient delivery and compromised fetal growth. The increase in anomalies with increasing duration and severity (white's classification)

of diabetes has been interpreted as indicating the degree to which maternal vascular disease may play a role. Their tenuous fetal physiology places them at increased risk of being compromised at delivery. IDM ‘s are at considerably higher risk for the occurrence of congenital malformations 6 - 10 % as compared with 2- 3 % in general population, which is a category at risk for growth retardation as well.

BIRTH ASPHYXIA

Perinatal asphyxia is an insult to the fetus or newborn due to a lack of oxygen (hypoxia) and or a lack of perfusion (ischemia) to various organs of sufficient magnitude and duration to produce more than fleeting functional and or biochemical changes.44

Perinatal asphyxia that occurs in IDM is perhaps a result of multiple factors .These include maternal hypertension maternal hypertension with resultant reduction in placental blood flow, premature labour fetal macrosomia. Mimouni et al, in their study showed significant correlation between perinatal asphyxia and nephropathy appearing in pregnancy, maternal hyperglycemia within 6 weeks preceding delivery and prematurity.46

HYPOGLYCEMIA

Fetal blood glucose levels approximate 70% to 80% of maternal concentrations. Peterson’s hypothesis states that maternal hyperglycemia leads to fetal hyperglycemia which leads to over stimulation of the islet cells of the fetal pancreas and to secondary fetal hyperinsulinism. Poor maternal glucose control, particularly during the last trimester of gestation, places the IDM at significant risk for the development of early onset hypoglycemia. If maternal hyperglycemia exists at the time of delivery, the fetal pancreas will be further stimulated to release insulin, there by aggravating the problem. Definition: Hypoglycemia is defined as a blood glucose level less than 40 mg/dl in any infant, regardless of gestational age and whether symptomatic or not.47

Cornblath et al, have suggested use of an operational threshold for blood sugar management in neonates. An operational threshold is that concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in the literature. Operational threshold as suggested by Cornblath et al.48.

1) Healthy full term infant:

a. <24 hours of age - 30 to 35 mg/dl may be acceptable once, but raised

40 mg/dl if it persists after feeding or recurs in the first 24 hours.

b. After 24 hours, threshold should be increased to 45 to 50 mg/dl.

2) Infant with abnormal signs or symptoms - 45 mg/dl

3) Asymptomatic infants with risk factors for low blood sugar - 36 mg/dl. Close surveillance is required and intervention is needed if plasma glucose remains below this level, it does not increase after feeding or if abnormal clinical signs are seen.

4) For any baby, if glucose level is < 20 to 25 mg/dl, intravenous glucose is needed to raise the plasma glucose to > 45 mg/dl.

There are no recent data to support the adoption of lower operational thresholds for the preterm infant.48

CLINICAL SIGNS: 48

• Changes in levels of consciousness

Irritability

- Lethargy
- Stupor
- Apnoea, cyanotic spells
- Coma
- Feeding poorly, after feeding well
- Hypothermia
- Hypotonia, Limpness
- Tremor
- Seizures

The overall incidence of hypoglycemia in all newborn infants is reported to range from 0.5% to 4% in the term newborn to 67% in the small for gestational age preterm infant. In contemporary neonatal care settings, however preterm infants at highest risk for this complication or given intravenous dextrose from shortly after the time of birth, and therefore rarely have this problem. The incidence of hypoglycemia in the IDM is reported to range from 25% to 40%, with large for gestational age term and preterm infants at greatest risk. The IDM must be screened carefully in the early hours of life for this possible complication. In clinical practice, serum glucose screening is done with chromogen strip tests (chemstrip and Dextrostix). Blood glucose levels measured with chromogen strips are on the average 10% lower than those obtained by the standard glucose oxidase method. Chemstrip readings correlate with 90% of serum glucose levels < 35 mg/dl and with 95% of those above 35 mg/dl.

If chromogen strip value is less than 40 mg/dl and the infant is asymptomatic, a blood glucose level should be obtained and feedings initiated. Follow up assays with chromogen strip with or without blood glucose determinations should be repeated as appropriate. If the infant is symptomatic from hypoglycemia intravenous dextrose therapy is necessary. The IDM needs to be delivered in a facility in which adequate paediatric support exists to provide this important services. 12

The risk for the occurrence of hypoglycemia in the IDM is not limited to the first hours of life. The chronic hyperinsulinemia in the inutero environment also depresses the ability of the infant to release glycogen from the liver via the maintenance of hepatic phosphorylase in the in active state, thereby inhibiting release of glycogen from the liver. This decreases the ability of the IDM to mobilize glycogen as an additional energy source in the early hours of life. 12

If the hyperinsulinemia in utero environment is perpetuated postnatally by dextrose therapy that leads to wide swings in infant blood glucose, the postnatal induction of the critical gluconeogenic enzyme, phosphoenol pyruvate carboxykinase, also can be delayed. This can potentially compromise the ability of the IDM to achieve glucose homeostasis even beyond the early days of life.12

IDMs exhibiting hypoglycemia have elevated cord c -peptide and free insulin levels at birth. An exaggerated, albeit temporary, pancreatic response to glucose loading has been demonstrated in IDMs. The insulin response to intravenous arginine is also exaggerated in infants of gestational diabetic mother. Together, these observations support the concept that the hypoglycemia in the new born can be in great part attributable to fetal and neonatal hyperinsulinemia.28

Another hypothesis that has been advanced as a contributing factor to the development of hypoglycemia in the IDM is exhaustion of the sympatho-adrenal neural axis. Studies showing decreased urinary catecholamines excretion in severely hypoglycemic IDMs have supported this theory. Presumably, this would occur as a consequence of chronic in utero hypoglycemic stress caused by poor maternal glucose control and secondary fetal adrenal exhaustion. Infusion of epinephrine to the IDM resulted in normal plasma elevations of glucose and free fatty acids and depression of insulin.12

In a study done by Aggrawal et al, the incidence of early hypoglycemia in well controlled diabetic mothers was still high, particularly in those mothers who had a longer duration of diabetes. In their study, cord blood glucose level did not identify the infants with hypoglycemia.49

Singh et al, in their study showed SFD and LFDs were at increased risk of manifesting hypoglycemia (7 and 10 times respectively) as compared to the AFDs babies. Approximately two thirds of hypoglycemic babies had one or more risk factors among which maternal diabetes was present in 23.8%. IDMs required higher amounts of glucose infusions to achieve a stable blood sugar level compared to Asymptomatic AFDs, SFDs and LFDs.50

Treatment of infants at risk for hypoglycemia:

One of the hallmarks of the clinical management of the IDM is to avoid hyperglycemia so that continued stimulation of the new born pancreas does not occur. The key to treatment of hypoglycemia is prevention.28 this is best accomplished by avoiding the use of excessive dextrose therapy in response to hypoglycemia and by initiation of enteral feeding at the earliest possible time. For the infants with poor sucking, gavage feeding should be provided.28

The hypoglycemic neonate (glucose < 40 mg/dl at 4 hours of age or less) should be treated with a minibolus infusion of 2 ml/ kg of 10% dextrose in water (200 mg/kg) given over 1 minute followed by a continuous infusion of dextrose at rate of 8 mg/kg/min. Bolus infusions by themselves with out a subsequent continuous infusion only exaggerate the hypoglycemia by a rebound mechanism. Once the plasma glucose stabilizes above 45 mg/dl, the infusion may be slowly decreased while oral feedings are initiated and advanced. If symptomatic hypoglycemia persists, higher glucose rate of 8- 12 mg/kg/min or more may be necessary.9 Glucagon therapy, except in an emergency, should generally be avoided. It promotes a large and rapid release of glycogen from the liver, leading to hyperglycemia. This will stimulate the already over primed pancreas to secrete insulin, which will lead to further episodes of hypoglycemia.12

Prompt recognition and treatment of the hypoglycemic neonate have minimized sequelae. Ultimately, the neonate requires full supplementation per oral. Although proprietary formulas are available, there is probably no contraindication to breast feeding by the mother who is metabolically stable.9

HYPOCALCEMIA AND HYPOMAGNESEMIA

Besides hypoglycemia, hypocalcaemia ranks as one of the most common metabolic derangements observed in the IDM.9 Hypocalcaemia is defined as total serum calcium level less than 7 mg/dl.9, 47 throughout gestation, calcium, phosphorus and magnesium are actively transported across the placenta from to fetus. During the last trimester of gestation, however, approximately 80% of the minerals accrue to the fetus. It is estimated that between 100 to 150 mg of calcium, 50-75 mg of phosphorus and 1.9 to 2.4 mg of magnesium per kilogram of fetal body weight per day are transferred from the mother to the fetus during weeks 25 to 40 of gestation. At the time of birth, the transfer of these minerals is abruptly terminated, leading to a dramatic decrease in both total and ionized calcium. This serves as a stimulus for increase in blood concentration of parathyroid hormone (PTH) and 1, 25 dihydroxycholecalciferol and the active form of vitamin D. The major role of vitamin D is to increase the absorption of calcium, magnesium and phosphorus from the intestinal tract and to prevent their loss through kidneys; it provides the means, in conjunction with adequate dietary intake, for the infant to acquire these minerals postnatally. For a smooth transition to extra uterine homeostasis of calcium, magnesium and phosphorus, increases in the active form of vitamin D and PTH must occur. Magnesium particularly critical to this scenario as magnesium deficiency suppresses PTH

production. It does this by altering the calcium sensitive magnesium dependent adenylate cyclase system that is important for PTH secretion from the parathyroid gland.12

Hypocalcaemia and Hypomagnesaemia occur within the first 72 hours of birth in up to 50% IDMs. IDMs that are ill with respiratory distress or have been asphyxiated are at higher risk. Abnormalities in calcium metabolism most likely represent a delayed transition from fetal to neonatal parathyroid control.

IDMs demonstrate a delay in the postnatal parathyroid hormone response, the pathophysiology of which is not well established. The delay of parathyroid hormone regulation in IDMs is independent of the presence or absence of birth asphyxia.10

Hypomagnesaemia defined as a serum magnesium concentration of less than 1.5 mg/d), may complicate hypocalcaemia in new born IDMs and make treatment of hypocalcaemia is more difficult. The cause of hypomagnesaemia is likely related to the same parathyroid issues that underlie hypocalcaemia but may be complicated by maternal hypomagnesaemia secondary to renal insufficiency in mothers with long standing diabetes. Excessive maternal urinary magnesium losses may decrease available magnesium for placental transport to the fetus.10

The signs and symptoms of neonatal hypocalcaemia and hypomagnesaemia include jitteriness, sweating, tachypnea, irritability and seizures. They present at 24 to 72 hours.10 Symptomatic hypocalcaemia is treated with infusion of I to 2 ml/kg of 10% calcium gluconate (10 to 20 mg/kg of elemental calcium) over 5 to 10 minutes. Heart rate should be monitored. Maintenance therapy may be given parenterally or orally at 2 to 8 ml/kg/day.9 Symptomatic hypomagnesaemia is treated with infusion or i.m injection of 0.1 to 0.2 ml/kg. 50% solution (4 meq/ml of mg) Heart rate should be monitored. The dose is repeated every 6 to 12 hours.9

POLYCYTHEMIA

Polycythemia is defined as central hemoglobin concentrations more than 20 g/dl and hematocrit levels more than 65%.10’12 It occurs in approximately 3%of all infants born at sea levels and 5% of infants born at higher altitudes.12 It is present in 20% to 30% of IDMs at birth.10 Mimouni et al in their study showed that there is a higher incidence of polycythemia in infants of diabetic mothers as compared to controls.51 Polycythemia is a result of increased erythropoietin - induced red blood cell production in response to fetal hypoxia.

Fetal hypoxia is a consequence of hyperinsulinemia and the resultant increased oxygen consumption that are characteristic of diabetic pregnancies with poor glycemic control .another possible etiology for fetal hypoxia may be increased maternal hemoglobin Ale,which binds tightly with oxygen, making maternal oxygen less available for placental transfer to the fetus this contribute further to neonatal hypoxia, in turn, leads to increased erythropoietin production and an increase in the red blood cell mass.

Another factor that may also contribute to polycythemia in the IDM is the shifting of blood that is known to occur during hypoxia within the fetal placental unit from the placental to the fetal

compartment. This mechanism may further contribute to the incidence of polycythemia in the perinatally stressed IDM.12

Symptoms related to polycythemia are manifestations of resulting blood hyperviscocity. Because blood viscosity is not routinely measured, red cell indices are used as marker of hyperviscosity and associated risks. Chronically accelerated erythropoiesis results in polycythemia, which in turn contributes to the increased incidence of stroke, seizures, necrotizing enterocolitis and renal vein thrombosis seen in the newborn IDM.10

The polycythemia IDM is plethoric, sluggish and lethargic. Sludging of hyperviscous blood in the cerebral microcirculation may be responsible for these symptoms and those of irritability, jitteriness and high pitched cry. These infants are at risk for venous sinus thrombosis that can be detected with neuroimaging studies. Polycythemic IDMs with neurologic symptoms should be treated with partial exchange transfusion regardless of whether abnormalities are detectable on neuroimaging tests.10

Similarly, renal, intestinal and pulmonary vascular bed sludging may present overtly or remain subtle. Renal vein thrombosis is more common in IDMs and presents with haematuria, flank masses, thrombocytopenia and hypertension. Intestinal sludging may present with feeding intolerance or full blown NEC, Pulmonary vascular bed sludging may manifest as PPH and can compromise significantly the 1DM with RDS.10

An initial hematocrit and platelet count should be obtained shortly after birth. The hematocrit should be followed on a daily basis, with an increase being common in the first 3 days of life. This increase is secondary to the free water dieresis and low fluid intake that occurs during the first 3 days in all newborns. Although a severely polycythemic fetus is at risk for intrauterine infarcts, the risk may increase further in the first 3 days of postnatal life because of this phenomenon. A falling platelet count in a polycythemia IDM is an indicator of significant micro vascular sludging and thrombosis in any number of vascular beds secondary to polycythemia. 0

Management of neonatal polycythemia and hyperviscocity should be based on clinical symptoms rather than absolute hematocrit values. Hematocrit and blood viscosity do not necessarily correlate in individual patients. Consequently, infants with a hematocrit of less than 65% may be symptomatic, whereas infants with hematocrit of more than 65% may remain asymptomatic. Asymptomatic infants with hematocrit from 65% to 70% should be hydrated with intravenous fluids at a rate of at least 100 ml/kg/day and the hematocrit should be measured daily for the first 3 days. A partial volume exchange transfusion should be performed if the infant becomes symptomatic or the hematocrit rises despite therapy. All symptomatic infants regardless of hematocrit and all IDMs with a central hematocrit of more than 70% requires an immediate partial exchange transfusion to dilute the blood viscosity.10

HYPERBILIRUBINEMIA

IDMs are at increased risk for hyperbilirubinemia because of an expanded red cell mass, ineffective erythropoiesis and relative immaturity of hepatic bilirubin conjugation and excretion. The large red cell mass commonly seen in IDMs provides a 30% large source of

bilirubin that must be conjugated and excreted by the liver. Inefficient conjugation by the relatively immature glucoronosyltransferase enzyme system results in increased serum unconjugated bilirubin concentrations. IDMs have an additional source of bilirubin because of inefficient erythropoiesis. Red cell precursors are circulated but are trapped in the spleen and removed. The breakdown of these red cells contributes an additional bilirubin load to the liver. The inefficient bilirubin processing system in the newborn IDM results in a more rapid rate of rise accompanied by a later peak in the serum bilirubin concentration. Because the neonatal hemoglobin is a function of the lack of maternal glycemic control, one can expect that macrosomic IDMs will have the most abnormal bilirubin metabolism. Serum bilirubin concentrations should be monitored starting in the first 24 hours and may need to be followed for upto 5 days.10

Peevy et al, in their study concluded that LGA IDM is at increased risk for hyperbilirubinemia and that increased heme turnover is a significant factor in the pathogenesis.52

RESPIRATORY DISTRESS

Respiratory distress, including respiratory distress syndrome (RDS) is a frequent and potentially severe complication in the IDM. The relative risk of RDS is 5.6 times higher in the IDM at 38 weeks or younger when other confounding variables are excluded.9

RDS occurs more frequently in IDMs because of later onset of maturity of the type 2 alveolar cells. Insulin is believed to antagonize the maturing effect of cortisol, which results in blunded production of dipalmityl lecithin. Lecithin is a much needed phospholipids present in surfactant, the lack of which causes poor stabilization of the fetal alveoli during exhalation and the development of RDS.30

Ideally, RDS is prevented by excellent maternal glycemic control during pregnancy. RDS is best prevented in the IDM by avoiding delivery while the lungs are immature. Because of a known delay in pulmonary maturation in infants born to mothers who are white class A-D, IDMs should be delivered when the lecithin/sphingomyelin (L/S) ratio exceeds 2:1 and phosphatidylglycerol is more than 3% in amniotic fluid samples. Persistant pulmonary hypertension complicates the course of RDS in the IDM, usually in the setting of polycythemia. Polycythemia and RDS are co morbid in IDMs because they both stem from the effects of maternal hyperinsulinemia.10

It thus appears that aggressive control of maternal diabetes, judicious use of amniotic fluid pulmonary maturity tests, ante partum biophysical surveillance with avoidance of unnecessary premature or surgical deliveries should result is no more than 5% surfactant-related RDS and in another 5% to 10% of cases of respiratory distress of

other origin, such as transient tachypnea of newborn, hypertrophic cardiomyopathy, meconium aspiration and polycythemia.28

Walter et al, in their study concluded that strict control of maternal glucose metabolism in the pregnant diabetic may be essential in reducing RDS in the infant of a diabetic mother.53

In a study done by Parker et al, an inverse correlation existed between maternal glucose levels and lecithin sphingomyelin ratios in amniotic fluid.53

In a series of 805 infants of diabetic mothers delivered over a 10- year period, Robert et al found the corrected risk for respiratory distress syndrome (RDS) to be nearly 5.6 times that of infants of non-diabetic mothers.55

IRON DEFICIENCY

Studies have shown that 65% of all IDMs and upto 95% of large for dates IDMs demonstrate abnormalities of iron metabolism at birth. Most of these infants have low ferritin concentration, but more severely affected infants have increased total iron binding capacity concentrations, decreased transferring saturation and increased free erythrocyte protoporphyrin concentration, which indicates accelerated erythropoiesis. The degree of iron abnormalities is a function of fetal hyperglycemia and maternal glycemic control.10

Iron deficient infants are at increased risk for neurodevelopmental and neurobehavioral abnormalities. Perinatal iron deficiency may place IDMs, who have an increased risk of acute and chronic hypoxemia, at even greater risk of perinatal brain injury.10 Treatment with iron in the newborn period is not likely to be acutely productive because infants are not anemic and repletion of tissue iron is a slow process. A natural redistribution of iron occurs as the newborn IDM breaks down the excess fetal red cells postnatally and iron becomes available to iron deficient tissues. Spontaneous partial recovery of iron status in these infants has been documented.10

Asha jyothi et al, in their study showed that IDMs suspected to have brain iron deficiency demonstrated impaired neonatal auditory recognition memory and lower psychomotor developmental scores at 1 year of age than IDMs with sufficient brain iron stores. These impairments map on to areas of the developing brain known to be vulnerable to iron deficiency.71

NEUROLOGIC FUNCTION:

IDMs can present with acute neurologic abnormalities secondary to central nervous system dysfunction .Central nervous system changes occur as a result of perinatal asphyxia, glucose and electrolyte abnormalities, Polycythemic vascular sludging and birth trauma. The timing of the neurologic symptoms may provide clues as to cause. Symptoms from perinatal depression or hypoglycemia typically have their onset in the first 24 hours post partum, whereas symptoms from hypoglycemia or hypomagnesaemia present between 24 and 72 hours of life. Cerebral symptoms may include seizures, jitteriness and lethargy, changes in tone and movement disorders. The spinal cord is also vulnerable to birth trauma with symptoms related to palsies of the brachial plexus.10

Neurologic state changes are common in compromised IDMs. More commonly, symptoms include lethargy and hypotonia, but jitteriness and hyper tonicity can occur. (10) The causes of jitteriness is likely is multifactorial and typically related either to glucose or electrolyte

abnormalities, which make the brain more irritable (i.e. hypoglycemia, hypocalcaemia, hypomagnesaemia) or to hypoxic events at delivery.10

Potential factors that contribute to the classic picture of the plethoric, sluggish IDM are perinatal depression, glucose and electrolyte abnormalities, polycythemia, cardiomyopathy and tissue (eg. brain) iron deficiency. These symptoms may persist for up to a week. The lethargic IDM tends to be a poor feeder.10

SMALL LEFT COLON SYNDROME

Small left colon syndrome presents as generalized abdominal distension because of inability to pass meconium. The infants may have some problems with passage of stool in the first week of life, but this usually resolves after treatment with half normal saline enemas (5ml/kg) and glycerine suppositories.47

HAIRY PINNA IN INFANTS OF DIABETIC MOTHERS

Pinna of most normal neonates have sparsely distributed lanugo hair which should not be accorded any significance .Hypertrichosis due to hypercorticism is a recognized feature in infants of diabetic women. The sign is striking when looked for and is seen in infants of either sex. It is unrelated to birth weight of infants through extremely large babies tend to have more significant hairyness of pinnae. Excessive hairyness of pinnae can serve as a useful clinical marker for infants of diabetic mothers.57

Massoud Rafaat reported hypertrichosis of external ears in most of the babies born of diabetic mothers. He suggested adding this physical characteristic (hypertrichosis pinnae) to the other well known features of IDM.58

PERINATAL MORTALITY

Perinatal mortality in diabetic pregnancy has decreased 30 fold since the discovery of insulin in 1922 and the advent of intensive obstetric and infant care in the 1970s.Improved techniques for maintaining euglycemia have led to later timing of delivery and reduced incidence of iatrogenic RDS.14

Perinatal mortality has historically been a common problem in type 1 diabetic pregnancies and is related to poor glycemic control .Specifically maternal and therefore fetal hyperglycemia and hyperinsulinemia may lead to fetal academia and hypoxia. Stillbirths in pregnancies complicated by GDM either occurs before the diagnosis of glucose intolerance is made or are associated with very poor glycemic control during the pregnancy. They also may be related to a previous history of stillbirth or concomitant hypertension.30

Despite all problems a diabetic woman has a 95 % chance of having a healthy child if she is willing to participate in a program o pregnancy management and surveillance at an appropriate perinatal centre ,47

LONG TERM SEQUELAE IN OFFSPRING OF MOTHERS WITH DIABETES

The long term health of IDMs can be affected by the periconceptional, fetal and neonatal pathologies to which these infants are exposed .The major issues revolve around long term risks of obesity and diabetes neurological outcome and iron status.10

Some studies have reported a strong correlation between amniotic fluid insulin levels and increased weight for height in 14 - 17 year olds indication an association between islet cell activation and resultant development of childhood obesity. This obesity childhood and in adolescence and then predisposes for obesity as an adult.

Offspring born to women with overt diabetes have a low risk of developing typel- diabetes the incidence ranges from 1 to 3 percent. The risk is 6 percent if only the father has overt diabetes. If both parents have type 1 DM the risk is 20 percent. Women with

GDM have a stronger maternal than paternal family history of type 2 diabetes .Women who were exposed to an abnormal metabolic environment during their own intrauterine development may not be able to meet the challenges of increased insulin resistance and may develop abnormal glucose tolerance themselves.

IDMs are at increased risk for delayed motor and cognitive development that may manifest later in life .The long term delays can be a function of acute perinatal events (eg .birth asphyxias) or may be related to alterations in brain development from the adverse environment characterized by hypoxemia hypoglycemia acidosis and iron deficiency. The risk of adverse neurologic outcome is a function of abnormal neonatal glucose, calcium and magnesium metabolisms degree of fetal hypoxia, polycythemia and iron deficiency and the presence of birth trauma and asphyxia.10

The prognosis of IDMs with neonatal seizures varies depending on the cause of o

these seizures .Infants who experience seizures secondary to metabolic derangement carry a 10 % to 50 % risk of subsequent neurodevelopmental abnormality; 80 % of infants who suffer seizures from hypoxic-ischemic encephalopathy exhibit developmental delays.10 Several studies centered on the long term neurodevelopment outcome of IDMs have suggested that poorer maternal metabolic regulation correlated with poorer child performance on standard measures of neuro psychological functioning . 10

Follow up studies of iron nutrition in a small number of IDM s suggest that they are truly iron deficient and do not simply exhibit a redistribution fetal iron .They are at risk for late -onset iron deficiency during the second postnatal year .IDMs with low ferritin concentrations should have follow up values determined at 6-9 months of age . If the values are persistently low iron supplementation using the same supplementation regimen as for other iron deficient children should be considered ,10

FETAL SURVEILLANCE IN PREGNANCIES COMPLICATED BY DIABETES

The goal of fetal surveillance differs with gestational age. The first trimester goal is to verify viability, whereas structural integrity is validated during the second trimester. The goal during the third trimester is to monitor fetal growth and ensure fetal wellbeing.10

Maternal serum alpha fetoprotein levels measured at 16 to 18 weeks gestation and fetal ultrasound studies should be reviewed to evaluate for possible congenital anomalies. Non stress tests are recommended twice weekly starting at 32 weeks gestation, with a contraction stress test if the no stress tests are non-reassuring. Results of these tests maternal history of fetal movement and quantitative bio physical profile provide information regarding fetal well being and potential for perinatal asphyxia .10

Assessment of fetal lung maturity particularly in persons with insulin dependent diabetes with borderline mature pregnancies (eg 35 -37 weeks gestation) is important .An attempt should be made to confirm fetal maturity before induction of labor or planned caesarean section .10

Preparation for delivery of and IDM who exhibits fetal distress or any such infant includes preparing for resuscitation of a depressed infant .Because of an increased risk of pulmonary hypertension, supplemental oxygen should be used to maintain oxygen saturations more than 95 % which allows for a smooth transition from fetal to neonatal circulation .10

Advances in the management of mothers with diabetes have reduced the rate of morbidity and mortality fortheir infants. Aggressive control maternal glycemia status is warranted because most morbidity is epidemiologically and pathophysiologically closely linked to fetal hyperglycemia and hyperinsulinemia. Although rates of complications are lower than in previous etas there may be a resurgence of IDMs within the next 10 years .The burgeoning public health problem of over weight and obesity in children likely will result in and increase incidence of metabolic syndrome X characterized by insulin resistance and type II diabetes in adulthood .An early manifestation of this may be glucose intolerance during pregnancy in over weight women without diabetes .10

IDMs remain a high risk population although there has been continuing improvement in outcome for these IDMs optimal results are obtained when meticulous medical obstetric care throughout pregnancy is combined with expert neonatal supervision. These high risk patients should optimally be delivered in tertiary care centers where those requiring specialized care **may be best treated.9**

MATERIALS AND METHODS

METHODOLOGY:

All consecutive live born babies born to diabetic mothers in Manipal Hospital, Bangalore during study period (October 2006 to September2008-10-13) formed the study population. Data regarding the diabetic status of the mother was obtained from antenatal records. Diabetic mothers were grouped in to two categories: pregestational (type 1 DM and type 2 DM) and gestational DM. The diagnosis of GDM was based on National Diabetes Data Group (NDDG) criteria .3'4'5 [NDDG criteria: FBS > 105 mg/dl, 1 hr post prandial value > 190 mg/dl, 2 hrs post prandial value > 165 mg/dl and 3 hrs post prandial value > 145 mg/dl. If two or more values are met or exceeded, the diagnosis of GDM is established.]

The glycemic status of the diabetic mothers was ascertained based on the serial estimation of fasting and post prandial glucose levels. Each patients fasting and 2 hr post prandial blood glucose type (fasting or 2 hr post prandial). Blood glucose control was defined according to American college of obstetricians and gynaecologists guidelines: a mean fasting value of < 95 mg/dl or mean 2 hour post prandial value of < 120 mg/dl. Two groups were identified: women with blood glucose averages within the recommended guidelines (blood glucose controlled or optimal control) and women with blood glucose averages higher than the recommended guidelines (blood glucose not controlled or suboptimal control)59

Mothers antenatal history included data regarding family history of diabetes mellitus (in parents) and ultrasonography findings.HbAlc levels during pregnancy (in 1 trimester in pregestational DM and at diagnosis in GDM) was estimated. Other associated obstetrical and medical problems were noted. Pregnancy induced hypertension was diagnosed if the systolic BP was more than 140 mm Hg and diastolic BP was more than 90 mmHg. Hypertension prior to conception was diagnosed if BP was above 140/90 mm Hg before pregnancy. Any infection in the mothers during pregnancy was noted.

Inclusion criteria

All consecutive live born infants of diabetic mothers born in Manipal Hospital, Bangalore from October 2006 to September 2008 were included under this study.

Exclusion criteria

• Stillborn babies of diabetic mothers.

• Abortions of diabetic mothers

Babies born to diabetic mothers were evaluated immediately after birth. Those requiring resuscitation were resuscitated according to National Neonatal Forum protocol for newborn resuscitation. Birth asphyxia was defined as an apgar score of < 6 at five minutes.60 All babies born to diabetic mothers were then shifted to NICU for monitoring and treatment.

At admission, weight was recorded using digital weighing scale (to nearest lOgms). Gestational age assessment was done by modified Ballard score. Macrosomia was defined as either birth weight greater than the 90th centile for gestational age or >4000 gm, independent of gestational age or sex.14'27 Small for gestational age was defined as birth weight less than the 10th centile for GA. Data regarding detailed examination of the new born was collected in a performed proforma. Congenital anomalies were identified clinically and supported by Echocardiography. Respiratory distress was defined as respiratory rate of >60/min and/or presence of sub costal and intercostals retractions.

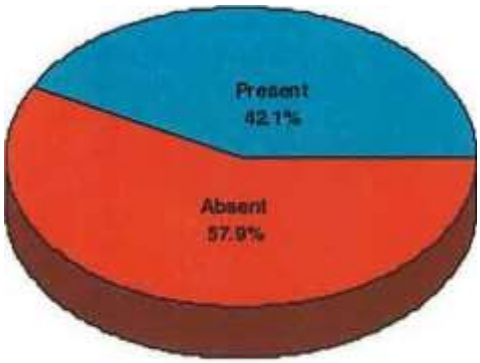
At admission, blood glucose estimation was done on venous blood sample by glucose oxidase method. Subsequent blood glucose estimation at 1,2,3,6,12,24,36 and 48 hours of postnatal age was done by glucose dextrostix. Infants with blood glucose <40 mg/dl were subjected to blood estimation by glucose oxidase method. Hypoglycemia was defined as a blood glucose level less than 40 mg/dl in any infant, regardless of gestational age and whether symptomatic or not.47

Estimation of hemoglobin, hematocrit and serum calcium levels were done in clinical laboratory by automated analyzer. Polycythemia was diagnosed if venous hematocrit was greater than 7mg/dl. Bilirubin level estimation was done at the onset of clinical jaundice and repeated if necessary. If jaundice was not clinically evident, then serum bilirubin estimation was done on day 4 of life. Hyperbilirubinemia was diagnosed based on standard guidelines.61

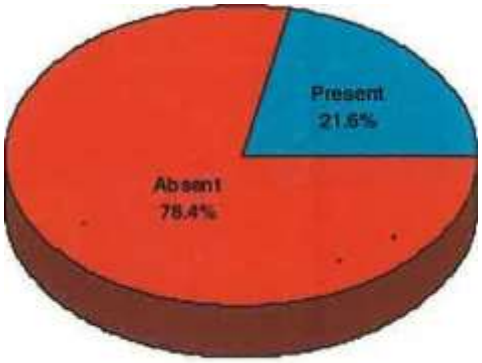
Chest x-ray and electrocardiography (ECG) was done for all babies and findings recorded. Electrocardiography was done for all the infants by an experienced cardiologist using standard 2D-echocadiography and findings recorded.

OBSERVATION AND ANAL YSIS

Study Design: A prospective clinical study consists of 56 babies bom to Diabetic Mothers



PGDM



GDM

Table 1: Family history of diabetes mellitus in mothers of the study sample

Family history	Total	PGDM	GDM
Absent	40(71.4%)	11(57.9%)	29 (78.4%)
Present	16 (28.6%)	8 (42.1%)	8 (21.6%)
Total	56 (100.0%)	19 (100.0%)	37 (100.0%)

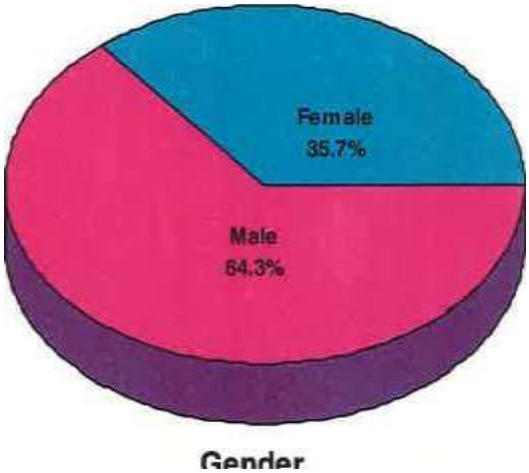
$\%^2$=2.581; P=0.108

In this study, Family History of DM (in parents of the mothers of the study sample) was present in 28.6% of the mothers of the study population.

Family History of DM was present in 42.1% of pregestational diabetic mothers and 21.6% of gestational mothers.

Table 2: Sex wise distribution of the study sample

Gender	Number (n=56)	%
Male	36	64.3
Female	20	35.7

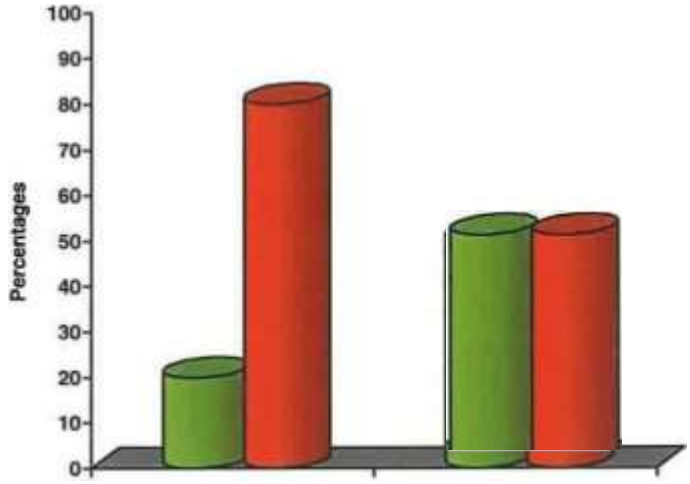


56 infants formed the study sample. Out of 56 infants, 36 (64.3%) were male and 20 (35.7%) were female.

Table 3: Maternal glycemic control in progestational and Gestational diabetes mellitus.

Glycemeic control	Total	DM	
		PGDM	GDM
Optimal	30	6 (20.0%)	24 (80.0%)
Sub optimal	26	13 (50.0%)	13 (50.0%)
Total	56	19 (33.9%)	37 (66.1%)

X^2-5.592; P=0.018*

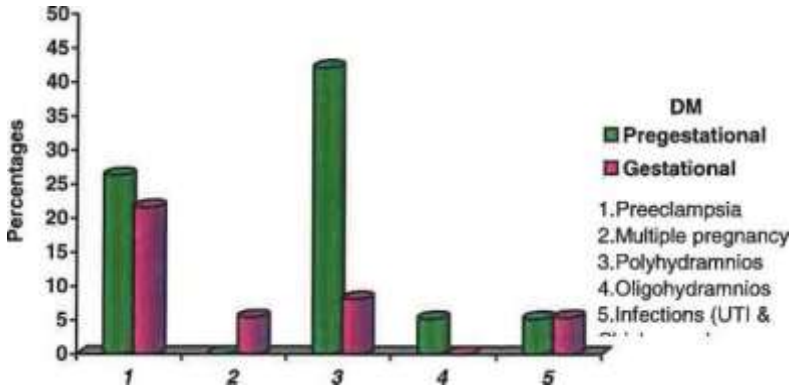


Glycemeic control

Sub optimal glycemic control was seen in 13(50%) mothers of Progestational and 13 (50%) with Gestational diabetes in the present study

Table 4: Antenatal factors in mothers of the study population

Antenatal Factors	DM Pregestational (n=19)	Gestational (n=37)	Total (n=56)	P Value
Preeclampsia	5 (26.3%)	8 (21.6%)	13 (23.2%)	0.745
Multiple pregnancy	0	2 (5.4%)	2 (3.6%)	0.544
Polyhydraminos	8 (42.1%)	3 (8.1%)	11 (19.6%)	0.004**
Oligohydramnios	1 (5.2%)	0	1 (1.7%)	0.339
Infections (UTI & Chickenpox)	1 (5.2%)	2 (5.4%)	3 (5.3%)	1.000

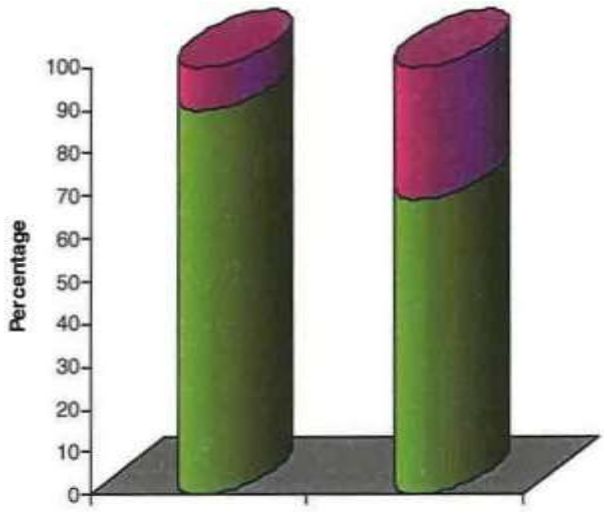


Preeclampsia was present in 8(61.5%) gestational diabetic mother and 5 (38.5%)

pregestational diabetic mothers. Polyhydraminos was present in 8(72.7%) pregestational diabetic mother and 3(27.3%) gestational diabetic mothers. The other complications seen in gestational diabetic mothers included multiple pregnancy in 2 (5.4%) and infections 2(5.4%) mothers.

Table 5: Polyhydraminos in relation to glycemic control in mothers of the study sample

Polyhydramnios	Total	Glycemeic control	
		Optimal (n=30)	Sub optimal (n=26)
Absent	45 (80.3%)	27 (90%)	18 (69.2%)
Present	11 (19.7%)	3 (10%)	8 (30.8%)
Total	56 (100%)	30 (100%)	26 (100%)
Inference	Presence of Polyhydramnios is significantly related to the sub optimal level of Glycemic control with $\%^2$=3.806; P=0.050*		

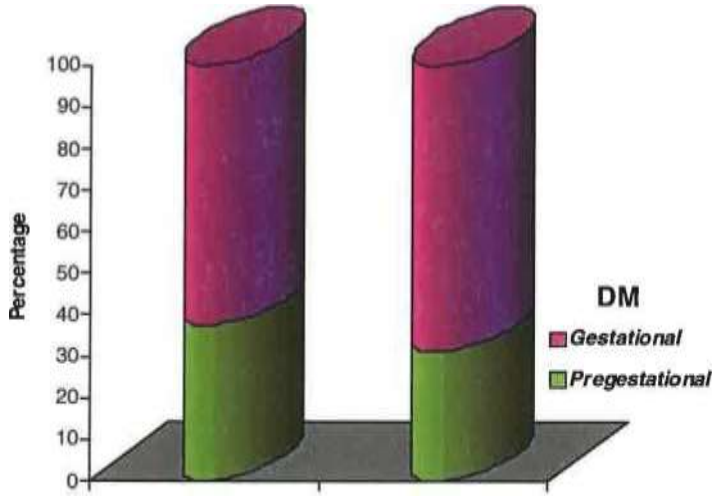


Glycemeic control

Polyhydraminos was observed in 11(19.7%) mothers of the study sample. It was present in 3(10%) mothers with optimal glycemic control and 8(30.8%) mothers with suboptimal glycemic control.

Table 6: Distribution of study sample based on gestational age

Gestational age in weeks	DM		Total	P value
	Pregestational (n=19)	Gestational (n=37)		
<37 weeks	9 (37.5%)	15 (62.5%)	24 (42.6%)	0.625
>37 weeks	10(31.2%)	22 (68.8%)	32 (57.1%)	0.625
Total	19 (33.9%)	37 (66.1%)	56 (100%)	-



Gestational age in weeks

Only 42.6% of the Diabetic Mothers delivered preterm babies as compared to term deliveries seen in 57.1% of diabetic mothers. There was no significant statistical difference between the groups with regard to preterm delivery.

Table 7: Distribution of study sample based on the birth weight for Gestational age

Birth weight for GA	DM		— Total	P value
	Progestational	Gestational		
SGA	3 (15.8%)	5 (13.5%)	8 (14.3%)	1.000
AGA	12 (63.1%)	26 (70.3%)	38(67.9%)	0.569
LGA	4(21.1%)	6 (16.2%)	10(17.8%)	0.655
TOTAL	19 (100%)	37 (100%)	56(100%)	-

4(21.1%) LGA infants were born to mothers with pregestational diabetes and 6(16.2%) were bom to mothers with gestational mothers. 3(15.8%) SGA infants were bom to pregestational diabetes mothers. There was no statistical significance in the incidence of LGA, AGA and SGA infants between the two groups.

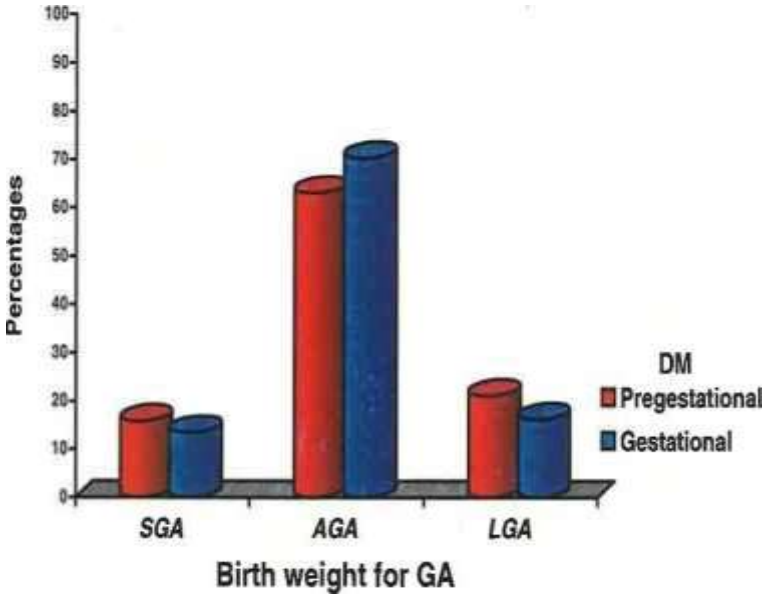


Table 8: Distribution of study sample based on the birth weight for Gestational age and its relation to maternal glycemic control

Birth weight for GA	Glycemic control		Total (n=56)
	Optimal (n=30)	Sub optimal (n=26)	
SGA	2(6.7%)	6(23%)	8(14.3%)
AGA	26(86.7%)	12(46.2%)	38(67.9%)
LGA	2(6.7%)	8(30.8%)	10(17.8%)
TOTAL	30(100%)	26(100%)	56(100%)

Inference

Birth weight for GA is significantly associated with the Glycemic control with P=0.005**

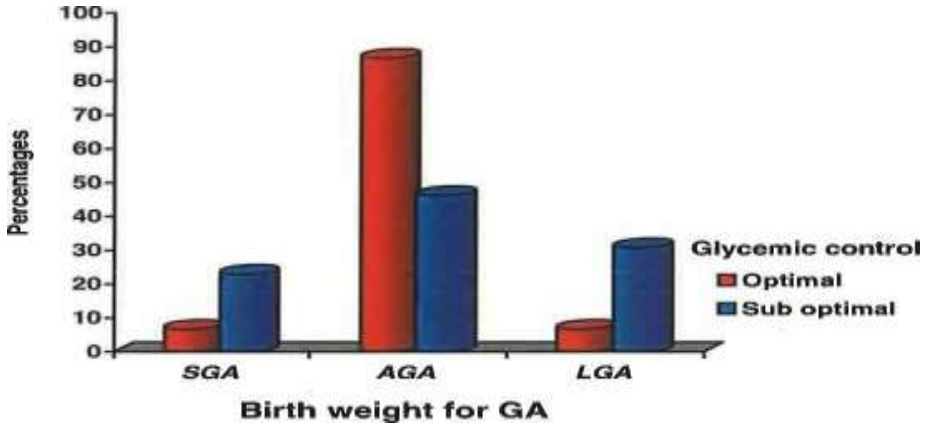
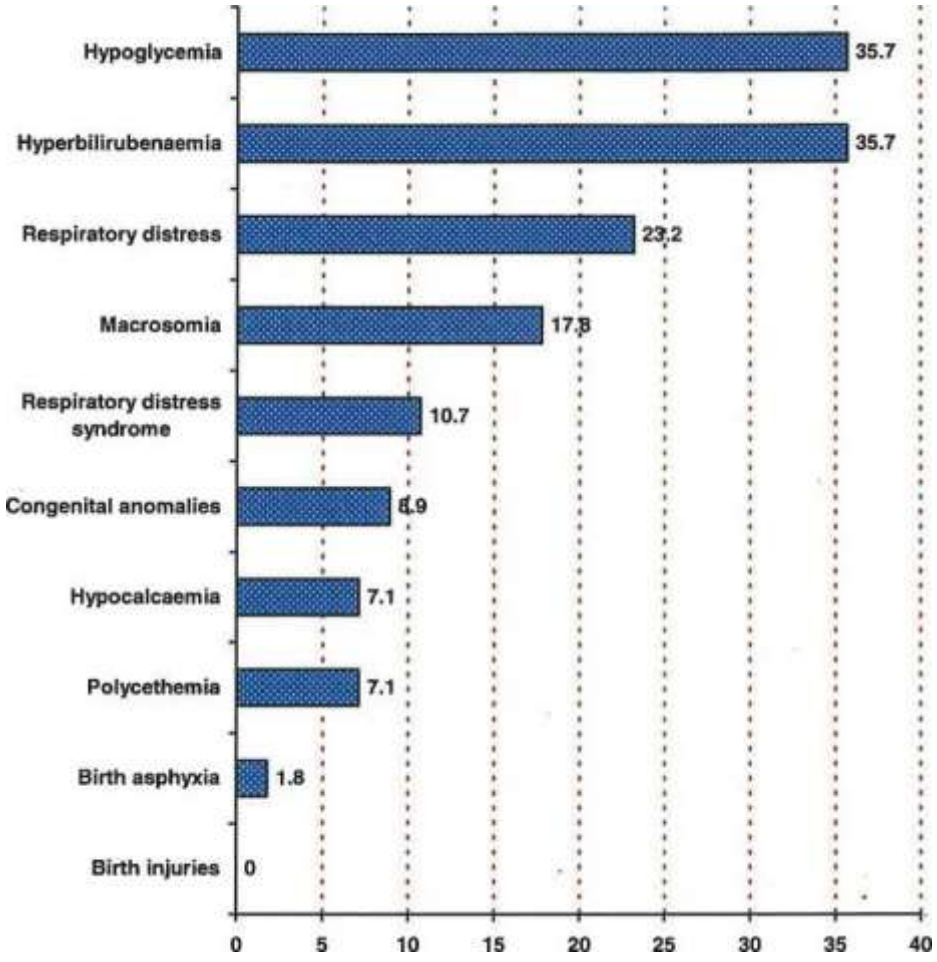


Table 9: Complications seen in infants of diabetic mothers

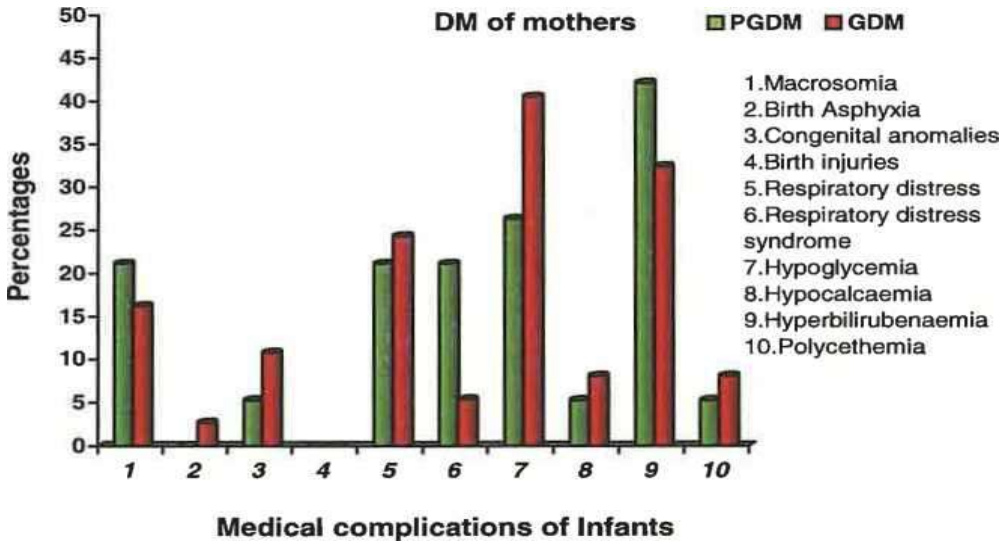
Complications	Number (n=56)	%
1 .Hypoglycemia	20	35.7
2.Hyperbilirubenaemia	20	35.7
3.Respiratory distress	13	23.2
4.Macrosomia	10	17.8
5.Respiratory distress syndrome	6	10.7
6.Congenital anomalies	5	8.9
7.Hypocalcaemia	4	7.1
8.Polycethemia	4	7.1
9.Birth Asphyxia	1	1.8
lO.Birth injuries	0	0.0



Hypoglycemia 20(35.7%) and Hyperbilirubinemia 20(35.7%) were the commonest complications seen in IDMS followed by Respiratory distress in 13 (23.2%) IDMs. Birth Asphyxia was the least common complication seen in 1(1.8%) IDM. None of the IDMs sub stained any birth injuries.

Table 10: Common medical complications in babies born to mothers with progestational and gestational diabetes mellitus.

Medical complications of Infants	Number (n=56)	DM		P value
		PGDM (n=19)	GDM (n=37)	
l.Macrosomia	10(17.8%)	4(21.1%)	6(16.2%)	0.720
2.Birth Asphyxia	1 (1.8%)	**0**	1(2.7%)	1.000
3.Congenital anomalies	5(8.9%)	1(5.3%)	4(10.8%)	0.652
4.Birth injuries	0	-	-	-
5.Respiratory distress	13(23.2%)	4(21.1%)	9(24.3%)	0.784
6.Respiratory distress syndrome	6(10.7%)	4(21.1%)	2(5.4%)	0.165
7.Hypoglycemia	20(35.7%)	5(26.3%)	15(40.5%)	0.293
8 .Hypocalcaemia	4(7.1%)	1(5.3%)	3(8.1%)	1.000
9 .Hyperbilirubenaemia	20(35.7%)	8(42.1%)	12(32.4%)	0.474
lO.Polycethemia	4(7.1%)	1(5.3%)	3(8.1%)	1.000



Hypoglycemia was the commonest complication observed in IDMs of both Gestational 15(40.5%) and Pregestational 5(26.3%). Hyperbilirubinemia was also the commonest complication observed in IDMs of both Gestational 12(32.4%) and Pregestational 8(42.1%).

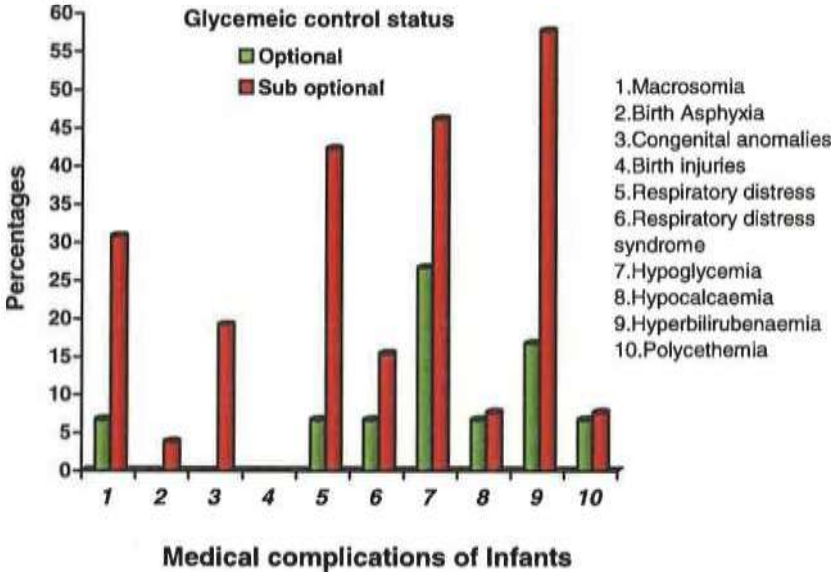
Table 11: Comparison of complications in infants of mothers with optimal and suboptimal glycemic control

SI. No	Complications	Number (n=56)	Glycemic control		P value
			Optimal (n=30)	Sub optimal (n=26)	
1	Macrosomia	10(17.8%)	2(6.7%)	8(30.8%)	0.033*
2	Birth Asphyxia	1 (1.8%)	0	1(3.8%)	0.464
3	Congenital anomalies	5(8.9%)	0	5(19.2%)	0.017*
4	Birth injuries	0	-	-	-
5	Respiratory distress	13(23.2%)	2(6.7%)	11(42.3%)	0.002**
6	Respiratory distress syndrome	6(10.7%)	2(6.7%)	4(15.4%)	0.401
7	Hypoglycemia	20(35.7%)	8(26.7%)	12(46.2%)	0.129
8	Hypocalcaemia	4(7.1%)	2(6.7%)	2(7.7%)	1.000
9	Hyperbilirubinemia	20(35.7%)	5(16.7%)	15(57.7%)	0.001**
10	Polycythemia	4(7.1%)	2(6.7%)	2(7.7%)	1.000

All 5(19.2%) congenital anomalies IDMs and 1(3.8%) IDM with birth asphyxia were seen in mothers with sub optimal control during pregnancy. Macrosomia was observed in 2(6.7%) with optimal control and 8(30.8%) with suboptimal control during pregnancy. Hypoglycemia was observed in 8(26.7%) with optimal control and 12(46.2%) with sub optimal control during pregnancy.

Table 12: Comparison of metabolic problems in LGA, AGA and SGA IDMs:

Complications	Total number (n=56)	Birth weight for GA			P value
		SGA (n=8)	AGA (n=38)	LGA (n=10)	
Hypoglycemia	20(35.7%)	2 (25.0%)	13(34.2%)	5(50.0%)	0.539
Hypocalcaemia	4(7.1%)	3 (37.5%)	1 (2.6%)	0	0.014*
Hyperbilirubinemia	20(35.7%)	8(100.0%)	6 (15.8%)	6(60.0%)	<0.001**
Polycythemia	4(7.1%)	1 (12.5%)	2 (5.3%)	1(10.0%)	0.385



There was no significant statistical difference in the incidence of Hypoglycemia, Hyperbilirubinemia and Polycythemia between the groups.

Hypoglycemia, Hyperbilirubinemia, and Polycythemia were seen in all LGA, AGA and SGA IDMs.

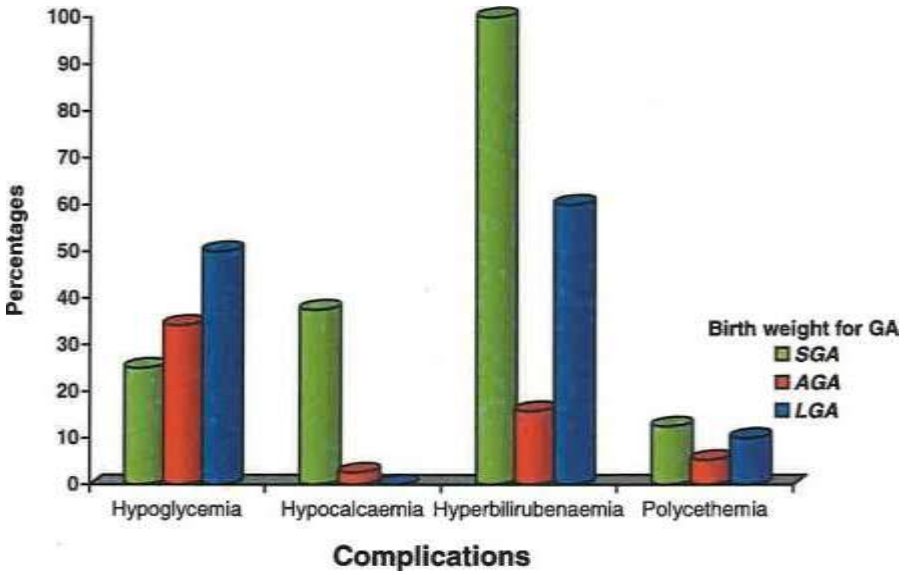
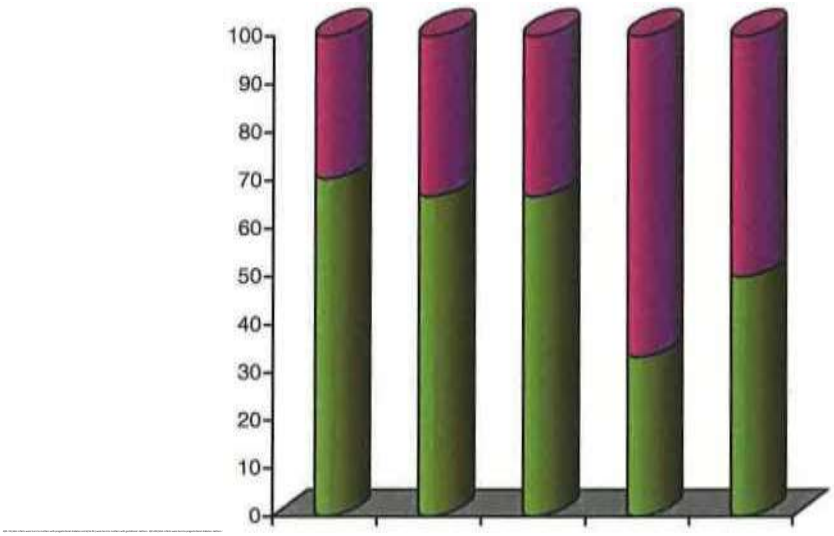


Table 13: Hypoglycemia in relation to birth weight

Birth weight	Total	Hypoglycemia	
		Absent	Present
<2.5	27	19 (70.4%)	8 (29.6%)
2.5-3.0	12	8 (66.7%)	4 (33.3%)
3.0-3.5	9	6 (66.7%)	3 (33.3%)
3.5-4.0	6	2 (33.3%)	4 (66.7%)
>4.0	2	1 (50.0%)	1 (50.0%)
Mean ± SD	2.41±0.77	2.77±0.93	2.54±0.85
Inference	Birth weight distribution is significant between presence hypoglycemia with P=0.122		not statistically and absence of



Birth weight

Table 14: Association of Congenital anomalies with Diabetics

Congenital anomalies	Total	DM	
		PGDM	GDM
cvs	3 (5.4%)	0	3 (8.1%)
None	53 (94.6%)	19 (100.0%)	34 (91.9%)
Total	56 (100.0%)	19 (100.0%)	37 (100.0%)
Inference	CVS is not statistically associated with type of DM with P=0.544		

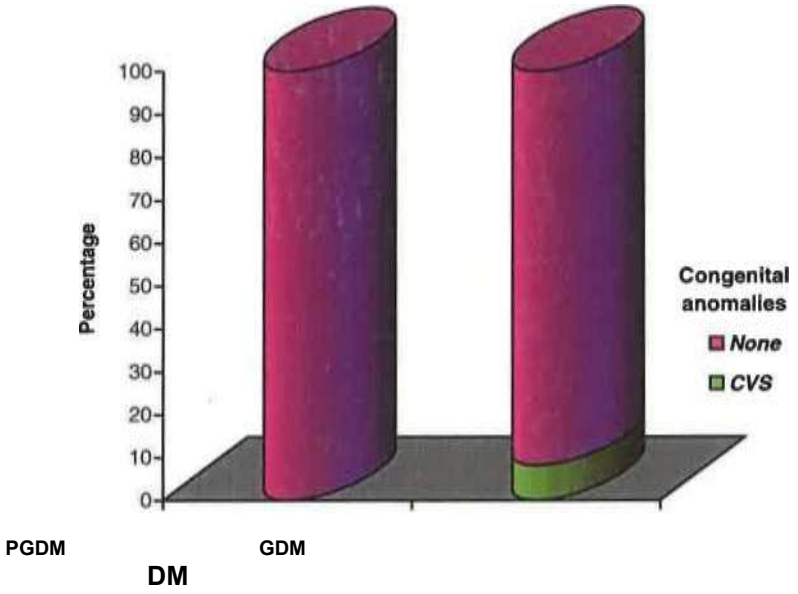


Table 15: Maternal glycemic control and congenital anomalies in infants

Congenital anomalies	Total	Glycemic control status	
		Optimal	Sub optimal
cvs	3 (5.4%)	0	3(11.5%)
None	53 (94.6%)	30 (100.0%)	23 (88.5%)
Total	56 (100.0%)	30 (100.0%)	26 (100.0%)
Inference	CVS is significantly associated with Sub optimal Glycemic control with P=0.094		

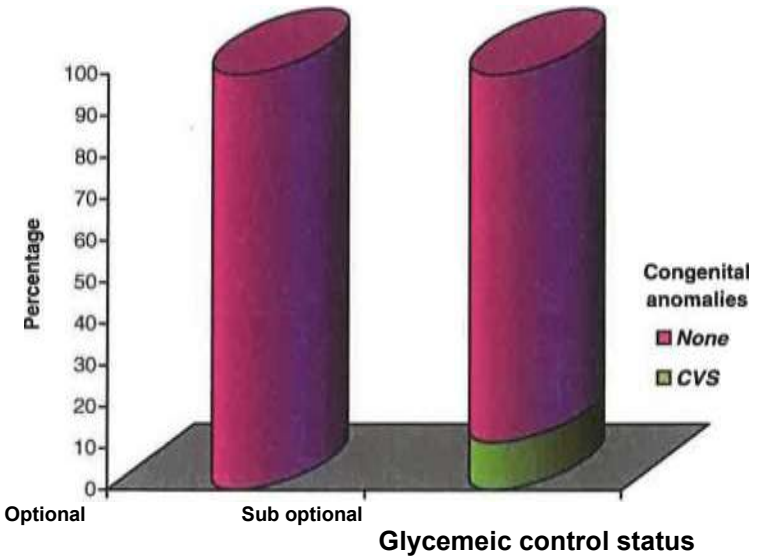


Table 16: Association of Respiratory problems in infants of Diabetic Mothers

Respiratory problems	Total (n=56)	DM		P value
		PGDM (n=19)	GDM (n=37)	
HMD	6 (10.7%)	3 (15.8%)	3(8.1%)	0.397
MAS	4(7.1%)	**0**	4 (10.8%)	0.288
Pneumonia	1 (1.8%)	**0**	1 (2.7%)	1.000
TTNB	3 (5.4%)	1(5.3%)	2 (5.4%)	1.000

Respiratory problems were seen more in infants born to gestational diabetic mothers. HMD was seen in 3 (15.8%) PGDM and 3 (8.1%) GDM, MAS in 4 (10.8%) GDM, Pneumonia in 1 (2.7%) GDM and TTNB were seen in 1 (5.3%) PGDM and 2 (5.4%) GDM.

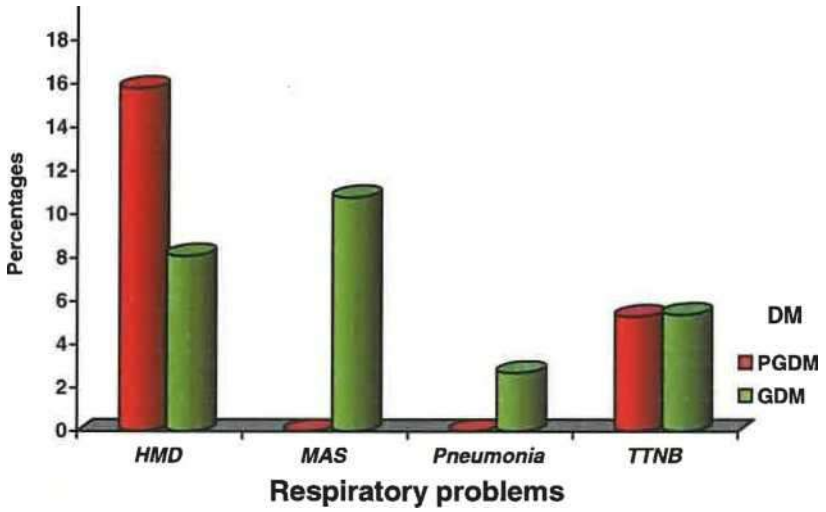
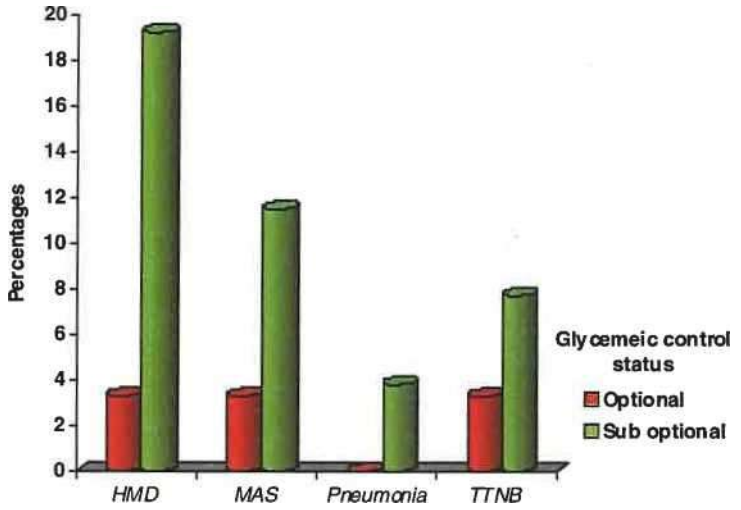


Table 17: Respiratory complications in IDMs and relation to maternal glycemic control

Respiratory problems	© II	Glycemic control		P value
		Optimal (n=30)	Sub Optimal (n=26)	
HMD	6 (10.7%)	1 (3.3%)	5 (19.2%)	0.086+
MAS	4(7.1%)	1 (3.3%)	3 (11.5%)	0.328
Pneumonia	1 (1.8%)	**0**	1 (3.8%)	0.464
TTNB	3 (5.4%)	1 (3.3%)	2 (7.7%)	0.592

HMD was seen in 1 (3.3%) infant in optimal control and 5 (19.2%) in sub optimal control group. MAS was seen in 1 (3.3%) infant in optimal control and 3 (11.5%) in sub optimal group. Pneumonia was seen in 1 (3.8%) in sub optimal group. TTNB was seen in 1 (3.3%) in optimal control and 2 (7.7%) in sub optimal control during pregnancy.



Respiratory problems

Table 18: Cardiac abnormalities detected by Echocardiography in infants of diabetic mothers

Echo findings	Number (n=56)	%
l.ASD	2	3.6
2.PDA	6	10.7
3.PDA+ Mild PAH	1	1.8
4.PDA+ Mild TP+ PAH	3	5.4
5.PDA+ Mod TR	1	1.8
6.VSD+PDA+PAH	1	1.8

PDA was the common cardiac finding observed in 6 (10.7%) IDMs and only 2(3.6%) IDMs had ASD and the others were observed with combination of PDA, VSD AND PAH.

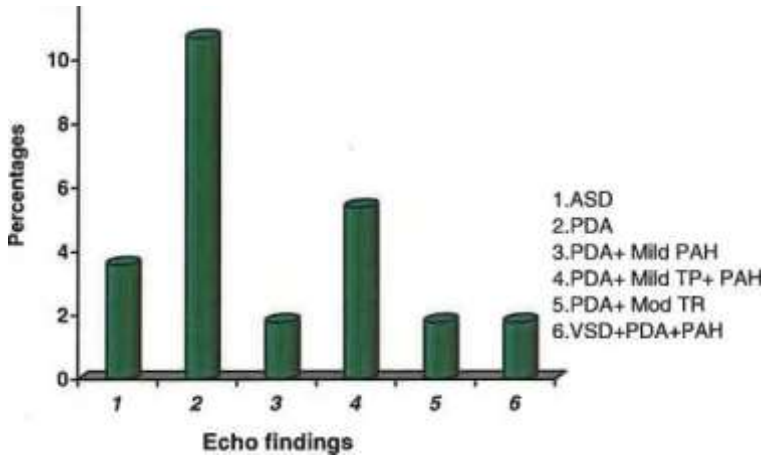


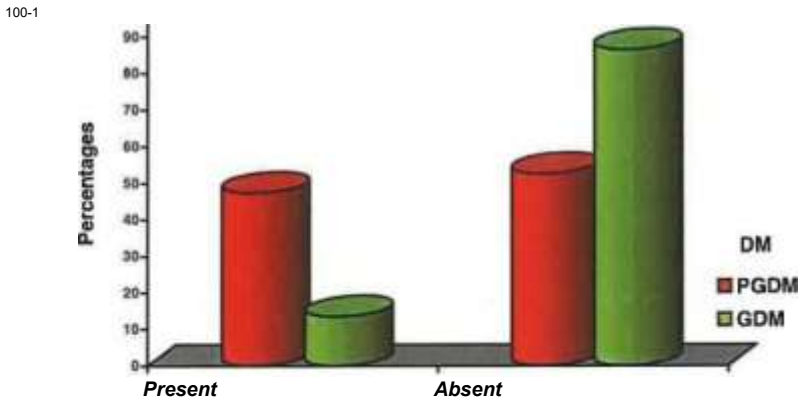
Table 19: Association of Hairy Pinna in infants of Diabetic mothers

Hairy pinna	(n=56)	DM	
		PGDM (n=19)	GDM (n=37)
Present	14 (25.0%)	9 (47.4%)	5 (13.5%)
Absent	42(75.0%)	10(52.6%)	32(86.5%)
Total	56(100.0%)	19(100.0%)	37(100.0%)

Inference

Hairy Pinna is significantly associated with Type of DM with

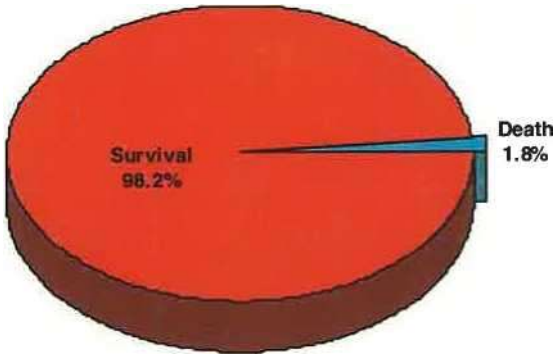
Hairy Pinna was observed in 14 (25%) of IDMs. It was seen in 9 (47.4%) IDMs of pregestational diabetic mothers and 5 (13.5%) EDMs of gestational diabetic mothers.



Hairy pinna

Table 20: Perinatal outcome in IDMs

Outcome	Number	%
Survival	55	98.2
Death	1	1.8
Total	56	100.0



Outcome

One baby was very premature and had HMD, PDA with moderate PAH and sepsis has died on day 8 of birth.

Table 21: Complications in IDMs in wards

Hyperbilirubinemia	**Total** (n=154)	**Percentage**
Present	51	33%
Absent	103	67%

HYPERBILIRUBINEMIA IN IDMs

H Present □ Absent

Hyperbilirubinemia (33%) was the only complication seen in IDMs in wards.

Statistical Methods:

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of

significance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two groups. Z-test for proportion has been used to find the significance of

1. Chi – Square test,

Where Oj is observed frequency and Ei is Expected frequency

2. Fisher Exact Test

	Classi	**Class2**	**Total**
Sample 1	a	b	a+b
Sample2	c	d	c+d
Total	a+c	b+d	n

(g + Z>)!(c + J)!(g + c)!(Z> + tZ)! 1 M! ^a\b\c\d\

2. Z-test for a proportion (Binomial distribution)

Objective: To investigate the significance of the difference between the assumed

Proportion and the Po and the observed proportion P

Z_(!P~JPQ!)-1/2M -jPoVo In

4. 95% Confidence Interval P ± 1.96* SE (P), Where SE (P) is the Standard error of Proportion = P*Q/^n

5. Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)

* Moderately significant (P value: 0.01 <P < 0.05)

** Strongly significant (P value: P<0.01)

Statistical software:

The Statistical software namely SPSS 15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

DISCUSSION

Diabetes Mellitus is the most common medical complication of pregnancy. The burgeoning problem of childhood obesity across the world has led to an increasing incidence of Type- Il DM early in life. The first manifestation of this could be variable degree of glucose intolerance first detected during pregnancy. More than half woman with GDM ultimately develop overt diabetes in the ensuing 20 years, and there is mounting evidence for long range complications that include obesity and diabetes in their offspring.

The IDMs are at an increased risk of complications compared to infants of non diabetic mothers. The causes of the fetal and neonatal sequelae of maternal diabetes are likely multifactorial, however, many of the perinatal complications can be traced to the effect of maternal glycemic control on the fetus. Many of the perinatal complications in IDMs can be prevented by appropriate periconceptional and prenatal care.

In the present study conducted at Manipal hospital, Bangalore, 56 infants born to diabetic mothers formed the study group. 4 infants were born of twin pregnancy to a gestational diabetic mother.56 infants were born to 54 mothers, 19 to pregestational diabetic (type -I and type -II DM) mothers and 37 to gestational diabetic mothers.

Family History of Diabetes Mellitus was present in 28.5% of the mothers in the present study. In a study done by Ranade et al in 1989 at B.J.Wadia hospital in Mumbai, family history of diabetes was present in 20%62. The higher percentage in our study could be due to the increasing incidence of type-II DM in our country.

In the present study, 36 infants were male and 20 infants were female which showed a male preponderance. In the present study, 53.5% of the mothers had optimal glycemic control during pregnancy and 46.46% had suboptimal control. The number of mothers with optimal control was more in the present study. Among pregestational diabetic mothers, 23.2% had suboptimal control and 21.4% among gestational diabetic mothers had suboptimal control.

Type of delivery:

Lower segment caesarean section for IDMs varies from as low as 35% in some studies to as high as 75% in some.

Type of delivery in IDMs in various studies:

Study done by	No. of IDMs	LSCS	Spontaneous vaginal delivery	Instrument assisted vaginal delivery
Ranade et al[62], 1989, Mumbai	50	58%	34%	8%
Deorari et al[6J] ,1985 ,Delhi	106	35%	65%	
Sudarshan et al[64],1987,Delhi	49	55%	45%	
Deorari et al[65],1991,Delhi	263	56.5%	40.2%	3.3%
Mangala et al[66],1991,B.lore	38	74%	26%	
Watson et al[67],Auckland	136	40%	60%	-
Present Study-Ban gal ore	56	71.4%	28.6%	

LSCS was done in IDMs either for Maternal or Fetal indications. In the present study, 71.4% were born by LSCS and 28.6% were born by spontaneous vaginal delivery. The present study correlates with other studies with some differences.

Incidence of prematurity in IDMs in various studies:

Study Done by	No. of IDMs	<37 weeks	>37 weeks
Ranade et al[62],1989,Mumbai	50	36.0%	64.0%
Deorariet et al[6j], 1985,Delhi	106	29.2%	70.8%

Deorari et al*", 1991, Delhi	263	16.0%	84.0%
Watson et al[67],2003, Auckland	136	46%	54%
Gabbe SG et al[68], 1978, US~	322	11%	89%
Akhlaghi F et al[6'2], 2005, Iran	100	13%	87%
Present study-Bangalore	56	42.8%	57.1%

In the present study, the incidence of prematurity was 42.8%. This varies in different studies from as low as 11% seen in a study done by Gabbe SG et al in 1978 to 46% seen in a study done by Watson et al in 2003.

The incidence of prematurity in the present study correlates with the study done by Ranade et al and Watson et al with some difference but deviates from studies done by Deorari et al in 1991.

Incidence of LGA/AGA/SGA IDMs in various studies

Study Done by	LGA	AGA	SGA
Ranade et al[62], 1989, Mumbai	40.0%	44.0%	16.0%
Deorari et al[6"5], 1985, Delhi	41.5%	44.3%	14.2%
Deorari et al[03], 1991, Delhi	20.2%	73.3%	6.5%
Present Study-Bangalore	17.8%	67.8%	14.3%

The incidence of LGA in IDMs varies between 20% in some studies to 42% in some. In the present study the incidence of LGA IDMs was 17.8% which nearly correlates with the study done by Deorari et al in 1991.

Comparison of complications seen in IDMs in various studies

Complication	**Ranade et al[62], 1989, Mumbai**	**Deorari et al[63], 1985, Delhi**	**Sudarshan et al[64], 1987, Delhi**	**Deorari et al[65], 1991, Delhi**	**Mangala et al[66], 1991 B.lore**	**Gabbe SG et al[68], 1978,US**	**Present Study, Bangalore**
Macrosomia	40%	41.5%	16.0%	20.2%	36.8%	■	17.8%
Birth Asphyxia	18%	13.2%	20.4%	9.1%	•		1.7%
Congenital anomalies	4%	3.8%		3.8%	7.9%	6%	7.1%
Birth injuries	2%			-	■	■	•
Respiratory Distress		5.7%	28.6%	8.0%			23.2%
Respiratory Distress Syndrome	14%	4.7%	10.2%	3.8%	5.2%	9%	10.7%
Hypoglycemia	50%	8.5%	28.6%	16.3%	18.4%	31%	35.7%
Hypocalcemia	14%			2.0%		13%	7.14%
Hyperbilirubinemia	8%	18.7%	42.9%	8.4%	15.3%	37%	35.7%
Polycythemia	20%			1.5%	10%	8%	7.1%

In the present study, hypoglycemia and hyperbilirubinemia were the commonest problems observed in IDMs, seen in 35.7% of IDMs. The incidence of hypoglycemia in IDMs varies from 8.5% -50% and hyperbilirubinemia varies from 8% -42.9%. The other complications seen in IDMs are comparable to other studies with some differences.

Comparison of neonatal complications in infants of mothers with optimal and suboptimal glycemic control

Complication	Quintero et al[a9], 2007, Florida		Present Study Bangalore	
	Optimal	Suboptimal	Optimal	Suboptimal
LGA	11.1%	19.8%	5.35%	12.5%
Hypoglycemia	7.1%	**9.3%**	14.3%	21.4%
Hyperbilirubinemia	**8.4%**	10.1%	8.9%	26.7%
Macrosomia (g) 4000-4500g	7.8%	12.3%		3.57%

In the present study, more LGA IDMs were born to mothers with suboptimal glycemic control during pregnancy .2 babies who weighed >4000g at birth were also seen in suboptimal control group. This is comparable to study done by Quintero et al in 2007 in Florida.

Congenital heart disease in infants of diabetic mothers: Echocardiography Study

CHD	Suleiman A et al70,2004, Riyadh(n=100)	Wren C et al23, 2003,Newcastle (n=609)	Present study- Bangalore (n=56)
1) Patent Ductus Arteriosus	70%		21.4%
2) Patent Foramen Ovale	68%		-
3) ASD	5%		3.57%
4)VSD	4%		1.78%
5) Mitral Valve Prolapse	2%		-
6) Pulmonary Stenosis	1%		-
7) Hypertrophic Cardiomyopathy	38%	-	-

8) TGA	1%	14.4%	-
9) TOF	1%	-	-
10) Hypoplastic Left Heart	1%	3.2%	-
11) Tricuspid Atresia	-	4%	-

The spectrum of cardiovascular malformations in various studies was compared. In the present study, PDA was the commonest CVS Anomaly detected by ECHO.

Perinatal outcome in IDMs in various studies

Study done by	Mortality
Rande et al62 ,1989, Mumbai	20.0%
Deorari et al63 ,1985,Delhi	7.4%
Sudarshan et al64 ,1987, Delhi	8.1%
Deorari et al65 ,1991,Delhi	3.0%
Present Study,Bangalore	1.78%

The mortality rate in IDMs in the present study was 1.78%, which is nearly comparable to the study done by Deorari et al in 1991, but deviates largely from the study done by Ranade et al in 1989.This may be because of better availability of facilities for neonatal care and monitoring.

CONCLUSIONS

The neonatal complications commonly seen in infants of diabetic mothers are macrosomia, birth asphyxia, congenital anomalies, respiratory distress, RDS, hypoglycemia, hypocalcaemia, hyperbilirubinemia and polycythemia. This has been reaffirmed in the present study.

Management goals in pregnancies complicated by Diabetes Mellitus should be to achieve optimal glycemic control, as neonatal complications are more common in woman with suboptimal glycemic control.

With appropriate care and management of diabetes during pregnancy, the perinatal outcome of IDMs can be improved.

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