

Case Report

Impact of Serum Progesterone Value on Embryo Transfer Timing, and Pregnancy Rate.

Aya Al-Ibraheemi^{1*}, Nouredine Louanjli², Mustafa Zakaria^{3*}, Mohammed Ennaji⁴, Wassym R. Senhaji⁵, Abdelhafid Natiq⁶, Romaina Boutiche⁷, Modou M. Mbaye⁸, Mohammed Zarqaoui⁹

1. Embryologist, UK. Researcher in the Scientific Research Group - and Member of the Association for Scientific Research of the IRIFIV-AISRG Group – UK.
2. Head of the LABOMAC Laboratory, and IRIFIV Fertility Center, AFC Fertility Center, and the Association for Scientific Research of the IRIFIV-AISRG Group Casablanca, Morocco.
3. MD. Senior Clinical Embryology and Assisted Conception, Deputy Executive Director and Administrative Coordinator of the Association for Scientific Research of the IRIFIV-AISRG Group, Consultant in IRIFIV Fertility Center, IVF laboratory, Casablanca ,Morocco.
4. Embryologist, Member in of the Association for Scientific Research of the IRIFIV-AISRG Group Casablanca, Morocco.
5. GYN OBT, Member in of the Association for Scientific Research of the IRIFIV-AISRG Group Casablanca, Morocco.
6. Genopath, Faculty of Medicine and Pharmacy, Mohammed V University Rabat Morocco, Team of Genomics and Molecular Epidemiology of Genetic Diseases (G2MG), Genomic Center of Human Pathologies (GENOPATH). Faculty of Medicine and Pharmacy. Mohammed V University in Rabat, Rabat, Morocco. Researcher in the Association for Scientific Research of the IRIFIV-AISRG Group.
7. Embryologist, Laboratory IVF Algeria, Rotary Fertility Center, Algiers, Algeria, Member in of the Association for Scientific Research of the IRIFIV-AISRG Group – Algeria.
8. Laboratory of Physiopathology, Genetics Molecular and Biotechnology (PGMB), Faculty of Sciences Ain Chock, Research Center. Health and Biotechnology, University Hassan II - Research Associate at the fertility center Irifiv a researcher in the Scientific Research Group – Casablanca, Morocco.
9. GYN OBT, Head of the Association for Scientific Research of the IRIFIV-AISRG Group Casablanca, Morocco.



***Corresponding Author: Mustafa Zakaria**, Senior Clinical Embryology and Assisted Conception, Deputy Executive Director and Administrative Coordinator of the Association for Scientific Research of the IRIFIV-AISRG Group, Consultant in IRIFIV Fertility Center , IVF laboratory, Casablanca, Morocco.
The Association for Scientific Research of the IRIFIV-AISRG Group.

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Abstract

The impact of progesterone on pregnancy and supporting embryo implantation before embryo transfer in IVF treatment have been well studied and several studies proved and demonstrated the positive impact of P4 on pregnancy. However, this impact can be influenced by various factors such as the timing of P4 administration and P4 dosage. Moreover, there are different types of P4 administration such as oral and vaginal P4 supplementation, which can alter the impact of P4 on the pregnancy rate. This research article will be discussing Progesterone function and the effect of P4 on embryo transfer and optimal level for serum level before embryo transfer.

Keywords: Progesterone function, Serum Progesterone and embryo transfer, Progesterone supplementation route and administration timing, Why optimal P4 level is vital.

Abbreviations

In-vitro fertilization (IVF), luteinizing hormone (LH), progesterone receptors (PGRs), selective progesterone receptor modulators (SPRMs), frozen embryo transfer (FET), Gonadotropin-releasing hormone (GnRH), follicle hormone (FSH), estradiol (E2).

Introduction

Progesterone is one of the steroids hormones which performs an essential function in many tissues other than the reproductive system, like in the mammary gland, to prepare the glands for breastfeeding, the cardiovascular system, central nervous system and bones. Firstly, progesterone was described as a molecular formula; yet, only in the mid-1940s, Russell Marker begins to manufacture progesterone from diosgenin, derived from the Japanese plant Dioscorea Tokoro Progesterone provides the endometrial transition from a proliferative to the secretory stage, support embryo development and is vital to



pregnancy maintenance (Taraborrelli, 2015). The corpus luteum substantially produces progesterone until the ninth week of pregnancy; following, the trophoblasts improve progesterone production, to become the most extensive resource of this hormone after the 12th-week gestation. Corpus luteum lack appears to happen in 35% of recurrent miscarriage cases. Progesterone is essentially manufactured from maternal LDL cholesterol through the placenta by a total enzyme system, and only a tiny portion will produce by fetal steroid genesis (Taraborrelli, 2015). Progesterone promotes interaction on particular receptors by inducing tubal motility and impacting endometrial maturation and uterine vascularization in the pre-implantation phase. Moreover, P4 inhibits the T lymphocyte-mediated tissue reaction, collectively with human chorionic gonadotrophin and decidual cortisol. Progesterone appears to produce tocolytic and immunosuppressive influences in the areas of significant contact within maternal and fetal compartments (Taraborrelli, 2015).

Progesterone function

P4 is an intrafollicular steroid that performs an essential role in ovulation, implantation, and pregnancy support and maintenance. P4 is short and elevated at 18 hours following the luteinizing hormone (LH) surge release; also, P4 is the main content of follicular fluid steroids in mammalian preovulatory follicles (Salehnia, et,al 2013) P4 was initially being considered as a contraceptive factor through reducing the luteinizing hormone surge and ovulation. It has an essential function in pregnancy maintenance and controlling biological processes in the ovarian tissue and fetomaternal unit. The processes consist of meiosis resumption, fertilization, embryonic development and implantation (Salehnia, et, al 2013). Clinically, it can be utilized in the female reproductive system as luteal support during in vitro fertilization (IVF), hormone replacement treatment for older women, and as a treatment for endometriosis and polycystic ovarian syndrome in younger women. Moreover, P4 has immunological roles for the maintenance of a fetomaternal. Some researches illustrate that P4 treatment for luteal maintenance increased uterine receptivity at the ultrastructure levels and improved mice's implantation rate (Salehnia, et, al 2013). The function of steroids is to get meiotic support and undergo regular fertilization and development to the blastocyst stage. The higher the ratios of P4 to E2 in follicular fluid in several species, the better embryo development. In one research, scientists tried to examine the impact of P4 on the developmental capability of mouse GV oocytes and following fertilization potential in concentrations comparable to that of preovulatory follicular fluid. The results pointed that P4 could not improve the embryo's fertilization rate and development to the blastocyst stage. Other studies have reported similar results, which indicate that the P4 maturation medium reduced the rate of blastocyst formation (Salehnia et al., 2013). However, on the other hand, another research showed that the presence of P4 in the porcine oocyte maturation medium improved sperm head decondensation and male pronuclei formation; moreover, they found out that the addition of P4 to the porcine oocyte maturation medium can increase both fertilization and cleavage rates, whereas E2 could not (Salehnia

et al. 2013). The importance of sufficient progesterone systemic concentrations through early embryo development is recommended by several researchers, including supplementation with exogenous progesterone. Progesterone's effects can be made both by a direct impact on the embryo or indirectly via the uterus or possibly both. As for the direct impact, progesterone receptors (PGRs) (**Figure 1**) must be present in the embryo; however, PGRs in mice couldn't be found until the blastocyst stage. Therefore, it is most likely for progesterone to affect embryo survival through an indirect effect on the uterus (*Morris and Diskin, 2008*). The indirect effect of P4 can impact embryo development by binding to uterine stroma or endometrial PGRs and starting a process of events containing differences in gene expression; thus eventually protein expression or variations in uterine permeability to ions, amino acids, or metabolites from plasma or by non-genomic effects on the uterine endometrium (*Morris and Diskin, 2008*).

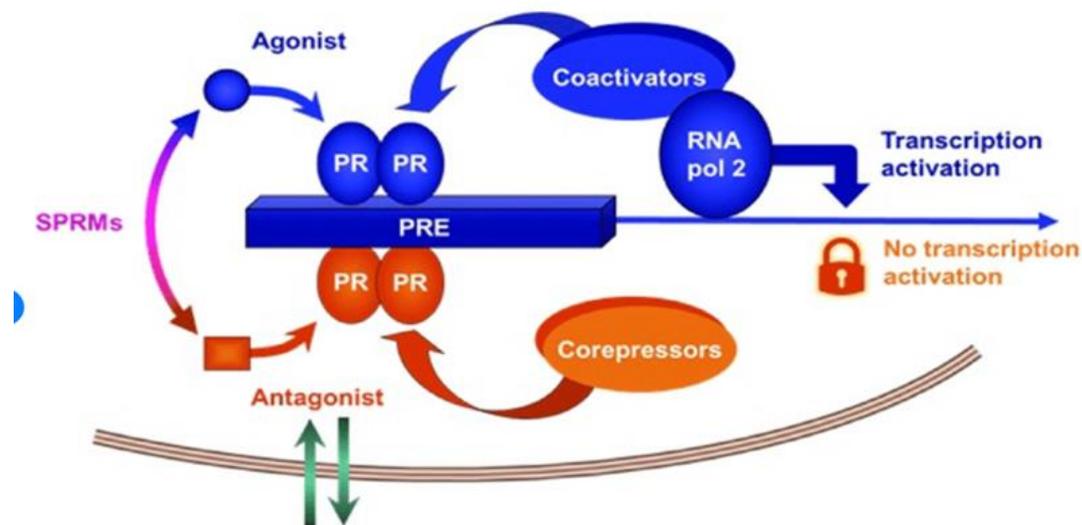


Figure 1: Action mechanism of selective progesterone receptor modulators (SPRMs, that have direct effects on uterine fibroids, endometrium and the pituitary gland; where it binds to the PR to mediate action either by activation or deactivation (Dolmans, Donnez and Fellah, 2019).

Serum Progesterone and embryo transfer

Several early studies suggested the importance of luteal phase support in frozen cycles, which has shown that progesterone supplementation does impact the outcome in frozen embryo transfer. Progesterone (P4) is needed for successful embryonic implantation into the endometrium and support of the pregnancy in natural cycles, fresh in vitro fertilization cycles, and frozen embryo transfer (FET) cycles. Thus rumors investigation has been done to illustrates the impact and importance of the P4 in Embryo transfer. Therefore P4 must be supplemented to enhance embryo transfer success and pregnancy rate.

Progesterone supplementation route and administration timing



For P4 supplementation, there are three administration routes, either oral, vaginal, or intramuscular. The oral P4 administration provides inadequately sustained plasma progesterone concentrations, although plasma progesterone concentration is a weak marker of bio-availability (Penzias, 2002). Regarding vaginal and intramuscular administration, it has been reported that intramuscular administration is more effective than vaginal supplementation (Jobanputra, Toner, Denoncourt and Gibbons, 1999). Several factors can change P4 serum levels following vaginal administration, like sexual intercourse, poor patient appliance, vaginal retention, disposition, and metabolism variations. Low P4 levels were recorded in more than one-third of patients who had daily vaginal P4 administration of 600 mg micronized progesterone. However, a high vaginal P dose of 1200 mg can increase the serum P levels (Boynukalin et al., 2019). P4 route of administration effectiveness can also depend on other factors, such as age and weight. For instance, in older women, the vaginal progesterone is more efficient as the vaginal mucosa of older women is thinner and more atrophic, increasing the absorption of vaginal progesterone. Moreover, other studies showed that body weight is an independent factor influencing serum progesterone concentrations following four days of vaginal progesterone administration. These results are biologically probable since body weight is a vital factor that affects drug absorption, distribution, metabolism and elimination (González-Foruria et al., 2021). P4 can be supplemented through Gonadotropin-releasing hormone (GnRH) agonists. GnRH agonists enhance GnRH production, which stimulates stimulating follicle hormone (FSH) and luteinizing hormone (LH), which excites ovulation and develops corpus luteum, which in return stimulates P4 production (Figure 2) (van der Linden et al., 2011).

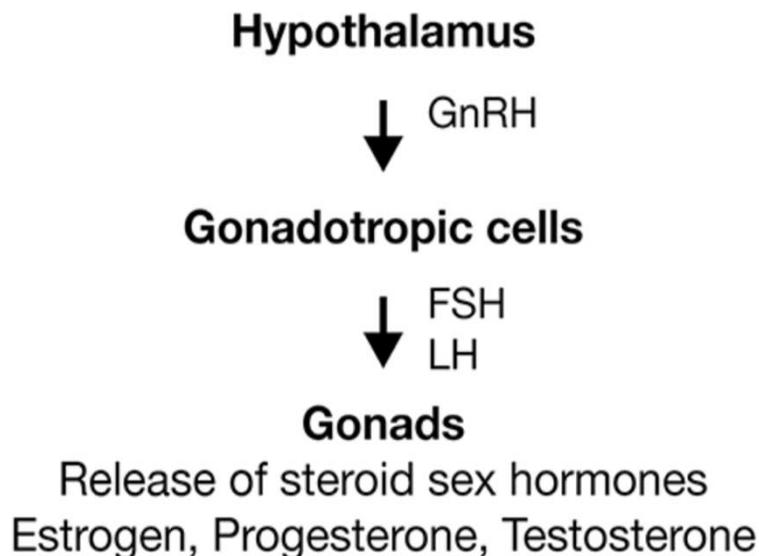


Figure 2: GnRH action mechanism. P4 is produced through a signaling cascade that starts from the hypothalamus in the brain till it reaches the gonads to produce P4 (Huerta-Reyes et al., 2019).



Another important aspect to consider in P4 administration is the timing and duration of the administration. The implantation window is the ideal length of progesterone supplementation and the growth of maximal endometrial receptivity which can be determined through endometrial biopsies collection and assessing the presence of pinopodes or by other biomarkers of implantation (e.g., the expression of @Vb3, PP14, and HOXA 10 gene expression); also it can be determined through transferring the embryos and examine the pregnancy and implantation rates. For most ART treatment, progesterone supplement practice is three days before embryo transfer; thus, if an embryo transfer is performed on Day 3 of development, progesterone supplement should be performed three days before embryo 3. Therefore, progesterone exposure days and timing before embryo transfer rely on the frozen embryos' stage to be transferred. In Sharma and Majumdar, progesterone supplementation for three days before embryo transfer (Embryo at cleavage stage 4–6-cell stage) had significantly higher pregnancy and implantation rates than four days of progesterone administration. Therefore, they concluded that progesterone supplementation for three days before embryo transfer had better pregnancy and implantation rates (*Sharma and Majumdar, 2016*)

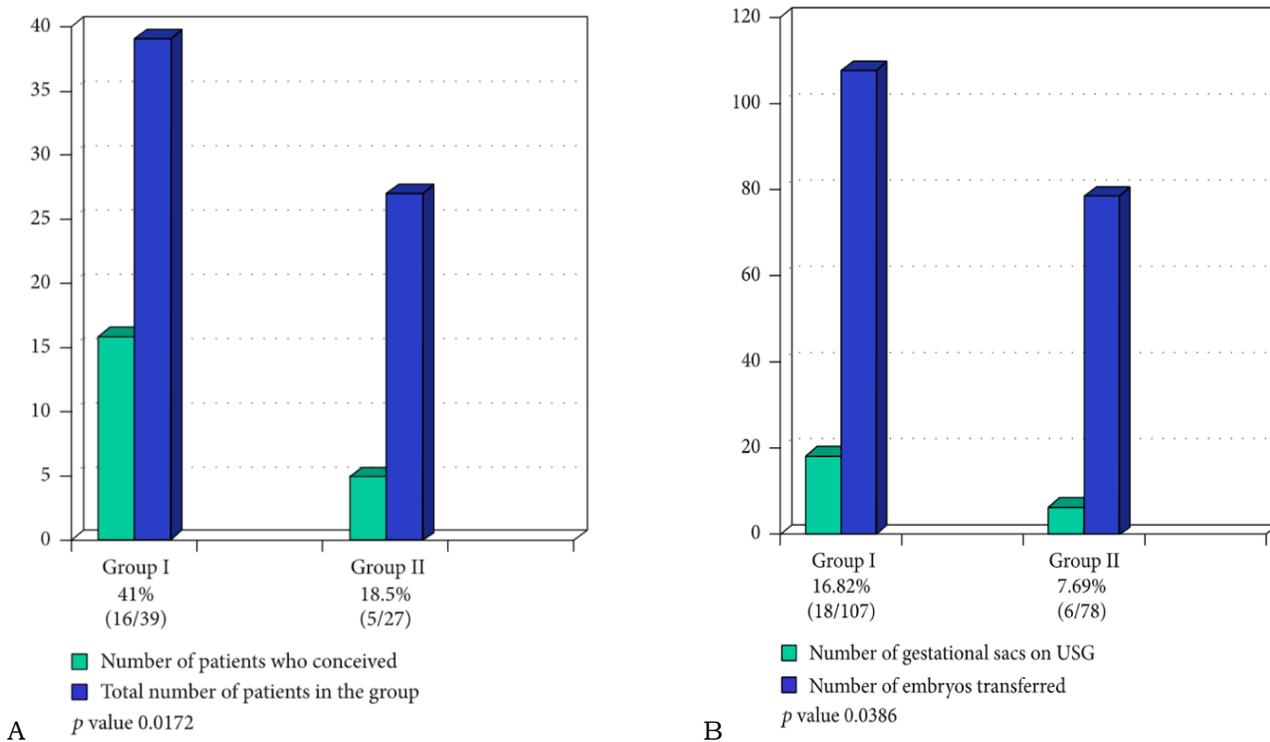


Figure 3: A) Pregnancy percentage in patients receiving progesterone for 3 and 4 days before embryo transfer. **B)** Implantation rates in patients receiving progesterone for 3 and 4 days before embryo transfer(Sharma and Majumdar, 2016).



Progesterone level and embryo transfer

P has a fundamental function in the endometrial transformation before frozen embryo transfer (FET). Endometrial transformation can be accomplished through a natural cycle or via an artificial endometrial preparation. (Gaggiotti-Marre *et al.*, 2020). Natural endometrial transformation requires no external medication, where corpus luteum secrete endogenous progesterone in the anovulatory cycle and, thus making this approach preferable to some patients. In artificial endometrial transformation, external administration of exogenous oestrogen and progesterone is applied to accomplish both adequate endometrial priming and serum hormonal values approaching the natural ovulatory cycle(Gaggiotti-Marre *et al.*, 2020). Progesterone serum level is vital to achieving successful implementation and pregnancy rate on the day of embryo transfer, several studies investigate abnormal P4 serum levels (low and elevated level), and their impact on embryo transfer, pregnancy rate, and live birth. In one study, a significant association was reported among positive pregnancy outcome and progesterone level at the day of HCG trigger were 79.2 % of a female with positive pregnancy at progesterone level < 1.5, while 9.3 % of a female with positive pregnancy at progesterone level > 2.5. In addition, 1107 women get pregnant when level of progesterone < 1.5 ng/mL, 127 get pregnant at level of 1.5- 2 ng/mL, 70 get pregnant at level of >2 - 2.5 ng/mL (Albdairi and Hussein, 2020)

Study variables	Pregnancy	
	Positive	Negative
Progesterone level at day of HCG trigger		
Less than 0.9	358 (49.7)	353 (47.9)
0.9-below 1.5	210 (29.2)	184 (25.0)
1.5- 2	56 (7.8)	75 (10.1)
> 2- 2.5	31 (4.3)	39 (5.3)
More than 2.5	65 (9.0)	86 (11.7)
Total	720 (100.0)	737 (100.0)

Table 1: Relationship among progesterone level at day of HCG trigger and pregnancy outcome (age 20-45) (Albdairi and Hussein, 2020).

Moreover, Gaggiotti-Marre *et al.* study showed the importance of serum levels on the day before FET in women undergoing a natural endometrial preparation cycle; their results indicated that low serum P levels on the day before embryo transfer (<10 ng/ml) are correlated with significantly lower clinical pregnancy rate and live birth rate. Also, low serum P4 level was associated with higher miscarriage rates



were (Figure 4).

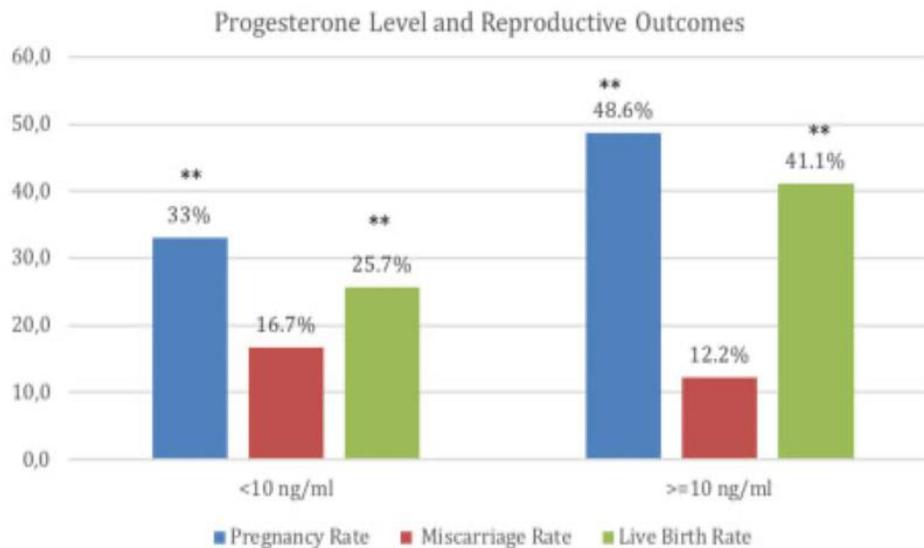


Figure 4: Progesterone level and embryo transfer outcome. The results indicate that P4 level >10 ng/ml, is associated with better reproductive outcomes.

Similar results to the above studies have been reported, which showed that patients with an artificial endometrial preparation cycle using vaginal progesterone had a significantly reduced ongoing pregnancy rate, like the serum, P was < 9.2 ng/ml on the day of embryo transfer (Labarta et al., 2017). Moreover, Labarta et al., observation point out no association for endometrial volume with either serum P levels or ongoing pregnancy rate, which implies if a minimal endometrial thickness is obtained, serum P levels would be the primary, more predictable marker for pregnancy more than ultrasound endometrium evaluations. Therefore, a minimal serum P threshold on the day of embryo transfer should be reached for a successful ongoing pregnancy rate (Labarta et al., 2017). The retrospective performed by Santos-Ribeiro et al., 2014, also evaluates the effect of low progesterone on the live-birth rate. The study conducted several evaluations according to various ordinal and normal progesterone levels (≤ 0.50 , 0.50–0.75, 0.75–1.00, 1.00–1.25, 1.25–1.50, .1.50 ng/ml) to compare the difference in live birth percentage. According to the previous serum progesterone levels, the live birth rates were 17.1, 25.1, 26.7, 25.5, 21.9 and 16.6%. The results confirm earlier studies' conclusion by finding the association between low P4 level and low birth rate (Santos-Ribeiro et al., 2014). Moreover, all patients had the same dose of exogenous FSH similar to the regular P group; they were also simulated using the same hCG criteria and had unaffected maturation and fertilization rates. Hence, the low birth weight associated with a low P4 level does not appear to be related to inadequate stimulation or poorer oocyte maturation or fertilization competence (Santos-Ribeiro et al., 2014). Throughout controlled ovarian hyperstimulation



(COH), progesterone serum elevation is always avoided through suppressing luteinizing hormone (LH) secretion by administering a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Therefore, various researches have been performed to record and evaluate elevated P4 impact on embryo transfer and pregnancy rate. The research examined the incidence of premature progesterone elevations in frozen-thawed embryo transfer cycles and the association with any adverse impacts on clinical outcomes. The elevated serum progesterone level was 4.6 nmol/l or higher in over one-fifth of patients undergoing IVF treatment. The results indicated no difference in clinical pregnancy rate, and ongoing pregnancy rate was seen within patients with and without elevated progesterone (*Groenewoud et al., 2017*). However, it has been demonstrated that a High P level before oocyte collection is linked with a noticeable endometrial receptivity reduction. Also, the gene expression profile of the endometrium will be affected when the P level is higher than its normal level at the end of the follicular phase. Elevated P levels on the day of hCG throughout the first fresh cycle are associated with poor pregnancy rate, although not in following frozen-thawed embryo transfer cycles (*Liang et al., 2018*). This finding has been supported by Ibrahim et al., where they demonstrate that the impact of elevated P4 can be extended to the level of fetal development itself and results in lower birth weights. The study also recommends that the progesterone on the day of hCG administration may be reasonable to delay the transfer in such circumstances. The research also points out that high progesterone on the day of hCG administration can be lined with various vascular endothelial growth factor expression in the endometrium. Accordingly, this can alter endometrial receptivity, ending in reduced implantation. Thus, it has been reported that that elevated progesterone can be correlated with adverse perinatal results (Ibrahim et al., 2017). Moreover, in one of the respective research, they assessed whether the hormone administration following the end of menstruation and till the day of hCG administration in GnRH antagonist/recombinant FSH cycles would be associated with pregnancy rate. The results suggested that elevated P4 serum level through the menstruation-free interval is correlated with a reduced likelihood of ongoing pregnancy (*Kyrou et al., 2011*). The impaired influence of high P exposure on pregnancy rate can be assigned to the increase and premature expression of P4 receptors on the endometrium in stimulated IVF cycles, which has been linked with the elevated E2 concentration through the follicular phase in these cycles (*Kyrou et al., 2011*). Furthermore, in the Bosch et al., study where they also evaluate elevated progesterone, they demonstrated no inverted association between ongoing pregnancy rates and serum progesterone levels on the day of hCG administration. In patients with elevated progesterone serum levels, ≥ 1.5 ng/mL, significantly higher ongoing pregnancy rates were recorded in comparison with patients with normal serum progesterone levels ≤ 1.5 ng/mL (31.0% vs 19.1%; $P = 0.00006$); the odds ratio was 0.53, with a 95% confidence interval of 0.38 to 0.72 (*Bosch et al., 2011*). The study also showed that elevated progesterone could be caused by an increase in a daily dosage of follicle-stimulating hormone, the number of oocytes collected, and estradiol (E2) values on the day of hCG administration. Additionally, women treated with GnRH agonists had significantly higher



serum progesterone levels than those receiving GnRH antagonists (0.84 ± 0.67 vs 0.75 ± 0.66 ng/mL; $P = 0.0003$) (Bosch et al., 2011). Finally, Ochsenkühn et al. also confirmed the above researches finding by proposing that high follicular P promotes the endometrium, and hence the replacement of a day-3 embryo in an asynchronous endometrium point out a failure of establishing embryo–endometrium cross-dialogue, this leading to embryo death and implementation failure. The study proposed that women who were experiencing pituitary down-regulation in addition to COH with by GnRH agonists and ET 5 days following collection display a significantly reduced live birth rate in the case of a slight P4 rise on the day of hCG administration (Ochsenkühn et al., 2012).

Why optimal P4 level is vital

Low serum progesterone can be a factor of low pregnancy rate; thus, this can be more serious with patients who already have low P4 in their blood circulation. According to González-Foruria et al., study, it has been found that certain factors affect progesterone concentrations on the day before embryo transfer, which can alter pharmacokinetics such as age, weight, and prior history of low progesterone concentrations, however other factors such as the timing of blood sampling do not depend on differences in drug absorption (González-Foruria et al., 2021). Also, high P4 serum level has been High P level before eggs collection is linked with a noticeable endometrial receptivity decrease. The endometrium's gene expression profile at the end of the follicular phase is certainly altered when the P level is above 1.5 ng/ml (Liang et al., 2018). Progesterone's importance in successful pregnancy rate and implementation rate have been clearly illustrated, however, significant progesterone elevation before HCG injection can point to a desynchronization within the endometrium and the embryo through reducing pregnancy rates (Groenewoud et al., 2017). In summary, successful implantation needs a competent blastocyst synchronization with the receptive endometrium, which is mainly coordinated by the endometrium receptivity are estrogen and progesterone. Thus an optimal P4 level is essential for successful implantation and pregnancy (Liang et al., 2018).

Conclusion

Progesterone is essential for establishing and maintaining embryo implantation and pregnancy; also, P4 is used for luteal phase deficiency in infertility treatment. Yet, progesterone therapy's optimal timing and dose can influence the impact of P4 on pregnancy. Also, low or elevated P4 levels can negatively impact embryo transfer timing and pregnancy rate.

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Reproductive Medicine and Reproductive Biology and Embryology, advocacy of interdisciplinary Department of Reproductive Medicine and Reproductive Biology and Embryology study, encompassing the areas of research, collections and publishing Articles.

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