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Review Article

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The Effect of Progesterone Elevation on the Day of Trigger Administration: A Review of the Literature

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Abstract

Since the advent of assisted reproductive technology, different variables have been shown to affect pregnancy outcomes. One of the most prevalent studied events is the premature rise in serum progesterone concentrations on the day of trigger administration during cycles of ovarian stimulation. This phenomenon, classically known as premature luteinization, has been observed significantly for decades and has been linked to adverse pregnancy outcomes and lower live birth rates. Ultimately, a quest to find a precise serum progesterone concentration cut-off value that can be effectively used to predict pregnancy outcomes prior to trigger administration is still underway. The purpose of the current research was to study the available literature on the relationship between serum progesterone on the day of trigger administration in controlled ovarian stimulation cycles used for IVF in an attempt to identify a cut-off serum progesterone concentration that can be used to effectively predict future pregnancy outcomes in fresh transfers. This study is a review of the literature and is based on information and data gathered from 36 published articles. The majority of the literature shows that a serum progesterone concentration cut-off of 1.5 *ng/ml* (4.77 *nmol/L*) can be used prior to trigger administration to effectively predict pregnancy outcomes. Premature progesterone elevation on the day or prior to the trigger administration is associated with adverse pregnancy outcomes in IVF cycles. Other factors such as follicle number, serum concentration of other hormones, and ovarian response to ovarian stimulation should also be considered to predict the success of IVF protocols.

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Introduction

The first successful cycle of in vitro fertilization (IVF) was achieved in 1978; since then, multiple different protocols and methods have been developed and studied to optimize this procedure and enhance its success rates by minimizing the risk of adverse pregnancy outcomes (1). In the natural female reproductive cycle, the gonadotropin releasing hormone (GnRH) is secreted by the hypothalamus in the brain. This hormone then exerts its effects on the anterior pituitary, or adenohypophysis, where it stimulates the release of follicle-stimulating hormone (FSH). FSH stimulates the growth and maturation of the developing ovarian follicle and luteinizing hormone (LH) which is most notable for its mid-cycle surge and induction of follicular rupture and

ovulation (2).

For decades, researchers have been attempting to develop protocols that could induce these hormonal patterns to accomplish successful fertilization in infertile women (3). These methods began with the use of human menopausal gonadotropin (hMG) extracted from the urine of postmenopausal women in the 1980s, progressing to the use of recombinant FSH in the 1990s to induce follicular maturation (4, 5). Today, purified hMG and rFSH are used in combination with a GnRH agonist or antagonist for optimal IVF protocols, and to prevent ovarian hyperstimulation syndrome (OHSS), a potentially fatal complication of IVF (6). Human chorionic gonadotropin (hCG) is subsequently administered to mediate mature follicular rupture on what is classically referred to as the "hCG trigger day" (7).

Multiple biologic and physiologic factors have been shown to affect IVF pregnancy outcomes, notably the serum progesterone level on trigger day. Progesterone is a steroid hormone synthesized by the corpus luteum after ovulation in the female menstrual cycle and during pregnancy by both the corpus luteum, and then the placenta (8). During menstruation and pregnancy, progesterone has multiple important functions, including preparing the placenta for a possible implantation and maintaining the pregnancy (9). In IVF cycles, it has been shown that serum progesterone levels rise during the late-follicular phase. This phenomenon, termed premature progesterone elevation (PE) or premature luteinization (PL), has been prevalently associated with adverse IVF pregnancy outcomes (10).

The relationship between elevated serum progesterone on trigger day and IVF pregnancy outcomes has been widely studied and debated. During the early follicular phase of ovulatory cycles, serum progesterone levels are generally low and tend to increase gradually 12-24 *hr* before the LH surge (11,12). In the early follicular phase, most of the circulating progesterone (P4) is of adrenal origin. However, as the follicular phase progresses, progesterone mainly accumulates from maturing ovarian follicles (13). In IVF cycles, progesterone levels above normal follicular-phase concentrations have been noted despite endogenous LH suppression with GnRH agonist/antagonist protocols (14). Some studies argue that this rise in late-follicular progesterone levels is not a result of PL but is rather caused by ovarian hyperstimulation (15). Although a premature rise in serum progesterone concentrations on trigger day has been associated with adverse pregnancy outcomes in IVF cycles, evidenced by various studies and clinical trials, the precise progesterone concentration associated with those adverse outcomes remains ambiguous (16). Most studies use the absolute serum progesterone concentration on trigger day as an indicator of PL by setting an arbitrary cut-off value ranging from 0.8 to 2 *ng/ml* (2.54 to 6.36 *nmol/L*) (17). Recent studies, however, have adopted a fixed cut-off value of 1.5 *ng/ml* (4.77 *nmol/L*), after multiple studies indicated that at this cut-off value, there is an evident distinction in endometrial receptivity between patients with progesterone concentrations below and those above the 1.5 *ng/ml* cut-off (4.77 *nmol/L*) (18). In all IVF cycles, multiple factors are required to ensure successful pregnancy outcomes in fresh transfers, most notably the synchrony between the receptive endometrium and the embryo (19). Premature serum progesterone elevations could potentially interfere with endometrial receptivity, thus leading to an asynchronous cycle, resulting in adverse pregnancy outcomes (20, 21). The aim of this article was to review some of the existing literature on premature luteinization to establish the most accurate cut-off value for progesterone in late follicular phase during fresh IVF cycles.

Methods

A multi-database search was performed, focusing on published articles that studied and analyzed the relationship between serum PE on trigger day in controlled ovarian stimulation cycles and IVF pregnancy outcomes. The articles selected were all written and published in English. The results of the 36 selected articles were analyzed and compiled to draw different conclusions. The reference lists of all the selected studies were thoroughly examined to search for other publications that analyzed and discussed similar concepts. Duplicate and irrelevant publications were discarded.

Results

Effect of premature progesterone elevation on IVF pregnancy outcomes: Premature elevations in serum progesterone concentrations prior to trigger medication administration can lead to adverse pregnancy outcomes. There are multiple mechanisms by which elevated serum progesterone levels adversely affect pregnancy outcomes, but there seems to be a general consensus that alterations in endometrial receptivity are the primary reasons

for these adverse pregnancy outcomes (22-25). A progesterone level above 1.5 *ng/ml* (4.77 *nmol/L*) on the last day of oocyte maturation prior to retrieval is correlated to a reduced endometrial receptivity, and hence a reduced pregnancy rate (26). High progesterone levels on the day of trigger alter endometrial receptivity, causing a decrease in implantation rate and quality, due to variation in expression of endothelial growth factors within the endometrium. It has also been shown that PL doesn't directly affect embryo quality or fertilization, but rather reduces the chances of embryo implantation after embryo transfer (27). One study found that due to the increased number of progesterone receptors on day of trigger administration, even slight elevations in progesterone levels made a significant difference in the endometrial maturity. This leads to an asynchrony between endometrium and embryo signaling. In this study, the quality of embryos didn't significantly change between the control and the high progesterone level groups. Hence, the issue did not reside in the embryo quality, but in the receptivity of the endometrium which was found to be hindered by high progesterone levels negatively affecting implantation and pregnancy rates (28). The purpose of another retrospective study was to determine whether P4 level 48 *hr* prior to hCG administration (P4 level 1) and the P4 ratio are better predictors of assisted pregnancy outcomes when compared to P4 levels on the day of hCG administration (P4 level 2). The study ultimately found that early P4 levels (P4 level 1, measured 48 *hr* prior to hCG administration) and the P4 ratio were better predictors of pregnancy and live birth rates than P4 level measured on the day of hCG administration (P4 level II) (29).

Factors influencing serum progesterone levels on trigger day: Many factors were shown to affect progesterone levels and many others remain unclear. In a study conducted to determine the main factors affecting elevated progesterone levels (considered ≥1.5 *ng/ml* (4.77 *nmol/L*) according to standard criteria), it was found that serum estradiol level on trigger day, the number of follicles exceeding 14 *mm* in diameter, the number of retrieved oocytes, and the degree of ovarian response were the main factors.

This study also attributed the pregnancy outcome to the serum progesterone to follicle index (PFI) instead of simply an isolated elevated progesterone level. A high PFI indicates elevated progesterone levels due to overproduction of follicular progesterone which would be detrimental to IVF outcomes. Other factors, including patient age, body mass index, method of pituitary suppression, and cause of infertility, did not seem to have a significant impact on the serum progesterone level on trigger day.

Another important factor determining progesterone levels is the level of LH. High levels of progesterone may be the reflection of high levels of LH since the latter increases the expression of progesterone and androgens (22). The definition of PL differs in the available literature. For instance, some studies select an arbitrary cut-off value to measure progesterone level on the day of trigger administration, whereas others define elevated progesterone level as an increase in the ratio of serum progesterone to serum estrogen (E2) levels.

Multiple hypotheses can be used to explain the phenomenon of PL, including granulosa cell-release of progesterone stimulated by elevation of follicular LH levels, LH activity upregulation from hMG administration, recombinant FSH-induced increase in LH receptor sensitivity of granulosa cells, poor ovarian response with increased LH sensitivity, and possible genetic predispositions that disrupt granulosa cell signaling pathways leading to PL (30). One study showed that several factors were associated with PL, including the type and dose of gonadotropin used, estrogen levels on the day of trigger (≥2500 *pg/ml*), and the number of mature follicles (≥10 follicles of ≥10 *mm* in diameter) (13). Other studies contradict this and show that the type of gonadotropin used in stimulation cycles does not play a role in the elevation of progesterone levels on the day of trigger administration. Instead, PL is associated with an increase in the number of follicles, oocytes, and E2 levels (32).

Freeze-all protocol to avoid adverse pregnancy outcomes: The freeze-all protocol has been used to halt embryo maturation and to avoid adverse pregnancy outcomes. A direct link was found between serum estradiol and serum progesterone levels concluding that higher serum levels of both hormones on trigger day may affect endometrial receptivity, thus resulting in a lower pregnancy success rate (24). For patients with very high serum progesterone concentrations (>6 *nmol/L*), a freeze-all protocol is recommended before resuming the clinical cycle. One study compared the blastula-

tion rates and pregnancy outcomes in people with high levels of progesterone who adopted the freeze-all strategy versus people with normal serum progesterone levels at induction (defined as P <1.5 *ng/ml* or 4.77 *nmol/L*) who adopted the freeze-all strategy for other reasons, such as risk of ovarian hyperstimulation syndrome. The study suggested that adopting a freeze-all strategy in cases of PL during COS due to high progesterone levels is the preferred management to prevent adverse pregnancy outcomes. There is also a belief, however, that adoption of the freeze-all protocol should not be standardized, but rather individualized and used on a patient-to-patient basis (34).

Serum progesterone concentration prior to maturation trigger administration: It was during the late 20th century that medical researchers began to understand the functions of progesterone during pregnancy and how its concentration varies during trials of controlled ovarian stimulation in assisted reproductive technology (ART). It was evident that a rise in progesterone hormone levels was leading to lower pregnancy rates in women undergoing ART; however, what remained unclear was the mechanism through which this phenomenon was happening and the serum concentration at which physicians can safely predict pregnancy outcomes to find alternative solutions to preserve the embryo. Many studies have adopted an arbitrary value of 1.5 *ng/ml* (4.77 *nmol/L*) as a cut-off for the serum progesterone concentration prior to trigger administration and have analyzed how this cut-off value can be used to optimize IVF pregnancy outcomes (13, 32-35). A study followed 235 patients undergoing conventional IVF or intracytoplasmic sperm injection (ICSI) to evaluate the incidence of PL on the day of trigger and its effect on clinical pregnancy rate. The cut-off for defining premature progesterone rise (PPR) was set at 1.5 *ng/ml* (4.77 *nmol/L*), as it represents the transition from the follicular to the luteal phase in the natural ovulatory cycle. Patients with a progesterone level below the cut-off had a clinical pregnancy rate of 33.3% compared to a 12.9% clinical pregnancy rate in patients with progesterone levels above the 1.5 *ng/ml* (4.77 *nmol/L*) cut-off (13). A 2017 retrospective study by Vanni et al. expanded further on this notion by studying the rate of successful pregnancy outcomes based on 4 different serum progesterone cut-off values ranging from 1 to 2.5 *ng/ml*, increasing in 0.5 *ng/ml* increments. They found that there was a significant reduction in the proportion of top-quality blastocyst formation with increases in serum progesterone concentrations at induction. Furthermore, they found that progesterone levels did not significantly affect fertilization and blastulation rates. Using receiver operating characteristic (ROC) curves, they derived that a progesterone level >1.49 *ng/ml* is "the best cut-off for identification of patients at risk for the absence of top-quality blastocyst" (33).

Park et al. (2015) showed that the premature rise in serum progesterone caused by the aforementioned factors did in fact lead to a decline in the pregnancy rate, with only 4.2% of pregnancies with P4 levels >1.5 *ng/ml* (4.77 *nmol/L*) being successful, as compared to 25.2% when P4 level was below 1 *ng/ml* (3.18 *nmol/L*), regardless of the ovarian stimulation protocol utilized (25).

A retrospective, observational, cohort study monitored 165 patients between the ages of 20 and 40 years who underwent IVF/ICSI using GnRH antagonist protocol. The patients were divided into two groups; 143 patients had serum progesterone levels ≤1.5 *ng/ml* on hCG trigger day and 22 patients had serum progesterone levels >1.5 *ng/ml* (4.77 *nmol/L*). Increased serum progesterone levels prior to hCG trigger were found to negatively affect IVF pregnancy outcomes. Patients with pre hCG serum progesterone levels >1.5 *ng/ml* had a pregnancy rate of 6% compared to a 45% pregnancy rate in patients with serum progesterone levels ≤1.5 *ng/ml* (4.77 *nmol/L*). The increased progesterone levels were not found to affect oocyte quality or fertilization, but rather reduced the chances of embryo implantation after embryo transfer (35). As aforementioned, the effect of PL on IVF pregnancy outcomes can differ depending on the degree of ovarian response. PL on maturation trigger day wasn't found to have a negative impact on pregnancy outcomes in all subgroups of ovarian responders. Although no clear progesterone cut-off value has been established, different cut-off values should be used for patients with different ovarian responses (32). For instance, a study conducted on 10,075 subjects implemented a cut-off of 1.5 *ng/ml* (4.77 *nmol/L*) for poor responders, 1.75 *ng/ml* (5.561 *nmol/L*) for intermediate responders, and 2.75 *ng/ml* (8.745 *nmol/L*) for high responders and found that PE is more marked in patients with higher ovarian response but still has detrimental effects on pregnancy rates in all ovarian responders (36).

Table 1. Characteristics of included studies to discuss association between pre-trigger serum progesterone levels and IVF outcomes

Author (s)	Year	Type of study	Population size	Ovarian stimulation regimen	Day of P4 measurement	P4 cut-off level	Outcome in fresh transfer
Park et al. (25)	2015	Retrospective	330 IVF/ICSI cycles	GnRH agonist (n=184) and GnRH antagonist (n=146) protocols	On trigger day	1.0 *ng/ml* (3.18 *nmol/L*)	25.2% pregnancy rate with P<1.0 *ng/ml*, 23.1% with P>1.0 *ng/ml* Only 4.2% of patients had P>1.5 *ng/ml*
Lee et al. (29)	2020	Retrospective cohort	710 IVF/ICSI cycles	GnRH agonist protocols with recombinant FSH	2 days before (P4 level 1) and on trigger day (P4 level 2)	1.5 *ng/ml* (4.77 *nmol/L*)	P4 level I of ≤0.975 *ng/ml* and P4 ratio of >1.62 were associated with a significantly higher implantation (30.8%, 61/198 *vs.* 10.3%, 19/184, p<0.001) and live birth rates (51.6%, 33/64 *vs.* 15.0%, 9/60, p<0.001)
Ashmita et al. (13)	2017	Prospective	235 IVF/ICSI cycles	GnRH agonist protocols	On trigger day	1.5 *ng/ml* (4.77 *nmol/L*)	12.9% pregnancy rate with P>1.5 *ng/ml*, 33.3% with P<1.5 *ng/ml* (p=0.037)
Vanni et al. (33)	2017	Retrospective	986 IVF/ICSI cycles	GnRH antagonist protocols	On trigger day	4 cut-off values were investigated: 1 *ng/ml*, 1.5 *ng/ ml* (4.77 *nmol/L*), 2.0 *ng/ ml* (6.36 *nmol/L*, 2.5 *ng/ml* (7.95 *nmol/L*)	Significant reduction in the proportion of top-quality blastocyst formation in relation to increasing P levels across all four cut-off values P levels did not correlate significantly with either fertilization rate (p=0.17) or blastulation rate (p=0.33)
Amin et al. (35)	2018	Retrospective cohort	165 IVF/ICSI cycles	GnRH antagonist protocols	On trigger day	1.5 *ng/ml* (4.77 *nmol/L*)	6% pregnancy rate with P>1.5 *ng/ml*, 45% with P<1.5 *ng/ml* (p<0.001)
Xu et al. (36)	2012	Retrospective cohort	11,055 IVF/ICSI cycles	Long GnRH agonist protocol	On trigger day	Cut-off value defined based on ovarian response: 1.5 *ng/ml* (4.77 *nmol/L*) for poor responders, 1.75 *ng/ml* (5.565 *nmol/L*) for intermediate responders, 2.25 *ng/ml* (7.15 *nmol/L*) for higher responders	Poor ovarian response: pregnancy rate 10.6% with P>1.5 *ng/ml*, 20.8% with P<1.5 *ng/ml* (p<0.05) Intermediate ovarian response: pregnancy rate 29.3% with P>1.75 *ng/ml*, 39.3% with P<1.75 *ng/ml* (p<0.05). High ovarian response: pregnancy rate 27.5% with P>2.25 *ng/ml*, 36.8% with P<2.25 *ng/ml* (p<0.05)

Apart from using an individual serum progesterone level on trigger day to subsequently predict pregnancy outcomes, some studies provide alternative measures which can be used to make better predictions. As such, a study found that using progesterone levels 48 *hr* prior to hCG administration, called P4 level 1 (cut-off value: 0.975 *ng/ml*), and having an elevated P4 ratio (cut-off value: 1.62 *ng/ml*) in women with progesterone levels >1.5 *ng/ml* (4.77 *nmol/L*) on hCG trigger day (P4 level 2) was more effective for predicting pregnancy outcomes than the P4 level on hCG trigger day alone. In this study, the P4 ratio was defined as the ratio of progesterone concentration 48 *hr* prior to hCG administration to the progesterone concentration on hCG trigger day. Using

ROC curves and predictive values for patients with P4 level 2 >1.5 *ng/ml*, the study found that even at this cut-off value, a P4 level 1 <0.975 *ng/ml* and a P4 ratio >1.62 were associated with positive pregnancy outcomes. In women with P4 level 2 >1.5 *ng/ml*, those with a P4 level 1 <0.975 *ng/ml* had higher rates of implantation (30.8% *vs*. 14.8%), pregnancy (67.2% *vs*. 25.9%), and live births (51.6% *vs*. 17.6%) compared to women with P4 level 1 >0.975 *ng/ml*. A similar trend was noticed in women with a P4 ratio >1.62. Patients with P4 level 1 >0.975 *ng/ml* and P4 level 2 >1.5 *ng/ml* (P4 ratio <1.62) had the poorest pregnancy outcomes (29).

These findings further solidify the fact that even though a universally adopted trigger day serum progesterone cut-off concentration has not yet been established, other factors still need to be taken into consideration when predicting pregnancy outcomes in ART cycles even when a cut-off value becomes universally accepted. A multitude of other factors should be taken into consideration when predicting pregnancy outcomes in women undergoing ART. The mechanism by which elevated serum progesterone affects endometrial receptivity and hence lowers the clinical pregnancy rate became even more clear than in the past. A serum progesterone concentration cut-off value of 1.5 *ng/ml* (4.77 *nmol/L*) was prevalently used an arbitrary standard but proved to be a statistically significant value in most studies. The factors contributing to the premature PE are now better understood and alternative practices to prevent any adverse pregnancy outcomes have been thoroughly studied and implemented. The characteristics and major findings of the aforementioned studies are summarized in table 1.

Conclusion

In conclusion, it is evident that the phenomenon of premature progesterone elevation on trigger day in controlled ovarian stimulation IVF cycles is still under investigation, and the exact mechanism that leads to this finding is not entirely understood. The articles presented in this review all acknowledge that there is a clear association between elevated serum progesterone levels on the day of trigger administration in ART cycles and adverse pregnancy outcomes. This detrimental effect is known to be caused by reduced endometrial receptivity or embryo-endometrial asynchrony, which limits the amount of time available for the transferred embryo to successfully undergo endometrial implantation, thus significantly decreasing the pregnancy and live birth rates. There were no harmful effects observed on the quality of the transferred embryo. Additionally, it was inferred that the freeze-all protocol should be utilized on a case-by-case basis to assess embryo viability in cases of premature progesterone elevation. The only limitation that can be highlighted is the fact that although premature elevations in serum progesterone levels are linked to adverse pregnancy outcomes in IVF cycles, a precise serum progesterone cut-off concentration remains ambiguous. Although most studies confirm that a cut-off of 1.5 *ng/ml* (4.77 *nmol/L*) should be adopted, there are other publications that argue otherwise based on other arbitrary values. In either case, it is important to remember that there are additional potential factors to consider when predicting pregnancy outcomes in IVF cycles, even when the progesterone level is elevated on the day of hCG trigger. Such factors include the ratio of progesterone to estrogen, the serum progesterone level 48 *hr* prior to trigger administration, the progesterone ratio of serum concentrations 48 hours prior to and on the day of hCG administration, and others discussed in this review. Determining a universal and precise cut-off value for serum progesterone concentration on hCG trigger day would be helpful and would allow physicians to clearly define and predict the goals and outcomes of an IVF cycle.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial interest that could be interpreted as a potential conflict of interest.

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