

CURRENT PREVENTIVE STRATEGIES FOR PREEVULATORY PROGESTERONE ELEVATION DURING OVARIAN STIMULATION FOR *IN VITRO* FERTILIZATION

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SUMMARY – The purpose of this review is to present contemporary measures for preventing the increase in preovulatory progesterone (P) and its adverse effects on ovarian stimulation in *in vitro* fertilization (IVF). For the last 20 years, the increase of preovulatory P has been a topic of numerous discussions because its role is not fully understood in terms of its impact on pregnancy outcome after IVF. Some studies failed to establish a connection between the preovulatory P increase and successful IVF outcome regardless of the level of P, while, conversely, most other studies have reported on adverse effects of elevated P concentrations. Current strategies to prevent the increase in preovulatory P include an individualized approach with the use of mild stimulation protocols and early application of human chorionic gonadotropin for ovulation induction among good responders, delay in the transfer of fresh embryos from 3rd to 5th day, and cryopreservation of all embryos with the thawed embryo transfer in the natural cycle. Nevertheless, further studies are needed to confirm the current preventive methods or enable the application of new strategies in order to lower or eliminate the detrimental effects of preovulatory P rise during ovarian stimulation in IVF.

Key words: *Female; Fertilization, in vitro; Progesterone – biosynthesis; Ovulation induction; Embryo transfer; Cryopreservation*

Introduction

Elevated preovulatory serum progesterone (P) is frequently ascertained during the late follicular phase at the end of ovarian stimulation on the day of ovulation triggering with human chorionic gonadotropin (hCG) during the *in vitro* fertilization (IVF) cycle. The incidence of premature P rise varies widely from 13% to 71% depending on definition, cut-off level of P, stimulation protocols and population characteristics¹.

The presence of premature luteinizing hormone (LH) surge during ovarian stimulation has been previously correlated with preovulatory P rise and it has been constantly associated with reduced pregnancy rates². In order to prevent premature LH rise and consequently premature P rise, gonadotropin-releasing hormone (GnRH) analogues have been introduced. Although the significance of GnRH analogues in the prevention of preovulatory P rise has been proven, higher P levels have been recorded in approximately 35% of GnRH agonist cycles and 38% of GnRH antagonist cycles³.

The ovarian response to follicle stimulating hormone (FSH) in recombinant (rec)-FSH/GnRH antagonist cycles has been associated with the risk of P

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elevation. Furthermore, a direct correlation between premature P rise and estradiol (E2) levels and the number of follicles on the day of hCG administration has been widely confirmed. The association between the high E2 and premature P elevation could be explained by an excess of proliferating granulosa cells that can lead to an increased P production⁴. According to the two-cell, two-gonadotropin theory and the fact that excessive FSH stimulation may increase the production of P, the inclusion of LH activity products in stimulation protocols to counterbalance the effect of FSH may help reduce the risk of late follicular P increases⁵. However, a systematic review of several studies comparing FSH administration alone or in combination with LH activity products could not demonstrate any significant effect of 'LH activity' on serum preovulatory P elevation. Therefore, the major determining factor for the risk of P rise at the time of hCG administration remains the degree of ovarian response to FSH⁶. However, early addition of increasing doses of hCG (0, 50, 100 and 150 IU) from the beginning of ovarian stimulation in combination with rec FSH + GnRH antagonist was associated with an increased risk of P elevation⁷. Furthermore, it appears that the choice of GnRH analogue has an impact on the risk of P elevation because preovulatory P levels were higher in women treated with GnRH agonist as compared with GnRH antagonist. These differences can be explained by stronger ovarian response to FSH as the main driver of P output and by higher endogenous LH concentration during the last few days of stimulation in favor of GnRH agonist^{8,9}. It appears that endogenous LH in the late follicular phase acts positively on P secretion and women treated with GnRH agonist protocols are more prone to P elevation¹⁰.

Since the early 1990s, there has been an ongoing debate in more than 60 studies in women undergoing ovarian stimulation with controversial conclusions regarding the impact of preovulatory P on IVF outcome. Several previous and recent studies failed to demonstrate any negative effect of P rise¹⁰⁻¹². The first meta-analysis of 12 studies, published in 2007, has reported that there was a nonsignificant negative association between P elevation and pregnancy rate in women with GnRH analogues and gonadotropins¹². However, the second meta-analysis from 2012 focused on women using GnRH antagonists and gonadotropins (five studies) states that P elevation on the day of hCG ad-

ministration is associated with a significantly decreased probability of clinical pregnancy *per cycle*¹³. Similarly, in the third meta-analysis from 2013 of over 60 000 fresh IVF cycles it was found that P elevation on the day of hCG was associated with a significantly decreased probability of pregnancy in women, whatever the GnRH analogue used. The thresholds of serum P on the day of hCG administration were arbitrarily chosen from 0.4 ng/mL to 3 ng/mL and the strongest effect size of P elevation for achievement of pregnancy was observed with P thresholds between 1.5 ng/mL and 1.75 ng/mL¹⁴. Several recent studies also established that P elevation on the day of hCG administration could be associated with a risk of reduced implantation rate. Despite the use of different thresholds of serum P, the optimal P threshold over which a detrimental effect on IVF outcome might be observed has been estimated to 1.5 ng/mL and this threshold has been commonly used^{10,15,16}. It seems that the P threshold in women using GnRH agonists is dependent on the degree of the ovarian response because in poor responders, the P threshold associated with a lower pregnancy rate was estimated at 1.5 ng/mL, in patients with normal ovarian response 1.75 ng/mL and in high responders 2.25 ng/mL¹⁷. Consequently, in patients treated with rec FSH and GnRH antagonists, P elevation does not compromise pregnancy rates in high responders, although its incidence increases with ovarian response and elevated P at a threshold of 1.5 ng/mL is independently associated with a decreased chance of pregnancy in low-to-normal responders. Therefore, it seems that the detrimental effect of P elevation on the implantation rate could be compensated for by an increased yield of high-quality oocytes¹⁸. Interestingly, the duration of P elevation could have a stronger impact on cycle outcome than the absolute serum P concentration on the day of hCG. The clinical pregnancy rate is significantly inversely correlated with the duration of premature serum P elevation above the cut-off value of 1.0 ng/mL, whatever the protocol used and the intensity of the ovarian response¹⁹. It seems that the use of a multivariable analysis is the proper way of assessing the adverse effect of preovulatory P elevation on live birth rates, when compared with the bivariate analysis that was used in most of the studies that failed to identify the detrimental effect in fresh IVF cycles²⁰.

Since preovulatory P rise during ovarian stimulation is not associated with any significant changes in

either oocyte or embryo quality, it is now convincingly accepted that P prematurely opens the window of implantation and modifies endometrial receptivity, leading to defective implantation and mainly contributing to the decreased pregnancy rate¹⁴. Indeed, any 3-day advancement in endometrial receptivity assessed by endometrial biopsy at the time of oocyte retrieval results in a significant decrease in implantation rate, presumably related to P elevation^{21,22}. However, direct evidence for an effect of P rise on the endometrium has been provided by the altered gene expression profile in a recent functional genomics analysis^{23,24}. Since the majority of published studies demonstrated a detrimental effect of preovulatory P elevation which contributes to a decreased pregnancy rate, the purpose of this review is to analyze current preventive strategies that may improve pregnancy outcome following IVF.

Prevention of Preovulatory Progesterone Elevation

Mild ovarian stimulation protocols are associated with lower E2 levels and therefore may be useful in the prevention of premature P rise due to strong correlation between ovarian response and preovulatory P rise²⁵, which may be achieved with limited gonadotropins or with alternatives such as anti-estrogens or aromatase inhibitors since they reduce the dose of gonadotropins required for stimulation and keep estrogen levels low²⁶. There are limited clinical data available concerning the use of aromatase inhibitors in IVF treatment. Up to date, only three randomized controlled trials involving a total of 80 women studied the use of aromatase inhibitors in IVF²⁷. However, new studies yielded promising results on the benefit of aromatase inhibitor use in terms of ovarian stimulation for IVF^{28,29}. Although mild stimulation is correlated with a reduced risk of premature P rise, lower pregnancy rates *per* cycle, fewer embryos for cryopreservation and still not available individualized FSH-dosing algorithms have been reported²⁷. Moreover, it is important to consider each patient's general condition including age, ovarian reserve, embryo grading and the capacity of frozen/thawed embryo transfer when mild protocols are used for stimulation³⁰.

An earlier hCG trigger, when follicles reach a diameter of 15-16 mm, has been suggested as a strategy for preventing premature P rise. It has been suggested

that earlier hCG trigger should take place when ≥ 3 follicles of ≥ 16 mm diameter are present on ultrasonography³¹. However, this early trigger has been associated only with lower preovulatory P but not with better ongoing pregnancy rates³². In order to avoid premature P rise and its detrimental effect on IVF outcome, earlier trigger in high responders is more suitable as compared with normal and poor responders^{31,33}. Due to the potential predictive role of E2 concentrations for premature P rise, final oocyte maturation can be triggered when the E2 concentration reaches the point of having a risk of preovulatory P rise³⁴.

One of the strategies that have been suggested to overcome the detrimental effect of advanced endometrial maturation is to enable endometrial recovery before transfer. Numerous studies investigated the benefit of day 5 compared to day 3 embryo transfer (ET)³⁵⁻³⁷; increased probability of pregnancy with day 5 ET was recorded in 2 independent trials^{36,38}. In other words, a higher rate of early pregnancy loss was recorded after day 3 single ET as compared with day 5 single blastocyst transfer in GnRH antagonist stimulated IVF cycles. Two different systematic reviews and meta-analysis independently confirmed previous findings; improved IVF outcome was associated with day 5 ET and not with day 3 ET^{38,39}. Analyzing both developmental stage and fragmentation rate, the implantation potential of advanced blastocysts was influenced by developmental stage on day 5 and fragmentation rate on day 3 ET⁴⁰. Lower implantation rate on day 3 ET is most likely associated with disturbed embryo-endometrium synchrony in terms of high preovulatory P. Furthermore, as the endometrium seems to be recovered from the supraphysiological P values on day 5, a better implantation rate is quite expected with day 5 single blastocyst transfer⁴¹. However, only a few studies failed to confirm the preference of day 5 ET as a potential strategy to overcome the deleterious effect of elevated P on IVF pregnancy outcome. Therefore, better embryo implantation and live birth rate could not be confirmed on day 5 fresh ET in terms of the rise of serum P levels ≥ 2.0 ng/mL on the day of hCG administration in cycles with GnRH agonists⁴². Similarly, a study from 2013 failed to demonstrate the preference of day 5 ET as a strategy to overcome the detrimental effect of P rise on IVF pregnancy outcome³³. Nevertheless, as the majority of studies yielded better implantation rate and IVF pregnancy outcome with day

5 single blastocyst transfer as compared with day 3 single ET, the selection of blastocyst transfer as a strategy for overcoming the adverse effect of high preovulatory P seems to be quite justified^{36,37,41}.

Elective cryopreservation of all embryos with subsequent transfer in a natural cycle or during ovulation induction has been proposed as a solution to avoid the negative effect of high preovulatory P on IVF outcome, as well as in the prevention of ovarian hyperstimulation syndrome^{42,43}. Indeed, various studies yielded significantly higher ongoing and clinical pregnancy rates when frozen ET was used as compared with fresh ET⁴⁴⁻⁴⁶. It seems that the adverse effect of P elevation on endometrium in terms of IVF outcome could be overcome by frozen-thawed embryo transfer (FET) in a later non-stimulated cycle, since the embryo-endometrium synchrony is thus re-established, although poor quality embryos could not be eliminated through the utilization of cryopreservation⁴⁶. In the past decade, the number of frozen-thawed embryo transfer cycles *per* started IVF cycle has increased steadily and at the same time the percentage of frozen-thawed embryo transfers that resulted in live births has increased. Currently, cryopreservation of human embryos is more important than ever for the cumulative pregnancy rate after IVF. It seems that freeze-all strategy, in which all embryos are frozen and no fresh transfer is conducted, has been proven to increase success rates in IVF cycles⁴⁷.

Conclusion

Current strategies in the prevention of preovulatory P rise include an individualized approach with the use of mild stimulation protocols with intensive monitoring of folliculogenesis and earlier use of hCG for ovulation induction in high responders. However, to avoid the negative endometrial effects of P rise, it should be useful to delay ET from day 3 to day 5. Finally, the most appropriate choice would be to cancel fresh ET and freeze all embryos with FET in the natural cycle. However, there is the need for further research which would confirm the current preventive methods or enable the application of new strategies in order to lower or eliminate the detrimental effects of preovulatory P rise during ovarian stimulation in IVF procedure.

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Sažetak

SUVREMENE PREVENCIJSKE STRATEGIJE PORASTA PREDOVULACIJSKOG PROGESTERONA TIJEKOM STIMULACIJE JAJNIKA U POSTUPKU IZVANTJELESNE OPLODNJE

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Svrha ovoga preglednog članka je prikazati suvremene mjere za prevenciju porasta predovulacijskog progesterona (P) i njegovih nepovoljnih učinaka kod stimulacije jajnika u postupku izvantjelesne oplodnje. Unatrag 20-ak godina porast predovulacijskog P tema je brojnih rasprava, jer njegova uloga nije u potpunosti razjašnjena u pogledu utjecaja na ishod trudnoće nakon postupka izvantjelesne oplodnje. Neka istraživanja nisu utvrdila nikakvu povezanost između porasta predovulacijskog P u odnosu na uspješnost postupka izvantjelesne oplodnje neovisno o razini P, dok nasuprot tome, većina drugih istraživanja izvješćuje o nepovoljnim učincima povišene koncentracije P. Suvremene strategije u prevenciji porasta predovulacijskog P uključuju individualizirani pristup primjenom blažih stimulacijskih protokola te raniju primjenu humanog korionskog gonadotropina za indukciju ovulacije kod bolesnica koje dobro reagiraju na stimulaciju, odgodu prijenosa svježih zametaka s 3. na 5. dan i krioprezervaciju svih zametaka uz transfer odmrznutih embrija u prirodnom ciklusu. Neophodna su daljnja istraživanja koja će potvrditi postojeće preventivne metode ili omogućiti primjenu novih strategija, sa svrhom onemogućavanja nepovoljnog utjecaja porasta predovulacijskog P na ishod trudnoće nakon postupka izvantjelesne oplodnje.

Ključne riječi: *Ženska osoba; Fertilizacija, in vitro; Progesteron – biosinteza; Ovulacija, indukcija; Zametak, transfer; Krioprezervacija*