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REVIEW

Revisiting debates of premature luteinization and its effect on assisted reproductive technology outcome

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Abstract

The impact of the prematurely elevated serum progesterone on the late follicular phase, commonly known as premature luteinization (PL), is a matter of continuing debate. Available evidence supports that serum progesterone ≥ 1.5 ng/ml on the day of ovulation triggering could reduce the pregnancy potential in fresh in vitro fertilization (IVF) cycles by jeopardizing endometrial receptivity. Causes of PL during ovarian stimulation are unclear. Recent studies point toward the daily follicle-stimulating hormone dosage, duration of controlled ovarian stimulation, number of oocytes retrieved, and peak estradiol level as factors affecting the incidence of PL. Emerging data show additional influence on embryo quality. The prevention of PL has been challenging. The key elements in preventing PL include individualization of ovarian stimulation according to patient's ovarian reserve, proper ovulation trigger timing, and use of medications such as corticosteroids and metformin. Embryo cryopreservation with deferred embryo transfer is the established strategy to overcome PL, yet it is an extra burden to the IVF laboratory and increased cost for patients. Herein, we review the up-to-date knowledge of this frequent IVF problem including causes, proposed diagnostic criteria, and its impact on endometrial receptivity, embryo quality, and pregnancy outcomes. The preventive measures and rescue strategies are also discussed.

Keywords Premature luteinization · Progesterone elevation · Diagnosis of PL · ART · Prevention of PL

Introduction

There has been a long debate about the significance of premature progesterone (P) rise during the late follicular phase, commonly known as premature luteinization (PL), and its implication on assisted reproductive technology (ART) outcomes. PL is usually defined as an elevation of serum P ≥ 4.77 nmol/L or ≥ 1.5 ng/ml in the follicular phase before triggering administration for final oocyte maturation in controlled ovarian stimulation (COS) cycles [1, 2]. PL is not uncommon and could not be completely prevented by the use of either gonadotropin-releasing hormone (GnRH) agonist or GnRH antagonist regimens. PL could be detected in all profiles of patients undergoing COS such as hyper-responders, normal responders, and poor responders, and no in vitro fertilization (IVF) cycle can be exempt from it [3].

It has been reported that PL could affect about 12.3% to 46.7% of fresh IVF cycles [4]. This wide range of incidence of PL could be attributed to the heterogeneity of methods, cut-off points, and even definitions used to diagnose PL [5]. Also, various risk factors could affect the incidence such as a history of recurrent IVF failure, and patient characteristics including age, ethnicity, and body mass index [6–9]. The COS protocol, daily follicle-stimulating hormone (FSH) dose [2], total dose of gonadotrophins [2, 10], duration of the COS cycles [11, 12], number of retrieved oocytes [2], and peak estradiol level [2], were assumed to be contributory for the chance of prematurely elevated (P) For example, ovarian stimulation using recombinant FSH alone without luteinizing hormone (LH) seems to be risky for higher PL incidence [10].

This article reviews debates on the impact of PL on pregnancy and live birth rates and embryo quality. Mechanism and possible causes of PL are summarized. Preventive measures and rescue strategies for this debatable yet important ART issue are discussed.

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Cut-off levels of PL in the literature

Many definitions based on heterogeneous cut-off levels utilized by researchers have been used to describe the occurrence of PL such as a single P level, P/estradiol ratio (P/E), P/oocyte ratio, or centiles of P level tailored on ovarian response.

A single P level

A retrospective analysis [2] of more than 4000 cycles concluded that P ≥ 1.5 ng/ml on the day of ovulation triggering is the best critical level to predict the harmful effects of PL. The authors reported an inverse relationship between ongoing pregnancy rates and serum P levels on day of human chorionic gonadotropin (HCG) triggering ($P < 0.001$ for overall trend), irrespective of the GnRH analogue used for pituitary down-regulation. Higher ongoing pregnancy rate was shown for patients with P levels ≤ 1.5 ng/ml than for those with P levels ≥ 1.5 ng/ml (31.0 vs 19.1%; $P = 0.00$) [2].

The analysis of gene expression profiles in the endometrial biopsies taken at the hCG triggering day in the GnRH antagonist/recombinant FSH IVF cycles revealed that a marked difference occurs after the P level exceeds 1.5 ng/ml [13]. This data was consistent with the results of Labarta et al. [14] that showed significant alterations in the gene expression profiles of endometrium in COS (GnRH agonist and GnRH antagonist protocols) with serum P > 1.5 ng/ml. Two prospective observational studies adopted this cut-off level and concluded that IVF cycles with follicular P > 1.5 ng/ml have a significant reduction in pregnancy rate (17.8% vs 32.7%; $P < 0.05$) [15], and live birth rate [16]. A large meta-analysis [4] conducted in this context including over 55,000 fresh IVF cycles concluded that serum P starts to affect pregnancy outcomes at a level of 0.8 ng/ml. However, the most significant decline in pregnancy rates occurs after P reaches 1.5 ng/ml.

Different cut-off points were suggested according to the degree of responsiveness [17–19] or the day of embryo transfer [20]. Singh et al. [17] showed an inverse association between pregnancy and P level at ≥ 1.075 for intermediate responders and at ≥ 1.275 for high responders. Likewise, a retrospective analysis of > 8500-long agonist cycles proposed that the cut-off levels for serum P are 1 and 1.75 ng/ml in intermediate and high ovarian responders, respectively, with no impact of serum P on pregnancy in poor ovarian response group [18]. However, the cumulative live birth rate per oocyte retrieval cycle was negatively associated with serum P levels in different ovarian response categories. The proposed P thresholds were 1.60, 2.24, and 2.50 ng/ml for poor, normal, and high ovarian responders, respectively [19].

In a large retrospective study which enrolled more than 10,000 cycles, thresholds of ≥ 1.5, ≥ 1.75, ≥ 2.25 ng/ml were proposed to predict cycle outcomes in poor (≤ 4 oocytes), normal, and hyper response (≥ 20 oocytes), respectively [20]. Indeed, it is problematic to define a threshold progesterone value beyond which a live birth rate is decreased as this is a continuous variable. Newer studies should focus on using advanced statistical methods including serum P values on ovulation triggering day as a continuous covariate in prediction models of live birth following fresh embryo transfer [21].

P/E ratio

P/E ratio has been studied as a predictive factor for the clinical outcomes of PL. Different ratios were recommended such as P/E ≥ 1.2 ng/ml [22], ≥ 1 ng/ml [23–26], and ≥ 0.48 ng/ml [27]. Arora et al. [28] retrospectively analyzed the impact of P elevation (PE) and high P/E ratio in GnRH antagonist cycles with day-5 embryo transfer. PE did not show a significant effect on implantation rate or clinical pregnancy rate (odds ratio, 0.56; 95% CI, 0.25–1.25; $P = 0.16$). In contrary, high P/E ratio (≥ 0.55) was associated with lower clinical pregnancy rates and poorer response to stimulation (odds ratio, 0.58; 95% CI, 0.34–1.00; $P = 0.05$).

Combining PE and P/E ratio demonstrated that patients with PE and high P/E ratio yielded significantly fewer oocytes than the group of PE and low P/E ratio. Patients with PE and high P/E have a 60% decrease in the implantation rate in comparison with the group with PE and low P/E ratio (17.9% ± 36.6 vs 45.5% ± 47.2; $P = 0.06$). Although it was not statistically different, the authors [28] concluded that combined assessment of P level and P/E ratio might give a better prediction for IVF outcomes than the absolute P levels.

The rationale proposed behind the use of P/E ratio is to consider the degree of ovarian responsiveness and to differentiate the source of P in hyper-responders and poor responders. In hyper-responders, P is expected to get higher levels due to enhanced P production from numerous growing ovarian follicles, but the synchronous increase in estradiol level will accompany it and the P/E ratio will be counterbalanced. While in poor responders; much of P production results from small numbers of dysregulated follicles [29], thus high P/E ratio is expected [24, 25]. The increase in P/E ratio in poor ovarian response could be due to intense stimulation with high FSH doses to overcome the defect in the steroidogenic pathway in poor responders [30]. In addition, the follicular aging process may contribute to the P increase in the follicular phase [31]. Granulosa cells of oocytes of elderly patients (≥ 43 years) exhibited apoptosis, weak growth, and specific gene expression profile in favor of PL [32]. In the past, PL was considered as an early manifestation of diminished ovarian reserve [30]. Thereafter, several reports have advised the use of the combination of both P/E ratio and P value for better prediction of cycle outcomes [33–35]. In contrast, Lee et al. [36] showed that the P/E ratio application has the limitation of having both low sensitivity and low positive predictive value.

P/oocyte ratios

Various researchers demonstrated to use neither the absolute value of P nor P/E ratio as good predictors to the cycle outcomes and supported the use of P to oocyte ratios instead. Cui et al. [37] have used P/oocyte ratio greater than 0.34, whereas Aflatoonian et al. [38] proposed P/metaphase II oocyte ratio > 0.32 as more predictive parameters of identifying the threshold at which the prematurely elevated P starts to be detrimental. Shufaro et al. [39] have shown P-to-follicle index, which is the P to ovarian follicles (≥ 14 mm), as more predictive to the clinical pregnancy rates in both agonist and antagonist protocols than P alone. Also, Grin et al. [40] investigated the P to collected oocyte index which was calculated by dividing the serum P on the day of HCG by the number of aspirated mature oocytes. P to collected oocyte index showed similar results to P-to-follicle index irrespective of patient age, body mass index, and ovarian response. These results are on par with the recent retrospective study of Simon et al. [41] which postulated that Pto mature oocyte index is negatively correlated with the live birth rate and implantation rates. Moreover, high P to mature oocyte index (> 75th percentile) was associated with poor intracytoplasmic sperm injection (ICSI) outcomes even without high P levels (< 75th percentile). However, Hill et al. [42] showed no additive predictive value of P to collected oocyte index, and the additional retrieved oocytes were not protective against the negative association between P and live birth rate.

The Mechanism of P increase

Role of FSH

It was suggested that enhanced FSH stimulation for achieving a multi-follicular growth in ART cycles may be a contributing factor for premature P rise. In an in vitro study, FSH has been found to increase the expression for 3β-hydroxysteroid dehydrogenase with a resulting stimulated P biosynthesis from the human cortical ovarian samples and the non-luteinizing FSH-responsive human mitotic granulosa cell line, which were used in the study. Thus, estrogen and P production from the stimulated samples increased in a dose-dependent pattern [43].

Two-cell-two-gonadotropin theory

According to the two-cell-two-gonadotropin theory of ovarian steroid hormone production, pregnenolone and P are formed by the granulosa cell and enter the theca cells to complete their conversion into androgens. The 17-alpha-hydroxylase enzyme could not rely only on FSH stimulation, but also on LH support for its activation. Therefore, continuous ovarian stimulation by high levels of FSH produces much amount of precursor steroids that might exceed the capability of the ovary to convert them into the estrogen synthesis pathway. Therefore P conversion into androgens, which occurs in the theca cells, becomes delayed and results in an increase of systemic P levels [44].

Progesterone increase affected by IVF cycle factors

Patient profile

Hill et al. [9] proposed that PL harms the live birth rate in all racial groups. However, the incidence of PL, based on 1.5 ng/ml as a cut-off value, was different among the 3 studied racial groups (10.6%, 18.0%, and 20.2% for White, Latino and Asian women, respectively). Liu et al. [8] conducted a retrospective observational study that categorized 6673 IVF cycles into 3 categories; no previous IVF/ET (embryo transfer) treatment, 1 previous IVF/ET treatment failure, and 2 or more previous IVF/ET. There was a significant difference in the proportion of patients with serum P > 6 nmol/L among the 3 groups at 16.8%, 31.7%, and 39.7%, respectively (P < 0.001).

The prevalence and impact of PL have been suggested to vary according to the degree of ovarian responsiveness. In hyper-responders, the threshold of serum P which could affect the cycle outcomes is higher than those in normal or poor responders [45]. It seems that the higher oocyte retrieval rate in hyper-responders can compensate for the endometrium asynchrony for higher amplitude of follicular progesterone concentrations [46]. Venetis et al. [4] demonstrated that the negative effects of PL on pregnancy outcomes were obtained only when P concentrations reached 1.9 to 3 ng/ml. A recent retrospective study was conducted in patients in whom hyper response is predicted with higher antral follicle count (≥ 15) in GnRH antagonist cycles. Lower 2 pronuclear embryo rate (P = 0.038), and fewer high-quality embryos (P = 0.020) were encountered in patients with PL [47]. On the other hand, it was suggested that PL results from diminished ovarian reserve, and is more common in poor responders and older women [48]. While Cui et al. [37] found no correlation between PL and IVF outcome for poor responders, other authors [17] have postulated lower embryo quality rate and cumulative live birth rate for patients with PL in the different ovarian responses.

Type of FSH

In practice, the shorter half-life of the recombinant FSH (30 h) necessitates daily injection of FSH to prevent dropping of the serum FSH levels below the threshold required for stimulating the ovarian response. Hence, the follicles are under the influence of FSH until the day of HCG triggering and final oocyte

maturation [49]. It has been shown that use of corifollitropin alpha, instead of recombinant FSH (rFSH) could decrease the premature P rise at the day of HCG triggering [50].

Corifollitropin alpha has different pharmacokinetics. It is long acting and gets its peak concentration after 2 days. After it reaches its peak, it starts to decline but remains above the threshold required for stimulating ovarian response for 1 week. Thus, it has a high starting dose followed by step-down of the serum FSH level which may relieve the pressure on the stimulated ovarian follicles [51]. This idea may provide a strategy to decrease the incidence of PL, but future studies are needed to prove its effectiveness.

Timing of HCG triggering

It is very crucial to find the optimal timing of administering the trigger for the final oocyte maturation. The oocyte maturity is mostly linked to the follicular size, and it was widely accepted that triggering is needed as soon as the size of at least 3 follicles has approached ≥ 17 mm. Follicular P production is positively correlated to the follicular size [44]. Therefore, delaying HCG triggering resulted in further growth of ovarian follicles and consequently increased serum P level [45]. Serum P levels increased from 0.8 ± 0.3 to 1.1 ± 0.5 when HCG was postponed for 1 day [43], and has risen from 1.1 ± 0.1 to 1.5 ± 0.1 when HCG was delayed for 2 days [11].

Relation of PL to type of trigger

A retrospective comparison of 647 GnRH agonist trigger cycles against 2679 HCG trigger cycles revealed a significant drop in live birth rate due to PL in both study groups [52]. P ≥ 2 ng/mL was more common in the GnRH agonist group compared with HCG trigger group (5.5% vs 3.1%). Nevertheless, the mean age was significantly lower in the GnRH agonist group which has a higher number of growing follicles, retrieved oocytes and the estradiol level at the triggering day [52].

Type of stimulation protocol

The type of stimulation protocol seems to affect the incidence of PL and its impact on IVF outcomes.PL was found in 5% to 35% of GnRH agonist cycles [53], and 20% to 38% of GnRH antagonist cycles [54]. GnRH antagonists were proposed to lower the risk of premature P rise in IVF cycles [55, 56]. A retrospective study conducted by Bosch et al. [2], which included 4032 patients, agreed this assessment with a higher incidence of PL in agonist versus antagonist groups (0.84 ± 0.67 vs 0.75 ± 0.66 ng/ml; P < 0.0003). Moreover, a large meta-analysis included more than 55,000 fresh IVF cycles regarding PL demonstrated that GnRH antagonists lower the incidence of PL, irrespective of the cut-off level used for diagnosing PL [4]. One of the underlying mechanisms that may explain this finding is the higher oocyte retrieval rate in GnRH agonist as compared with the antagonist protocol. More oocytes will produce more P and increase PL [57]. It is worthy of mentioning that PL incidence was reported to be lower in short protocols than in long GnRH agonist protocol [58].

On the other hand, no difference in the incidence of PL between GnRH agonist and GnRH antagonist ovarian stimulation protocols (24.1% vs 23%, respectively) has been reported [16]. In another retrospective study using P 1.5 ng/ml or more as a cut-off point to diagnose PL, concluded that PL lowered pregnancy rate in only flexible multidose GnRH antagonist protocols and did not affect pregnancy rate in a long GnRH agonist protocol [55].

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Role of HCG/LH and rFSH

Some authors suggested that a decline in HCG/LH activity may lead to premature P rise [59, 60], and that HCG/LH activity has a protective role against PL [60]. A study supporting this idea [49] found higher PL in a group of patients stimulated by rFSH compared with another group stimulated by human menopausal gonadotrophins (HMG). However, there was a confounding factor, as the rFSH-stimulated group had more number of growing follicles (≥ 12, ≥ 15, and ≥ 17 mm) than the HMG group. Therefore, the increase in follicular number and size may be the cause behind higher P concentrations [61]. The idea that rFSH might be a risk factor for increasing PL was supported by 2 studies [10, 62] that compared stimulation by rFSH vs HMG in IVF cycles. It was found that usage of rFSH alone without LH could result in elevated P in the follicular phase. In contrast, another study suggested that hCG/LH does not protect against PL, but it instead enhances P production in the follicular phase [63].

LH: FSH ratio in HMG medications

Werner et al. [59] highlighted the importance of LH: FSH ratio in gonadotropins medications, and its link to the incidence of PL. Surprisingly, it was found that ratio in a range of 0.3 to 0.6 has the lowest incidence of PL. Ratio extremes (≤ 0.3, or ≥ 0.6) were found to be risky for PL, especially the lowest (≤ 0.3) that carries the most significant risk of premature P elevation.

Relation of PL to luteal phase induction

The benefit of luteal phase induction in poor responders, or polycystic ovarian syndrome, has been reported [64, 65]. A meta-analysis has compared late luteal phase with early follicular phase induction by clomiphene citrate [65]. Luteal induction showed better endometrial thickness and yielded more oocytes, but no difference was observed regarding the pregnancy or miscarriage rates. Furthermore, the group of luteal induction had more top-quality embryos (TQE) and lower cancellation rate. Comparing induction with clomiphene citrate and human menopausal gonadotrophins in early luteal phase vs early follicular stimulation in poor responders, Li et al. [66] demonstrated that the peak of both estrogen and P were higher in luteal phase induction than in the group of early follicular stimulation. The limitation of this study is that all embryos of luteal phase group were cryopreserved and transferred in subsequent cycles.

Impact of PL on IVF cycles

Effect of PL on endometrial receptivity

Noyes et al. [67] described the classic histologic endometrial dating paradigm for clinically evaluating the luteal phase. Diagnosis of "out of phase" endometrial biopsy is made when there is a difference of more than 2 days between the histologic endometrial dating and the actual day of the cycle [68]. It was assumed that the supraphysiologic hormonal state achieved in COS might impair endometrial receptivity by the prematurely elevated P during the follicular phase [69]. PL causes advancement of the endometrium and could block the essential synchrony between the endometrium and the developing embryos [27, 70]. Ubaldi et al. [71] investigated the relationship between the pregnancy rate and the histologic appearance of endometrial biopsy in patients having elevated levels of serum (P) Patients have no chance of pregnancy if they have an endometrial advancement of more than 3 days and the histologic examination of their biopsies was out of phase. The difference discovered in the endometrial gene expression profiles between patients having serum $P \geq 1.5$ ng/ml and patients with $P < 1.5$ ng/ml may support the evidence of the detrimental effect of PL on endometrial receptivity [13, 14].

In the same context, serum $P \geq 1.7$ ng/ml on the HCG triggering day was found to modify the epigenetic modification status in 3 compartments of the endometrium and subsequently can alter endometrial receptivity [72]. Also, high P concentrations might cause gene-dysregulation in expression profiles of the endometrial components involved in natural killer cell-mediated cytotoxicity in both the day of and the day after HCG triggering [73]. These results suggest the molecular basis of the altering effect of PL on the different endometrial gene expression at the implantation window.

Effect of PL on embryo and oocyte quality

In contrast to the well-established adverse effect of PL on endometrial receptivity, the impact of PL on embryo or oocyte quality is debatable. Several reports have proposed that PL does not affect embryo quality [74–76]. In line with these studies, a large meta-analysis indicated that patients receiving donated oocytes resulting from stimulation cycles complicated by PL have no risk of decreasing their chance of pregnancy [4]. Also, no negative association was present between embryos originating from ovarian cycles with PL and the success of their frozen-thawed transfers. Kofinas et al. [77] have prescribed that PL does not affect the euploidy status of embryos and the success of frozen-thawed transfer of these embryos in the subsequent cycles does not decrease.

However, Bu et al. [17] have demonstrated higher number of retrieved oocytes, lower embryo TQE rate, and lower cumulative live birth rate in patients with PL in the different ovarian responses. Therefore, PL seems to curtail the benefits obtained from having a higher ovarian response and a higher number of oocyte retrieved. Likewise, top quality blastocyst formation rates have been reported to be negatively correlated to P levels on the day of oocyte maturation in GnRH antagonist cycles [78]. In addition, Huang et al. [78] proposed that serum $P \geq 2$ ng/ml on day of HCG triggering leads to a statistically significant reduction of the overall oocyte quality and rate of formation of TQE.

Racca et al. [79] have investigated the effect of PL on cumulative live birthrate, and embryo utilization rate which was calculated as the total number of embryo transferred and cryopreserved divided by the total fertilized oocytes. They found that the utilization rates were significantly lower for both cleavage and blastocyst stages in the groups of PL. Moreover, conducting a retrospective cohort study to investigate the impact of PL on autologous IVF cycles with fresh embryo transfers on day 5 and day 6, Healy et al. [80] concluded that PL is detrimental to the slow-growing blastocysts (day 6) in comparison to day 5 blastocysts measured by live birth rate of fresh embryo transfers. Recently, Simon et al. [81] demonstrated that follicular phase P levels above 1.0 ng/ml reduce TQE and implantation rates.

PL and pregnancy rate

A meta-analysis [46] analyzed 6 studies with 1866 patients and the effect of elevated serum $P \geq 1.5$ ng/ml on different types of ovarian response (low, normal, and high). Negative impact on pregnancy rates was observed in low and normal responders only, whereas pregnancy rate was not affected in ovarian cycles that have shown a hyper response. In addition to the absolute value of serum P, the duration of prematurely elevated serum P could impact the effect of PL on ART outcomes. The longer the period of prematurely elevated P levels in the follicular phase, the

lower observed pregnancy rates, regardless the degree of ovarian response or type of stimulation protocol [82].

Contrary to the well-documented adverse effects of PL on clinical outcomes, some authors objected that PL has a significant negative correlation with the outcomes of COS cycles [83–87]. Some even suggested that premature P elevation could be positively linked to the clinical outcomes [88–90].

PL and live birth rate

Two retrospective studies investigated the impact of PL on live birth rate and concluded that PL could reduce significantly live birth rate [17, 91]. Another retrospective study included 1022 IVF-ICSI cycles reported that PL was associated with both increase in miscarriage rate and decrease in live birth rate, despite equivalent initial implantation and clinical pregnancy rates between the study groups of with and without PL [92]. Surprisingly, PL ($P \geq 2$ ng/ml) was linked to low birth weight in fresh embryo transfer cycles, after adjustment of confounding factors like estradiol levels and maternal age [93].

Success rate in relation to day of embryo transfer

It seems that the threshold of the prematurely elevated P levels to affect pregnancy rate differs according to the developmental stage of transferred embryos [94]. Reduction of pregnancy rate was observed in case of cleavage-stage embryo transfers starting from a minimum P level of 1.0 ng/ml [95, 96]. The available data are controversial as for blastocyst stage embryo transfers. Huang et al. [95] proposed a threshold level of 1.75 ng/ml for the negative impact of high P on day 5 blastocyst embryo transfer, while Papanikolaou et al. [96] denied that PL could affect implantation of day 5 embryos. It could be assumed that the endometrial advancement due to PL could be balanced by transfer of embryo at an advanced stage, which has a higher chance to synchronize with the endometrium [94].

Prevention of PL

Mild stimulation and step-down approach

Performing step-down approach to avoid the intense ovarian stimulation toward the second half of the follicular phase will reduce P elevation at the day of triggering [11]. Also, mild stimulation protocols may lower both estradiol and P production in the follicular phase. P level was found to be related to the estradiol level and number and size of the growing follicles. Therefore, a rise in P level in the follicular phase could be anticipated and prevented by modification of the stimulation protocols or timing of triggering for final oocyte maturation [15].

Optimal triggering timing

The choice of the optimal timing of HCG triggering is crucial to prevent further growth of the growing follicles, which will result in progressive P elevation. Sonographic detection of at least 3 follicles of 17 mm or more in size, in combination with the estradiol levels evaluation, is proposed to be the required criteria for HCG triggering [11]. Some authors advised earlier HCG triggering for patients anticipated to have higher responses than those of average or poor responders may avoid increments in P levels in the follicular phase [97]. Moreover, the effect of PL on cycle outcomes did not seem to be related to triggering type. PL negatively affected the live birth rates in cycles triggered by HCG as well as cycles triggered by GnRH agonists [52].

Kyrou et al. [98] designed a prospective randomized controlled trial to investigate the relationship between timing of HCG administration on the follicular P level, estradiol level, and ongoing pregnancy rate in cycles stimulated by rFSH/GnRH antagonists. Patients were randomly divided into 2 groups according to HCG-trigger timing. One group has underwent HCG triggering as soon as 3 or more follicles of size ≥ 16 mm were present on ultrasonography (early-HCG group), and the other group was triggered 1 day after the above criterion was met (late-HCG group). Whereas P and estradiol levels were significantly lower in the early-HCG group, no statistically significant difference was found regarding chemical pregnancy and ongoing pregnancy between early-HCG and late-HCG groups. Papanikolaou et al. [96] investigated the relationship between follicular size and oocyte morphology in cycles stimulated by HMG and revealed that mature oocytes were found to be from follicles as small as 11 mm in size. It appeared that earlier triggering will not compromise the overall quality of the retrieved oocyte cohort.

Corticosteroids

P is not formed exclusively by the ovary; the adrenal gland contributes by 50% of P produced in the follicular phase of natural cycle [99]. Glucocorticoids administration can suppress, in a dose-dependent fashion, the hypothalamic-pituitary-adrenal axis and decreases the adrenal P production [100]. Dexamethasone has been proposed to reduce serum P in the follicular phase of natural cycle [100]. Therefore, corticosteroid administration could be used to decrease the baseline levels of P and subsequently reduce P levels on the day of triggering [101, 102].

Metformin

Jinno et al. [103] proposed that metformin can inhibit the first step of steroidogenesis, and consequently decreases P output from the granulosa cells. Metformin inhibits steroidogenic

acute regulatory protein and 3β-hydroxysteroid dehydrogenase, which are essential for steroid biosynthesis [104]. Low-dose metformin was found to be useful to improve IVF outcomes in non-PCO repeaters [103]. Manno and Tomei [105] have reported that metformin could be used from the day of ultrasonographic monitoring of stimulation cycle irrespective of patient ovarian reverse to decrease the incidence of PL. However, they compared a cohort of patients who are administered metformin against historical controls. Therefore, a properly designed randomized controlled trial is needed to confirm the efficacy of metformin in the prevention of PL in COS cycles.

Mifepristone and letrozole

Mifepristone, an anti-progestin, was used in a daily dose of 40 mg along with FSH in a small number of egg donors undergoing COS cycles [106]. Lower premature LH surge and PL were observed in those cycles. However, the safety of this protocol regarding endometrial receptivity was not proved yet. Further trials are needed to assess its evidence [106].

Aromatase inhibitors, such as letrozole, may play a role in decreasing P level on the follicular phase. When letrozole was compared with the natural cycle for patients undergoing intrauterine insemination, it did not show any PL effect and improve success rates [107]. Likewise, letrozole reduced the required total dose of FSH stimulation in poor responders without affecting the IVF success rate [108]. A recent Cochrane review has confirmed its superiority to clomiphene citrate in infertility due to polycystic ovarian syndrome [109]. However, the data on the efficacy of letrozole in decreasing PL are still limited and further studies are needed to rationalize its use for this purpose [3].

Rescue strategies to overcome the negative impact of PL on IVF cycles

One of the possible strategies to overcome PL is to delay embryo transfer to blastocyst stage. Day 5 embryo transfers may provide a good cross-dialogue between developing embryos and the advanced endometrium due to the effect of prematurely elevated (P) It is also assumed that endometrium could be significantly recovered from the violation caused by the supraphysiologic levels of steroid hormones [96].

Shapiro et al. [110] demonstrated that cryopreservation of all 2PN oocytes from cycles with PL followed by thawing and culture until the blastocyst stage could improve implantation and ongoing pregnancy rates. In line with this study, more evidences suggested that embryo cryopreservation is the best way to bypass the negative impact of elevated P on the live birth rate in a fresh cycle embryo transfer [111, 112].

Although a freeze-all policy has a higher success rate due to an elimination of the effect of PL on the endometrium [113], it is costly and the possibility that freeze-thawing technique may induce epigenetic modifications in key genes and transcripts should be considered. Those modifications may have long-term sequelae for the child resulting from a transfer of frozen-thawed embryos [114]. However, a recent study demonstrated that frozen embryo transfers have a lower risk of ischemic placental diseases such as small for gestational age (SGA) and intrauterine fetal death due to placental insufficiency than fresh cycles [115]. All in all, it would seem that the added IVF costs and the small risk of the embryos not surviving the thaw process pale in comparison with some of the obstetrical complications that have been suggested to be associated with fresh transfers.

Interestingly, Groenewoud et al. [84] reported that elevated P is not uncommon and can occur in about 40% of modified natural cycles for frozen-thawed embryo transfers. Yet, it did not result in significant consequences on clinical pregnancy rate, ongoing pregnancy rate, miscarriage rates, or live birth rates in those cycles.

Summary

An obstacle in studying PL is that authors are not speaking the same language regarding the P cut-off, measurement methods, days of measurement, and even the terminology. Meanwhile, it is widely accepted that P level at ≥ 1.5 ng/ml on the final day of oocyte maturation could reduce the pregnancy rates when embryos are freshly transferred in this cycle. Tailored cut-off levels according to the degree of ovarian responsiveness or the day of embryo transfer were suggested.

The critical threshold for the PL-induced detrimental effect on pregnancy was found to be lower in cleavage-stage than in blastocyst embryo transfers. It could be assumed that the endometrial advancement due to PL could be balanced by the transfer of embryo at an advanced stage, which has a higher chance to synchronize with the endometrium.

Various studies have reported different levels of P/E or progesterone/oocyte ratios to be more predictive than the use of serum P level alone. The rationale proposed behind these ratios is to consider the degree of ovarian response and to differentiate the source of P in hyper-responders than poor responders. PL incidence was shown to be linked to different factors such as type of COS protocol, daily FSH dose, number of retrieved oocytes, peak estradiol level, cycle duration, and the patient profile characteristics.

PL deleteriously affects IVF cycles through causing advancement of the endometrium which blocks the essential synchrony between the endometrium and the developing embryos. This was supported by the differences discovered in the endometrial gene expression profiles between patients having

serum P ≥ 1.5 ng/ml, and patients with P ≤ 1.5 ng/ml. Several measures were demonstrated to reduce the incidence of PL on IVF cycles: (1) addition of corticosteroids to COS in patients with higher basal progesterone, (2) optimal timing of HCG triggering, (3) aromatase inhibitors, (4) metformin, and (5) step-down stimulation approach and avoidance of enhanced ovarian stimulation toward the late follicular phase. Nevertheless, further well-designed studies are needed to prove their success in prevention of PL in IVF cycles.

Contrary to the well-established adverse effect of PL on endometrial receptivity, the impact of PL on embryo or oocyte quality is still debatable. In literature, several reports have proposed that PL does not affect oocyte or embryo quality. The data of oocyte donation cycles and the success of frozen embryo transfers for embryos originating from ovarian cycles with PL have supported this judgment. However, there is growing evidence about the negative impact of PL on the rate of TQE formation regardless of the degree of ovarian response.

The freeze-all policy with deferring embryo transfers on artificial endometrium is the widely accepted rescue strategy to eliminate the hazards of PL on endometrial receptivity. However, embryo freezing has an extra burden on IVF laboratory, increase IVF cost, and may be complicated by embryo damage during freezing or thawing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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