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REVIEW

The curious case of premature luteinization

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Abstract

Purpose Premature luteinization (PL) affects 12.3–46.7% of fresh in vitro fertilization cycles, and there is accumulating evidence confirming its negative effect on success rates. However, despite its clinical significance, PL is poorly understood and defined. This narrative review aims to provide a fresh look at the phenomenon of PL by summarizing the existing evidence and re-evaluating fundamental issues.

Methods A thorough electronic search was conducted covering the period from 1978 until January 2018 in PubMed, Embase, and Medline databases, and references of relevant studies were cross-checked. Meeting proceedings of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine were also hand searched.

Results In the curious case of PL, one should go back to the beginning and re-consider every step of the way. The pathogenesis, definition, measurement methods, clinical implications, and management strategies are discussed in detail, highlighting controversies and offering "food for thought" for future directions.

Conclusions Authors need to speak the same language when studying PL in order to facilitate comparisons. The terminology, progesterone cut-off, measurement methods and days of measurement should be standardized and globally accepted; otherwise, there can be no scientific dialog. Future research should focus on specific patient profiles that may require a tailored approach. Progesterone measurements throughout the follicular phase possibly depict the progesterone exposure better than an isolated measurement on the day of hCG. Adequately powered randomized controlled trials should confirm which the best prevention and management plan of PL is, before introducing any strategy into clinical practice.

Keywords Premature luteinization · Progesterone · IVF · ART · Ovarian stimulation · Day of hCG · Progesterone elevation

Introduction

Premature luteinization (PL) is well reported in the literature during the last 30 years. It seems to affect 12.3–46.7% of fresh in vitro fertilization (IVF) cycles depending on the progesterone value used as threshold [1]. The incidence is influenced not only by the stimulation protocol but also from patient characteristics such as age, body mass index (BMI), ethnicity, ovarian response, and history of recurrent IVF failures [2–5]. Various authors have discussed its effect on IVF success rates [6–24], on embryo quality [25–29], and on endometrial implantation potential [30–38] with contradictory outcomes, and various solutions have been proposed in order to eliminate this phenomenon in an effort to maximize results [39–41]. A large systematic review and meta-analysis of more than 55,000 fresh cycles has confirmed its adverse effect on pregnancy rates (PRs) [1]. The adverse impact on live birth rates (LBRs) also extends to patients with favorable profile and good embryo characteristics [42]. A recent study has even demonstrated significantly lower birth weight in cycles with progesterone > 2 ng/ml on the day of human chorionic gonadotropin (hCG) in fresh embryo transfers after adjusting for maternal age and estradiol levels [43]. However, despite its clinical significance, PL is poorly understood and poorly defined. Even the term "premature luteinization" is strictly speaking incorrect, creating a debate around the terminology itself. It is also still unclear which progesterone levels should be used as cut-off and during which days of stimulation should

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the measurement be done, if it should be done at all. Also, there is no consensus regarding the effect on assisted reproductive technology (ART) outcome if it affects the embryo, the endometrium, or both, and there are no clear guidelines regarding the management options for these patients during the current cycle and for future regimens.

The aim of this review is not to include every paper around PL but to highlight controversies and offer "food for thought" for future directions. This narrative review is a fresh look at the phenomenon of PL which summarizes the existing evidence and re-evaluates fundamental issues starting from the definition, the pathogenesis, and the technical aspects which ultimately affect the every-day clinical practice and the standards we should set for future work in the field. A thorough electronic search was conducted covering the period since the birth of Louise Brown in 1978 [44] until January 2018 in PubMed, Embase, and Medline databases and references of relevant studies were cross-checked. The Mesh terms included progesterone "AND" IVF, premature luteinization, and synonyms. The phenomenon of PL was explored without any restrictions in the search (regardless of progesterone cut-off, stimulation protocol used, fresh or frozen cycles, patient characteristics, etc.). Meeting proceedings of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine were also hand-searched.

Definition

Traditionally, premature luteinization is defined as the rise of progesterone above a certain cut off, on the day of hCG administration. However, the term, the cut off value, and the day of measurement are all surrounded by controversies.

Luteinization, by definition, requires lutenizing hormone (LH) surge which acts on granulosa cells and makes them increase in size and assume a vacuolated appearance with characteristic yellow pigment, lutein. Therefore, the term "premature luteinization" refers to premature LH surge. However, nowadays with the use of gonadotrophin releasing hormone (GnRH) analogs for ovarian stimulation the rise in progesterone should not be attributed to luteinization as there is suppression in gonadotrophin production, rendering the current term inadequate to correctly describe this phenomenon. Thus, the need to revisit the terminology has been well established [1, 45–48] along with the need to exonerate LH action as the main culprit for premature progesterone rise. Table 1 provides a glimpse of the various terms and acronyms which have been used to describe PL until now. Due to lack of consensus in the literature, this is a condition with many names where it all comes back to PL which seems to be the most recognized, although admittedly inaccurate, term.

Taking in to consideration the pathogenesis of the condition which does not seem to be totally an LH dependent phenomenon, and the fact that progesterone could also be elevated earlier in the follicular phase and not just on the day of hCG, follicular-phase progesterone rise (FPPR) may be a more accurate term.

Origins of progesterone elevation

The causes of progesterone rise during the follicular phase can either be located centrally or peripherally at the level of the ovary (increased production from developing follicles, increased sensitivity of LH receptors or decreased progesterone metabolism to androgens) and rarely the adrenal glands or can be attributed to exogenous administration of factors with LH activity (human menopausal gonadotropins/LH/hCG).

Stimulation with GnRH agonist versus antagonist protocols

Both GnRH agonist and antagonist protocols have been shown to eliminate premature LH peaks [54–56]. However, incomplete pituitary desensitization leading to LH surges has been examined and, although rare, it seems to occur more with antagonist cycles and less than 1% with the long protocol [57]. Thus, one would expect that the GnRH agonist protocol would be preferable in terms of pre-ovulatory progesterone rise. However, the relationship between GnRH agonist or antagonist protocol and progesterone with LBR was not significant even though premature progesterone rise was more likely with the antagonist protocol in a large retrospective cohort analysis of more than 1600 cycles [42]. GnRH agonists have also been associated with an LH rise during the late follicular phase while lower granulosa cell steroidogenic activity was documented for the GnRH antagonist group [58]. Moreover, there is now evidence demonstrating higher rates of PL for the GnRH agonist protocol versus the short protocol [58–60]. Indeed, in the largest most recent meta-analysis by Venetis et al. [1], it was demonstrated that irrespectively of the progesterone cut-off used, GnRH antagonist cycles present lower premature progesterone rise than GnRH agonist protocols. This could be partially explained because GnRH agonist protocols in the general IVF population yield higher ovarian response [57].

Stimulation with and without LH activity

Efforts have been made to examine the difference of stimulation with and without LH activity on follicular dynamics and the hormonal milieu. The difference between menotrophins and recombinant follicle-stimulating hormone (rFSH) has been extensively studied [61]. In the past, several authors have demonstrated that the rFSH group had significantly higher late follicular-phase progesterone than the human menopausal gonadotropin group (hMG) both in GnRH antagonist cycles [47]

Table 1 Terms and acronyms which have been used to describe PL

Proposed name	Study
Elevated luteinized origin progesterone (ELOP) where the origin of progesterone lies in luteinization	[45]
Elevated non-luteinized origin progesterone (ENLOP)	[45]
"Progesterone elevation" (PE) on the day of hCG administration	[1]
"Elevation of progesterone in the follicular phase of controlled ovarian stimulation"	[48]
"Progesterone elevation during ovarian stimulation"	[49]
"Elevated progesterone on triggering day	[50]
Preovulatory progesterone rise or premature progesterone rise (PPR)	[51–53]
Raised follicular-phase progesterone concentration (RFPPC)	[48]

and agonist cycles [62, 63]. However, the most recent meta-analysis by Venetis et al. [1] did not find a difference in FPPR whether an LH containing gonadotrophin was used for ovarian stimulation or not. In addition, a systematic review did not find a consistent relationship between the supplementation with LH-activity products during ovulation induction and progesterone rise [64], thus the role of LH rise on progesterone concentration during the late follicular phase has not been confirmed [65]. The supplementation with hCG during ovarian stimulation with rFSH has been studied in a randomized trial by Thuesen et al. [66]. The authors found a dose-dependent increase in progesterone and androgens with increasing hCG doses. The concept that the cause of premature luteinization lies in the hCG content of hMG had been introduced earlier by Copperman et al. [67]. However, even though LH activity in the late follicular phase (in two studies using hCG supplementation) caused elevated progesterone levels, the best predictor for progesterone rise was the intensity of ovarian stimulation. Similarly, in GnRH agonist cycles with exogenous LH administration, progesterone value was not found to correlate with LH [68], but positively correlated with the FSH dose administered [69]. Stimulation with rFSH increased the number of patients with high ovarian response, resulting in more oocytes and more patients with hyperechogenic endometrium as a result of increased progesterone exposure during the follicular phase leading to an adverse effect on ongoing pregnancy rates (OPR) and proportionally less top-quality embryos than the hMG group, as described in the MERIT trial [62]. Indeed, LH supplementation during FSH stimulation has been shown to increase grades 1 to 2 embryos and implantation rates (IRs) [70].

While the LH component has been in the center of the debate, little attention has been given to the isoform used in the commercial gonadotrophin preparations. There is emerging evidence showing that the type of FSH used is also important and this is possible related with the acidity of the preparation. The recombinant products which are less acidic than the ones of urinary origin seem to be more potent and therefore could have a distinct effect on progesterone regulation [71]. Moreover, stimulation with corifolitropin alpha (CFA) instead of rFSH results in lower incidence of progesterone elevation [72]. CFA does not have LH function and the key pharmacokinetic difference with rFSH is that it reaches the maximum action during the first 48 h and then mimics a step-down protocol avoiding constant follicle stimulation [73].

FSH versus LH

Before luteinization occurs, FSH acts on granulosa cells which proliferate and produce steroids with progesterone as an end product. LH can only act to reduce progesterone by increasing its metabolism to androgens on theca cells which in turn are aromatized to estrogens back in the granulosa cells according to the two-cell two-gonadotrophin theory [74]. Bosch et al. [59] noted that in GnRH antagonist cycles that had premature progesterone rise, no LH rise was observed, but these women did require more intense stimulation with FSH. Therefore, FPPR is most likely an FSH-dependent phenomenon rather than an LH one and could be associated with the increased number of progesterone-producing growing follicles as a result of FSH stimulation, unbalanced by LH action which could reduce progesterone through conversion to androgens [46, 75, 76]. Therefore, ovarian stimulation without sufficient LH action could enhance the phenomenon instead of alleviating it [48]. Besides, a correlation has been documented between late follicular phase progesterone value and the area under the curve (AUC) of FSH during stimulation [77] and not of LH [24]. Indeed, more oocytes were retrieved in FPPR cycles for all progesterone thresholds in the most recent large meta-analysis and there was evidence linking this with the total amount of FSH used [1]. The risk of progesterone rise on the day of hCG administration seems, therefore, to correlate with the number of retrieved oocytes and estradiol levels and not with other factors which have traditionally been considered important (BMI, antral follicular count (AFC), infertility cause, or chosen protocol) [50, 78].

To conclude, the old dogma that the phenomenon of PL is attributed to LH action is now clearly challenged. FSH seems to play the central role, and the number of recruited oocytes cannot be the only mechanism for FSH to induce increased progesterone. The number of growing follicles was accounted

for, and there was still significantly raised progesterone in the rFSH group. This is attributed to paracrine signals and deregulation of the balance between progesterone production and progesterone decrease through metabolism to androgens. In particular, FSH action on granulosa cells can stimulate factors such as IGF1 (insulin-like growth factor 1) and inhibins to increase progesterone [79, 80] and can also increase factors such as transforming growth factor-beta (TGF-b) which suppresses the progesterone conversion to androgens [81]. This occurs more with rFSH compared with hMG [82]. Increased exposure to FSH and estradiol possibly increases the sensitivity of granulosa cells to even low levels of LH [59, 77, 83, 84]. This is the tip of the iceberg as there is a delicate interplay between various factors and pathways which ensures the balance between preventing luteinization but maintaining cell proliferation and follicle growth [85].

Luteal phase ovulation induction

Luteal ovulation induction is a concept which was first introduced in ART for fertility preservation purposes in oncological cases [86]. It has recently been introduced as a way to increase success rates in women with PCOS or in women with poor ovarian reserve either alone or in combination with follicular phase stimulation within a single menstrual cycle (dual stimulation) [87, 88]. Clomiphene citrate (CC) administration during the luteal phase has the advantage that it allows sufficient time up to implantation in order to overcome the adverse CC effect on the implantation potential of the endometrium and on the early pregnancy. A 2015 meta-analysis comparing CC use during the late luteal phase versus the early follicular phase concluded that luteal induction yielded more oocytes and improved endometrial thickness without this translating into higher pregnancy rates or reduced miscarriage rates [88]. Although the protocols vary between the studies on luteal ovulation induction (in terms of type and timing of stimulation—early/mid/late luteal phase), it would be interesting to see if this approach affects PL rates. A retrospective study by Li et al. is one of the few on the matter which report on progesterone value on the day of hCG [89]. This study compared early luteal with early follicular phase stimulation with CC and HMG in poor responders and demonstrated that luteal induction resulted in more oocytes, more top-quality embryos, and lower cycle cancelation rates. The luteal group had significantly higher peak progesterone and estradiol levels but significantly lower LH level on the day of hCG. All embryos from luteal phase stimulation cycles were cryopreserved therefore the effect of progesterone rise on the endometrium cannot be accounted for. More RCTs are needed to compare outcomes and to report on progesterone values during stimulation in these protocols.

Adrenal origin progesterone

Trying to demystify the cause of progesterone rise in GnRH agonist cycles with hMG, Eldar-Geva et al. [90] proposed the contribution of the adrenal glands. Progesterone has been detected in the circulation of women that had undergone bilateral oophorectomy and administration of adrenocorticotropic hormone (ACTH) has been shown to increase progesterone during the follicular phase for premenopausal women highlighting the contribution of the adrenal glands to pre-ovulatory progesterone levels [91–93]. Adrenal origin progesterone could result from rare cases of adrenal hyperplasia but also from the complex hormonal interplay created by the exogenous ovarian stimulation which alters the balance of the steroid axis [90].

Patient profile

Speaking of the strong correlation between ovarian response and FPPR, one would wonder if this is a condition relative only to high responders. For high responders, the negative impact of progesterone elevation on pregnancy achievement applied only for progesterone concentrations as high as 1.9–3 ng/ml [1]. Possibly in this category of patients, the high number of oocytes achieved, compensate for the endometrium asynchrony for quite a large amplitude of progesterone values. This has been confirmed by Griesinger et al. [22] where progesterone rise above the cut-off of 1.5 ng/ml was associated with lower success rates for low and normal responders but not for high responders. Similarly, Requena et al. [94] did not find a negative impact on implantation and pregnancy rate from progesterone values higher than 1.8 ng/ml on hCG day for high responders. On the contrary, the effect of a premature progesterone rise in the follicular phase was found to be more prominent for high responders by other authors [48, 62].

PL is also documented for poor responders, maybe because they require stronger FSH stimulation or due to a defect in their steroidogenic pathway. The same paracrine factors which co-ordinate the highly important phase of oocyte maturation (BMP-4, BMP-6, BMP-7, and BMP-15 among others) are normally acting to prevent FPPR [85]. Therefore, an underlying imbalance of this delicate interplay between the oocyte and its cumulous could also be postulated for this group of patients, Besides, PL has been identified as a characteristic of an aged follicle. Granulosa cells from women aged above 43 exhibited little growth and higher apoptosis and a gene expression profile that favored premature luteinization [95]. Some authors have not found a correlation between progesterone value and IVF outcomes for poor responders [24] whereas others have demonstrated lower cumulative LBRs and impaired embryo quality for patients with FPPR and different ovarian responses including poor responders (different progesterone cut-offs were adopted for each group) [96]. In any

case, it is important not to omit progesterone measurements irrespectively of patient profile keeping in mind that PL has, in the past, been considered an early manifestation of ovarian failure [97]. Caution is advised when adopting and interpreting progesterone cut-off values for the extremities in ovarian response.

To summarize, there is now a plethora of studies looking at every step of the way as a possible cause for premature progesterone rise in IVF. However, there is no clear culprit; the pathogenesis seems complex and multifactorial, and it all comes down to ovarian stimulation itself rendering the management and prevention even more challenging.

Progesterone cut-off value

Except form the definition and origin of the progesterone rise, progesterone cut-off value is also a point of controversy. The results of FPPR on success rates are dependent on where the authors draw the line for the progesterone value. In simple words, which value do we consider raised and why? It is evident that if there is no clear answer to this question, there can be no constructive scientific dialog as we cannot proceed to comparisons for a phenomenon we cannot unanimously define.

Historically, the passage to luteal phase of the cycle signifies progesterone concentration of around 1.19 to 1.31 ng/ml [98]. However, values used to define progesterone elevation differ widely from 0.4 to 2 ng/ml (Table 2). Extreme values such as 2.47 to3.41 ng/ml have also been studied in egg donation cycles [19].

On many occasions, the choice of the progesterone threshold comes arbitrarily [46]. The justification for some of the various cut-offs originates from statistics, which progesterone value better predicts cycle outcome taking into consideration the sensitivity, specificity, and positive and negative predictive value with the use of receiver-operating characteristic (ROC) curve analysis. This method, however, yields contradictory results (Table 3). The optimal value, for instance, was 0.9 ng/ml for Urman et al. [109], 1 ng/ml for Saleh et al. [20], 1.04 ng/ml for Cui et al. [24], 1.05 for Wu et al. [21], 1.25 for Li et al. [123], 1.44 ng/ml for Groenewoud et al. [126], and 1.2 for Bosch et al. [59]. A recent retrospective study from the same author including more than 4000 cycles, selected 1.5 ng/ml as the critical cut-off after conducting a trend analysis, concluding that the AUC may be insufficient to predict success rates as there is a non-linear relationship between progesterone values and pregnancy outcome [76]. Indeed, it is expected that progesterone will increase during ovarian stimulation, so the negative impact from progesterone rise will come from subtle changes over an expected median. Hence, due to lack of linearity, Papaleo et al. [125] calculated the partial AUC for high specificity regions above the median

Table 2 Cut-off values which have been used to define PL in different studies

Cut-off	Study
Progesterone (ng/ml)	
0.4	[10]
0.5	[2]
0.6	[11, 99]
0.8	[100, 101]
0.9	[8, 10, 14, 30, 102–112]
1	[13, 20, 25, 31, 39, 113–116]
1.04	[24]
1.05	[21]
1.1	[84, 117]
1.2	[3, 12, 17, 118, 119–122]
1.25	[123]
1.26	[62]
1.3	[124]
1.35	[125]
1.44	[126]
1.5	[18, 36, 127–131, 132–134, 52, 60, 78]
1.75	[18]
1.88	[134]
1.9	[26, 135]
1–2	[9, 40]
2	[43, 52, 136, 137]
2.25	[18]—high responders
2.47–3.41	[19]
P/E ratio	
1	[16, 75, 138, 139]
1.2	[140]
0.48	[141]
P/oocyte ratio	
0.32	[142]
0.34	[24]

Table 3 Proposed days of progesterone measurement (other than the day of hCG administration)

Proposed days of measurement except from trigger day	Studies
Basal progesterone (within 3 days from the beginning of stimulation)	[15, 23, 53]
Basal progesterone and then serial measurements until 12 h before trigger	[125]
Days 1, 6, and 8 and day of hCG	[15]
Days 2–6	[114]
Day 8	[3]
Days 3, 5, and 7 and then daily from day 8 until egg collection	[40]
Day 4	[159]
Day 7 until a day before hCG	[9]
2 days before trigger	[33]

value of progesterone for the study population on the day of hCG and identified as optimal cut-off the 1.35 ng/ml. This enhances the evidence around the non-suitability of the AUC assessment to show an accurate correlation between progesterone values and pregnancy outcome.

Based on the large study by Bosch et al. [76], numerous authors designed their work around the 1.5-ng/ml threshold [34, 60, 78]; 1.5 ng/ml was also the point where a marked difference was noted in the endometrial gene expression profile after Pipelle biopsy [35]. In the above-mentioned large meta-analysis, progesterone values above 0.8 ng/ml were associated with adverse effect on success rates, and this effect increased for progesterone concentration to 1.2 and remained stable after this cut-off [1]. However, the strongest effect was documented for the 1.5–1.75-ng/ml threshold when all datasets were combined demonstrating that we are far from selecting one isolated absolute value as the gold standard. It should be highlighted that even though this is the largest meta-analysis so far, only 11 out of the 63 included studies were prospective, and there is great heterogeneity among the studies in their definition of PL and the methods of progesterone measurement. Therefore, the results should be interpreted with caution.

Other authors use the progesterone to estradiol (P/E) ratio above 1 [16, 75, 138, 139], or greater or equal to 1.2 [140], or > 0.48 [141]. Li et al. [143], however, aiming to identify a minimum cut-off for this ratio, concluded that P/E ratio < 0.25 led to significantly decreased IR, clinical pregnancy (CPR), OPR, and LBRs. The logic behind using the P/E ratio instead of an absolute value is to take into consideration ovarian responsiveness. An increased progesterone value could originate from multiple growing follicles as a result of FSH stimulation and a synchronous rise in estradiol would be expected. An isolated value of progesterone is confounding; an increased P/E ratio, however, underlines poor ovarian response which could be linked with poor ovarian reserve [97, 144, 145]. Isolated progesterone values combined with a P/E ratio have also been used [146–148], again the cut-off differed among the studies. Lee et al. [149] has, however, doubted the clinical application of the ratio due to low sensitivity and positive predictive value. In a different approach, Aflatoonian et al. [142] postulated that neither progesterone value nor P/E ratio are good predictors of the cycle outcome and proposed the use of progesterone/metaphase II oocyte ratio that is greater than 0.32. Cui et al. [24] used progesterone/oocyte ratio > 0.34. Sonographic signs examining the follicular structure which possibly correlate with the hormonal milieu have also been described historically [150].

Different threshold within the same study have been used for patients with different ovarian responses [96, 145, 151] or according to day of embryo transfer [52]. The patient characteristics in relation to the preferred threshold is a matter that warranties further investigation as high responders should presumably be subjected to higher thresholds, as discussed above. Cut-off values of 1.5, 1.75, and 2.25 ng/ml have been proposed for poor (≤ 4 oocytes), normal, and high (≥ 20 oocytes) responders respectively in a retrospective analysis of more than 11,000 cycles [18].

How to measure progesterone?

Another point to think about is if the progesterone measurement is performed correctly as discrepancies have been highlighted in the performance of commercial assays for progesterone measurements [152]. Most automated assays currently used to measure progesterone are designed to test for ovulation and therefore the small pre-ovulatory differences in the progesterone value could be lost. Also, in measuring small progesterone values, some steroid metabolites could be falsely measured and alter results. For instance, in IVF protocols which involve the use of dehydroepiandrosterone sulfate (DHEA-S) supplement, the assay could falsely measure this as progesterone due to cross-reactivity and therefore give falsely elevated progesterone values. For DHEA-S concentration of 5000 ng/ml, the false elevation of the progesterone value can be up to 0.33 ng/ml which is enough to influence clinical decisions. This was confirmed for two out of three commercial assays examined in a recent study by Franasiak et al. [153].

Large inter-laboratory differences while processing the same sample have been reported [154]. Intra-assay and inter-assay coefficients of variation are rarely reported in the existing literature [15, 125]. Assay sensitivity and reliability could alter results especially for such subtle differences in progesterone values. Besides, progesterone normal values for the follicular phase differ widely between different kits. Thus, internal and external quality assessments and proper calibration are needed [76]. Patton et al. [155], assessed the performance of four commercial assays for progesterone measurement comparing their results with liquid chromatography tandem mass spectrometry. The results were correlated but intra-assay and inter-assay coefficients of variation < 10% were only achieved for two of the assays each and the mean progesterone values differed among the assays.

Technical issues should be resolved and standardized in the design of future studies in order for safe conclusions to be drawn and to ensure reproducibility and consistency. Internal audit of the assay and customization of the progesterone threshold according to internal data within the IVF laboratory has also been proposed [49], but this would not facilitate comparisons.

When to measure it?

Timing of progesterone measurement is of paramount importance. The vast majority of studies have looked at the

progesterone value on the day of hCG trigger or the day before, and the huge 2013 meta-analysis by Venetis et al. [1] was designed around this axon. However, a rapid progesterone rise precedes LH and FSH surges by 12 h in natural cycles [98] and is required to establish the normal dimension of the LH surge [156]. Besides, administration of a progesterone antagonist at this stage inhibits LH surge [157]. Significantly lower LBRs were documented for cycles with progesterone value of less than 0.5 ng/ml on triggering day [131]. Hence, at this specific time point, is progesterone rise strictly speaking abnormal? Should the adverse effects be attributed to only a day of progesterone rise? Or is this just a snapshot of an earlier progesterone elevation throughout the follicular phase? Should the measurement be done earlier during the cycle or even before starting the stimulation? In this setting, maybe we should be looking at serial measurements during the follicular phase, the AUC for progesterone, in order to take into consideration the duration of exposure rather than an isolated measurement. Table 3 provides a glimpse of the proposed timing to measure progesterone in various studies.

Progesterone should reach the lowest levels at menstruation after the regression of the corpus luteum so is there a role for baseline progesterone measurement? The answer is yes as elevated baseline progesterone could still be observed in a proportion of cycles due to incomplete luteolysis. This could be the case in ART if a short protocol or GnRH antagonist is used. Long agonist protocol should by definition suppress the pituitary gonadotropins and stimulation should start with normal progesterone. Indeed, basal progesterone (within 3 days from the beginning of stimulation) was shown to be the single most crucial factor in order to predict progesterone rise on the day of hCG in contrast with other parameters which have been traditionally proposed, such as patient characteristics and other hormonal measurements (LH, FSH, anti-Müllerian hormone, estradiol) or AFC [125]. The authors measured basal progesterone and then did serial measurements until 12 h before the trigger injection concluding that basal progesterone measurements could identify whether the cycle is at risk and offer a window of action. However, does basal progesterone rise per se correlate with adverse clinical outcomes? Kolibianakis et al. [15] studied prospectively the effect of progesterone elevation on day 2 of the cycle and concluded that a progesterone value above 1.6 ng/ml at the beginning of ovarian stimulation can affect the chance of pregnancy in patients treated with rFSH and GnRH antagonists. The authors delayed the cycle for 1/2 days if baseline progesterone was elevated but later normalized and canceled the cycle if baseline progesterone did not normalize within 2 days. Hamdine et al. [23] yielded similar results. Progesterone values > 1.5 ng/ml on day 2 were found to adversely affect OPR. Mutlu et al. [53] showed an association of basal progesterone above 0.65 ng/ml with preovulatory progesterone rise above 1.5 ng/ml; in this study, cycles with basal progesterone above 1.6 ng/ml were canceled. However, Faulisi et al. [158] did not confirm the clinical value of basal progesterone value before the onset of stimulation with GnRH antagonist (day 3).

Tang et al. [159] measured progesterone on day 4 of stimulation. Values above 3 ng/ml were associated with a significant decrease in IR, PR, and OPR. Chetkowski et al. [33] showed with histology impact on endometrium of even subtle increase in the value of progesterone measured 2 days before the trigger injection.

Few have measured progesterone also on the day after hCG/oocyte recovery day [6, 65, 107, 160]. Interestingly, progesterone elevation (greater or equal to 11.7 ng/ml) measured on oocyte recovery day has been associated not only with higher number of viable embryos [27] but also with reduced IR and PR and increased miscarriage rate (MR) [161].

A recent interesting study tried to associate impaired implantation with the total exposure to estrogen or progesterone during ovarian stimulation [162]. Although it appears that estrogen exposure was the main hormonal determinant of endometrial receptivity, there was a significant correlation between the AUC for estrogen and progesterone and emphasis was given to the duration of exposure throughout the cycle. Besides, the success in achieving the desirable implantation window has been shown to be related with the duration of progesterone exposure rather than an isolated value at a certain time-point [163]. Fanchin et al. [30] found that a 2-day increase in progesterone could induce secretory transformation in the endometrium. It should be noted that in natural cycles, progesterone elevation on the day of LH surge was not correlated with adverse outcome but earlier progesterone rise for two or more days, impaired PR in frozen-thawed embryo transfers [164]. Therefore, the duration of exposure and not an isolated measurement is key to draw safe conclusions [48]. This is only possible to assess with serial measurements throughout the follicular phase.

In the study by Kolibianakis et al. [15] except from the baseline progesterone, measurements were also done on days 1, 6, and 8 and day of hCG. Patients that started with high progesterone, even if the value normalized postponing stimulation, still had increased progesterone concentration in the subsequent measurements on days 6 and 8 and lower estradiol in all measurements. Besides, an elevated progesterone above 1.2 ng/ml on trigger day has been found to significantly correlate with earlier progesterone rise (as early as day 8 and through days 9, 10, and 11) demonstrating that this rise is most likely present from earlier in the cycle. Progesterone elevation from day 8 could predict similar elevation on the day of hCG [3]. Sims et al. [114] used measurements throughout days 2 to 6. Early follicular phase progesterone rise was associated with impaired follicular growth and recruitment, higher requirements for gonadotropins, and lower peak estradiol. In a retrospective study including 1784 IVF/intracytoplasmic sperm injection (ICSI) cycles, the duration of progesterone elevation before the administration of trigger injection has a more

significant adverse effect on CPRs compared with a single progesterone measurement on the day of hCG after adjusting for confounders and irrespectively of the protocol used or the ovarian response [115]. This effect translated, on average, to 22.7% decrease in pregnancy probability for 1 day of elevated progesterone. An earlier prospective study by Kyrou et al. [165] also gave emphasis on the role of progesterone exposure rather than isolated progesterone measurement for the achievement of pregnancy. In support of these results, Dai et al. [151] concluded that the duration of progesterone elevation is proportional to its adverse effect on CPR. Harada et al. [9] defined as subtle progesterone rise, the progesterone elevation to 1–2 ng/ml from day 7 until a day before hCG and demonstrated that this early mild increase in progesterone concentration was related with poor outcome and progesterone rise on the day of hCG. Based on these results, the same group tried to find a way to avoid progesterone rise on the day of hCG in cycles that had an early progesterone rise [40]. Progesterone was, therefore, measured on days 3, 5, and 7 and then daily from day 8 until egg collection. For patients that had subtle progesterone rise above 1 ng/ml, the hCG injection was administered a day earlier. These "rescued" cycles had better outcomes in terms of embryo quality and implantation.

The knowledge around the physiology of the cycle and the understanding of the kinetics of progesterone, even slight changes for every day of the follicular phase, are of great importance in order to define what is normal and what is abnormal and which are the key time points to better predict the adverse impact of a possible progesterone rise on success rates. Also, emphasis should be given on the biological basis of the detrimental effect of progesterone rise. Therefore, more studies are needed in order to understand the physiology behind this phenomenon, but it is safe to conclude that based on the existing literature, we cannot focus on just an isolated value ignoring the cumulative effect of progesterone rise. Maybe a good starting point would be to measure baseline progesterone and then plan progesterone measurements from day 2, every second or third day until the day before the hCG injection. Early measurements can predict FFPR sooner rather than later, and serial measurements better depict the hormonal environment and could lead to the development of a personalized fine tuning of the cycle. Again, in order to reach safe conclusions, authors should speak the same language in terms of days of measurement and relative cut-offs.

Clinical significance

Success rates

There has been a lot of discussion regarding the effect of FPPR on success rates in IVF. Schoolcraft et al. [2] was one of the first authors to report an adverse impact on PRs. The first large review on the matter including studies up to 2010, also showed decreased PRs, but the results did not reach statistical significance [46]. However, Kolibianakis et al. [166] in a subsequent review demonstrated a significant adverse effect on PRs in GnRH antagonist cycles and the large 2013 systematic review and meta-analysis of more than 55,000 cycles from 63 publications, confirmed that progesterone rise on the day of hCG, decreases the probability of pregnancy in fresh IVF cycles [1]. Since then, the scientific dialog on the matter continues with various cut-offs, and even though there is some scars evidence of improved clinical results of preovulatory progesterone rise [7, 12, 167], or conclusions of no significant effect [122, 124, 126, 168–170], there are also clear reports of unfavorable results on CPR and LBR [22, 24, 52, 96, 99, 112, 116, 117, 129, 131, 137, 145, 151]. Venetis et al. [133] demonstrated in a retrospective study that multivariable analysis taking into consideration multiple confounding factors revealed statistically significant decrease in LBR for cycles with progesterone rise on trigger day whereas bivariate analysis failed to do so in the same cohort. Thus, design flaws in the data processing step could make a difference between a statistically significant or not result. A recent study even correlates progesterone rise on the day of hCG, with lower birth weight of the offspring highlighting that, when detected, premature progesterone rise should not be ignored [43]. The existing evidence pinpoints this effect either at the level of the endometrium (impact on endometrial receptivity) or at the level of the oocyte/embryo (impact on embryo quality) or at the synchrony between the two (premature closure of the "window of implantation").

Oocyte/embryo quality

The theory that increased progesterone affects the oocyte/embryo development has been extensively studied in the literature. There are some interesting laboratory findings in *Xenopus laevis* oocytes linking oocyte maturation process to progesterone providing an insight into the possible effect of progesterone in regulating the oocyte cell cycle [171]. Harada et al. [9, 40] demonstrated a combined adverse effect since cycles with premature progesterone elevation yielded fewer embryos beyond the four-cell stage, fewer good quality embryos, and lower IR. However, this was not confirmed by other authors who demonstrated comparable oocyte quality, fertilization, cleavage rates and embryo grades between the high progesterone and the normal progesterone groups [17, 18, 25, 30, 129, 172–174]. The meta-analysis by Venetis et al. [1] suggested that the adverse impact of progesterone rise on the day of hCG comes from the endometrium and not the oocyte/embryo. This conclusion was based after meta-analysis of egg donation cycles (eight retrospective studies) or frozen-thawed embryo cycles (pooled datasets of 16 studies). Premature progesterone rise during induction in the fresh

cycle did not have an impact on the success rates of a subsequent frozen cycle, and the same conclusion came from recipients who received oocytes from an egg donor with PL. On the contrary, this meta-analysis has raised substantial evidence highlighting the effect on embryo quality. Bu et al. [96] concluded that irrespective of the ovarian response, the high-quality embryo rate was lower for cycles with premature progesterone rise. Huang et al. [175] in a retrospective study of more than 4200 fresh IVF cycles also demonstrated that progesterone levels above 2 ng/ml during the follicular phase have an adverse effect on the oocyte and top embryo quality rate. Furthermore, progesterone rise of more than 1.49 ng/ml has been associated with less top-quality blastocysts. Progesterone elevation during ovulation induction along with sperm motility were the only two factors able to significantly affect top-quality blastocyst formation rate after accounting for confounders [28]. The authors highlighted that previous studies worked around success rates of the first frozen thawed cycle and did not focus on the cumulative birth rate accounting for the total number of blastocysts which could explain the different end outcomes. A retrospective analysis of more than 3400 GnRH antagonist, ICSI cycles showed increased embryo wastage for cycles with premature progesterone rise which translated in reduced cumulative LBRs [29]. Reassuring results in terms of embryo chromosomal status for cycles with progesterone rise on the day of hCG came from a study using preimplantation genetic screening (PGS) and freeze-all strategy by Kofinas et al. [176].

Women with recurrent IVF failure were found to be more than twice more likely to present PL [4]. The reason was not identified in this study, but the results pointed more towards the level of the oocyte. Is the PL responsible for the failed cycles or is it just a symptom of this patient group? The answer is not clear from human studies yet but animal studies demonstrate a link between progesterone and oocyte developmental competence [177, 178]. The evidence so far, mostly retrospective in nature, does not conclude with certainty that FPPR is the culprit for impaired embryo quality, but certainly gives us a lot to think about the importance of preventing PL in future cycles in order to ensure the best possible environment and possibly enhance success rates. Thus, more research is needed; even if future studies do not confirm the adverse impact of PL on embryo quality, the results will indicate whether this phenomenon is a cause or just a symptom of poor follicular development.

Endometrial implantation potential

Egg donation cycles represent an excellent opportunity to differentiate between the two effects. Lower PR both in donors with PL and recipients, locates the detrimental effect on the oocyte/embryo quality [26]. However, in several other studies, recipients who received oocytes from donors with elevated progesterone levels on the day of hCG, had better success rates than the donors which indicates that the endometrium and not the embryo quality is affected by this change of the hormonal milieu [31, 32, 179]. Indeed, endometrial biopsies and ultrasound assessment of the endometrial echogenicity confirmed that FPPR causes premature secretory transformation of the endometrium creating an asynchrony at the embryo-endometrium crosstalk therefore impairing the implantation process [33, 105]. Pipelle biopsies revealed altered regulation for 140 genes in women with elevated follicular phase progesterone above 1.5 ng/ml [34] leading to altered gene expression [35, 36, 123]. In addition, endometrial sampling 7 days after the trigger injection in cycles with elevated progesterone on the day of hCG administration and the day after, revealed not only advanced endometrial development but also increased uterine Natural Killer (NK) cells [37, 180]. These epigenetic modifications due to progesterone rise during ovulation induction have an adverse effect on endometrial receptivity [38]. On this scope, it is no surprise than freezing the embryos and transferring them during a natural cycle restores the endometrial receptivity improving the LBR [181, 182].

To conclude, there is a lot of scientific discussion around the impact of FPPR on the IVF outcomes both for the embryo and for the endometrium. However, future research should focus on what do these findings mean in vivo in terms of IRs and LBRs and what can we do it in order to establish safety and improve results as this is the main concern from a clinician's point of view.

What should we do?

Prevention is of pivotal importance therefore, since ovarian stimulation is the key in the pathogenesis of FPPR, mild stimulation protocols are recommended. Keeping the FSH dose to a minimum, avoiding hyperstimulation and also avoiding protocols with FSH action without an LH component [48, 51, 72] are key recommendations. GnRH antagonist protocols seem to be safer in terms of FPPR especially for patients at risk for hyper-response to FSH [1, 58]. GnRH antagonist along with rFSH has also been shown to reduce premature LH rise and FPPR in stimulated intrauterine insemination (IUI) cycles compared with rFSH alone [183–186]. Similar results supporting the use of GnRH antagonist to the stimulation protocol were documented for PCOS patients and IUI although this did not translate in improved success rates [186–188]. Measuring estradiol and the number of follicles could provide an idea of the expected risk of progesterone rise and an opportunity to tailor the stimulation protocol and the time of triggering accordingly [189]. GnRH antagonist administered every other day was not inferior in terms of prevention of

progesterone rise compared with the daily regime but lacked the power to reach conclusions on LBR [190].

Aromatase inhibitors have recently started to gain their place in ART and could possibly be a promising option. The use of letrozole reduces the required FSH dose for stimulation without affecting success rates, and it seems to improve ovarian response to FSH in poor responders [191]. In a retrospective study comparing letrozole stimulation versus natural cycle for IUI, letrozole increased success rates and did not have a PL effect [192] which agrees with the results of a previous study by the same team [193]. A 2014 Cohrane review confirmed that letrozole is superior to CC for subfertile PCOS women [194]. However, the results on the use of aromatase inhibitors are still limited, and their effect on follicular phase progesterone are not thoroughly studied, therefore, more research is needed to confirm their value. Metformin administration from the beginning of the cycle may reduce progesterone synthesis and therefore inhibit premature progesterone rise, but this approach warrants further research to prove its clinical value [195]. The same applies for the use of anti-progestins. A prospective study including a small number of egg donors concluded that mifepristone in a daily dose of 40 mg orally along with FSH yielded good results in preventing FPPR; however, the adverse effect on the endometrium maturation highlights the need for further dose modification before clinical application [196]. Dexamethasone administration in order to suppress the adrenal input in progesterone rise has been proposed. Patients with progesterone elevation 36 h before trigger injection in GnRH agonist cycles were included, and the authors demonstrated after randomization a significant decrease in progesterone concentration after dexamethasone administration compared with the control group where progesterone values increased [90].

Needless to say that progesterone measurements should be accurate. The assay used should be properly assessed, and every laboratory should run internal validation and calibration algorithms. Before adhering to a certain cut-off, one should be sure of the logistics that the laboratory can detect the small differences in progesterone value in order to support this cut-off. Furthermore, here is a strong evidence suggesting that one progesterone measurement on trigger day is not enough and is too late. Therefore, a baseline progesterone value along with serial progesterone measurements early in the follicular phase regardless of the patient profile could help us personalize the cycle by triggering ovulation sooner [39–41] or adjusting the stimulation protocol especially for patients at risk [51]. There is also evidence that different cut-offs should be used according to patient response in order to develop personalized strategies to minimize the adverse effect, but this is also a matter that warrants further research [1, 18, 22].

Endometrial biopsy before embryo transfer in order to assess the impact on the endometrium has also been proposed. In the past, it has been postulated that in cases with asynchronous follicular development (one leading follicle and many smaller follicles), aspiration of the leading follicle would prevent premature progesterone rise and permit the growth of the other follicles and avoid cycle cancelation [197]. The timing of trigger injection depends on the number and size of follicles; therefore, taking into consideration the patient profile, there could be some flexibility to adjust the timing especially in high responders and in cases of advanced maternal age [95, 189] Besides, many authors have documented that mature oocytes are also derive from smaller follicles starting from a diameter of 10 mm [198, 199]. Kyrou et al. [41] in a prospective randomized study demonstrated that hCG administration 1 day earlier was associated with fewer mature oocytes and lower progesterone levels but did not affect the probability of pregnancy, which agrees with the result of an earlier retrospective study [200] demonstrating that such a strategy is probably feasible. Wu et al. [95] published improved IVF results for women of age above 43 by avoiding premature progesterone rise with early trigger injection at leading follicle size of 16 mm. In any case, the prolongation of the follicular phase by delaying the trigger injection causes progesterone rise, endometrial advancement, and less top-quality blastocysts and should be avoided [201, 202]. Delaying for 1 to 2 days or canceling the cycle has also been adopted by some authors in cases with increased baseline progesterone since elevated baseline progesterone has been associated with lower OPRs [15].

Since there is strong evidence suggesting that progesterone elevation on the day of hCG has an adverse impact on pregnancy rates and if we accept that the impact is more prominent on the endometrium and not on the oocyte/embryo quality, the safest practice would be to continue with the egg collection and then freeze the oocytes or embryos and transfer in a subsequent cycle when the hormonal effect on the endometrium will have faded [1, 14, 119, 203, 204]. A retrospective cohort analysis of more than 5000 cycles supported the amelioration of the effect of PL on LBRs with the freeze-all strategy [205]. The only prospective randomized study on the matter by Yang et al. [206] included 123 patients with raised progesterone on the day of hCG and confirmed that patients who had frozen thawed embryo transfer had significantly higher CPR rather than the ones who proceeded with fresh cycle. Among the fresh cycles, however, the blastocyst transfer group had better results. Therefore, another postulation is that this embryo-endometrium asynchrony impairs the implantation of the cleavage stage embryos but not of day 5 embryos [128, 146, 207]. However, this has not been confirmed by recent retrospective studies with large sample sizes by Hill et al. [42] and Huang et al. [168] as adverse effect was noted for progesterone values above 2 and 1.75 ng/ml, respectively. Corti et al. [129] in another retrospective study had impaired CPR for progesterone values above 1.5 ng/ml even though all patients had blastocyst stage embryos. Thus, the value of blastocyst

transfer in overcoming the adverse impact of premature progesterone rise has been doubted [1]. A slow growing embryo combined with an advanced endometrium leads to poor outcomes as shown in a study by Healy et al. [134] where the adverse effect of progesterone rise on the day of trigger was more pronounced for embryos which reached blastocyst stage later and were transferred on day 6 compared with day 5 while this did not affect subsequent frozen cycles. RCTs should be designed to confirm the value of all the above approaches. Such studies should use a widely accepted definition of PL, the same assay for progesterone measurement, same stimulation protocols, and same days of measurement. Patients who fulfill the criteria for PL should be randomized to continue with the cycle or to intervention group (such as freeze-all group) and confounders should be accounted for before comparing outcomes in order to reach safe conclusions. Live birth rate should be the main outcome of interest. The first and most challenging step in designing these prospective studies is probably to agree on definition, cut-offs, and days of measurement in order to facilitate comparisons and to account for the great heterogeneity in stimulation protocols and patient characteristics.

Conclusion

In the curious case of PL, one should go back to the beginning and reconsider every step of the way from definition and pathogenesis to clinical implications. The main message of this narrative review is that this issue is more complex than initially thought, and authors need to speak the same language when studying FPPR in order to facilitate comparisons and reach safe conclusions. The terminology, the progesterone cut-off, the measurement method, and the days of measurement should be standardized and globally accepted otherwise there can be no scientific dialog. We argue that an isolated raised progesterone value on the day of hCG could be normal and does not correctly depict the progesterone concentration during stimulation. Thus, earlier progesterone measurements could be performed throughout the follicular phase with a baseline value not only to depict the effect on the cycle better but also to provide an opportunity for prediction and prevention of progesterone elevation on the day of hCG. Future research should also focus on specific patient profiles such as poor responders or PCOS patients who could require different cut-offs and different approach. The aim would be to adopt a personalized approach for each patient taking into consideration that the choice of the stimulation protocol was chosen dictated by individual needs and should be tailored accordingly. There is now strong evidence demonstrating an adverse effect on cycle outcomes, therefore, if FPPR is established, embryo freezing or earlier trigger should be considered. However, multicenter, adequately powered, RCTs should confirm which the best management plan of FPPR is, for the current and for future cycles before introducing any strategy into clinical practice.

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Compliance with ethical standards

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