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REVIEW

Effects of different progesterone levels on reproductive outcomes in assisted reproductive technologies: from molecular basis to treatment strategies

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ABSTRACT

Purpose: The aim of this narrative review is to offer an overview about the role of progesterone levels on pregnancy outcome in patients undergoing assisted reproductive technologies (ARTs).

Methods: A detailed computerized search of the literature was performed in the main electronic databases (MEDLINE, EMBASE, Web of Science) to determine the importance of elevated progesterone levels at different stages of the cycle for pregnancy rates in the *in vitro* fertilization (IVF) cycle. Our review also provides information on the differences between elevated progesterone levels and their interpretation in normal and in poorly responding women.

Results: After careful evaluation, our search strategy yielded a total of 15 included articles, showing the possible factors that may have had an impact on the increased progesterone level before human chorionic gonadotropin (HCG) injection and the different thresholds above which the pregnancy rate was lower. Furthermore, increased progesterone on cycle day 2 or 3 could serve as a marker for increased progesterone in the late follicular phase, which is associated with a lower pregnancy rate.

Conclusion: Despite the literature data that support the negative effect of elevated progesterone on fresh cycles, due to lack of randomized controlled trials, the value of measuring progesterone in daily practice is questionable. Available evidence supports the detrimental effect of elevated progesterone in different subgroups of women, although there is still the need for defining different thresholds and durations of high progesterone exposure. The need for various thresholds for different cohorts of women, the inter-assay variability is making this decision harder.

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Introduction

Progesterone allows the endometrial transition from a proliferative to the secretory stage, facilitates blastocyst nesting and is essential to the maintenance of pregnancy. Progesterone levels at certain stages of the menstrual cycle and its role in medically assisted reproduction are frequently the subject of investigation, and although many researchers around the world are making efforts to address this, there is still no consensus, and further study is probably needed. The endometrium does indeed prepare for embryo implantation under the influence of progesterone. The preparation of the endometrium begins in the proliferative phase of the menstrual cycle and continues in the luteal phase [1,2]. We assume that mid-luteal phase serum progesterone determinations provide an objective assessment of luteal function, but due to menstrual variability, progesterone measurements should be scheduled approximately 1 week before the next menstruation. A detected serum concentration of progesterone >3 ng/mL is therefore related to presumed evidence of ovulation [3]. Nevertheless, serum progesterone determinations are better used as a qualitative rather than a quantitative test (demonstrating evidence that ovulation has occurred). Although levels >10 ng/mL are typically found in the mid-luteal phase and reflect appropriate luteal function, problems with cycle variability and the pulsatile nature of progesterone secretion limit its usefulness as a determinant of luteal adequacy [4]. In case of fertility treatment during which one or more embryos were transferred, less than a third of the cases carries the pregnancy to term [5,6]. Implant failure, as pointed out by these data, is therefore an important limiting factor of *in vitro* fertilization (IVF) results.

Considering these elements, the aim of this narrative review is to offer an overview about the role of progesterone levels on pregnancy outcome in patients undergoing assisted reproductive technologies (ARTs).

Materials and methods

We followed the quality standards for narrative reviews as defined and quantified by 'SANRA – a scale for the quality assessment of narrative review articles' [7]. The relevant publications were identified after a systematic search of the following

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sources: PubMed, Google Scholar, Web of Science and publishers' databases, supplemented by a cross-check of reference lists. We used a combination of the search terms 'progesterone', 'assisted reproductive technology', 'treatment', with 'reproductive outcome', 'pregnancy', and 'poor ovarian responders'. The search was limited to sources in English. All articles describing the effects of different levels of progesterone on reproductive outcomes in assisted reproduction were considered for the review. Only original articles that reported specific experiential data on this topic were considered.

We searched the literature to determine the importance of elevated progesterone levels at different stages of the cycle for pregnancy rates in the IVF cycle. We also observed the different thresholds of progesterone levels. We focused on the progesterone levels at the beginning of the cycle and in the late follicular phase, before human chorionic gonadotropin (HCG) injection. Our review also provides information on the differences between elevated progesterone levels and their interpretation in normal and in poorly responding women. In addition, factors such as the total amount of follicle-stimulating hormone (FSH) used in stimulation and the number of follicles or oocytes that might have an impact on the elevated progesterone level were identified. Various protocols have been used in the ovarian stimulation articles reviewed, mainly with gonadotropin-releasing hormone (GnRH) agonists or antagonists.

Results

After careful evaluation, our search strategy yielded a total of 15 included articles, which are clearly presented in Tables 1 and 2, respectively.

Table 1 shows the possible factors that may have had an impact on the increased progesterone level before HCG injection, the protocols used for ovarian stimulation, and the different thresholds above which the pregnancy rate was lower.

Table 2 shows the cycle day at the start of ovarian stimulation when progesterone was measured. Different thresholds are shown that were used as cutoff values for elevated progesterone levels. Increased progesterone on cycle day 2 or 3 could serve as a

Table 1. Factors contributing to progesterone elevation in the late follicular phase [8–16].

Author, year	Risk factor	P_4 level	Protocol used	Pregnancy rate
Bosch et al. 2010 [8]	Number of follicles Number of oocytes Daily FSH dose	P_4 elevated (on the day of HCG administration, >1.5 ng/mL)	GnRH agonists and antagonists	Lower
Hill et al. 2015 [9]	Number of follicles Number of oocytes Total FSH dose	P_4 elevated (on the day of HCG administration, >1.5 ng/mL)	GnRH agonists and antagonists	Lower (both cleavage- and blastocyst-stage ETs)
Hill et al. 2018 [10]	Number of follicles Number of oocytes P_4/oocyte ratio does not have effect	P_4 elevated (on the day of HCG administration) Proportional change in live birth rate (from P_4 >2.0 ng/mL)	GnRH agonists and antagonists	Lower
Koo et al. 2015 [11]	Total FSH dose, number of oocytes, E_2 level	P_4 elevated (>0.9 ng/mL)	GnRH antagonists	Lower
Kyrou et al. 2012 [12]	FSH-only protocols Number of follicles	P_4 elevated (on the day of HCG administration, >1.5 ng/mL)	R-FSH + GnRH antagonist	Lower
Oktem et al. 2017 [13]	FSH-only protocols	P_4 elevated: in ovarian tissue sample- effect of FSH on P_4 production from human granulosa cells *via* upregulation of 3β-HSD expression and increasing its enzymatic activity	FSH	Not measured
Papaleo et al. 2014 [14]	Total dose of FSH Basal P4 level	P_4 elevated (on the day of HCG administration)	GnRH agonists and antagonists	Lower (cleavage- stage ETs)
Venetis et al. 2015 [15]	Number of oocytes Number of follicles Total dose of FSH	P_4 elevated (on the day of HCG administration, >1.5 ng/mL)	GnRH agonists and antagonists	Lower
Werner et al. 2014 [16]	LH addition	P_4 reduced (<1.0 ng/mL when LH was used along with FSH)	GnRH agonists and antagonists	Not measured

Abbreviations: 3β-HSD, 3-beta-hydroxysteroid dehydrogenase; E2, estradiol; ET, embryotransfer; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone; P4, progesterone; R-FSH, recombinant follicle stimulating hormone.

Table 2. Progesterone at the beginning of the cycle as a marker for elevated progesterone in late follicular phase [14,17–22].

Author, year	Cycle day and P_4 level	Protocol used	Pregnancy rate
Blockeel et al. 2011 [17]	2nd, P_4 > 1,5 ng/mL (antagonist used to normalize P_4 values)	rFSH + GnRH antagonist	No statistical significance
Hamdine et al. 2014 [18]	2nd, P_4 > 1.5 ng/mL	rFSH + GnRH antagonist	Lower clinical and ongoing pregnancy rate, but the differences did not reach statistical significance
Kolibianakis et al. 2004 [19]	2nd, P_4 > 1.5 ng/mL (antagonist used to normalize P_4 values)	rFSH + GnRH antagonist	Lower clinical and ongoing pregnancy rates
Mutlu et al. 2017 [20]	2nd, P_4>0.65 ng/mL (predictor for premature P_4 rise >1.5 ng/mL)	rFSH, hMG + GnRH antagonist	No statistical significance
Papaleo et al. 2014 [14]	2nd, P_4 >0.4 ng/mL (predictive factor for later elevated P_4)	rFSH, Rfsh + rLH, hMG, GnRH agonist and antagonists	Lower when P_4 before HCG administration is >1.35 ng/mL
Sims et al. 1994 [21]	2nd to 6th cycle day P_4 >1 ng/mL	Leuprolide acetate + FSH	Lower clinical and ongoing pregnancy rate, but the differences did not reach statistical significance
Tang et al. 2007 [22]	4th, P_4 >1 ng/mL	rFSH + GnRH agonist	Lower clinical and ongoing pregnancy rates

Abbreviations: FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; P4, progesterone; rFSH, recombinant follicle stimulating hormone; rLH, recombinant luteinizing hormone.

marker for increased progesterone in the late follicular phase, which is associated with a lower pregnancy rate.

Discussion

Progesterone and its role at the beginning of the cycle

In natural menstrual cycles, implantation occurs six days after fertilization. During the luteal phase, the corpus luteum undergoes morphological and biochemical changes known as 'luteinization'. The hormone that most influences this phase is luteinizing hormone (LH), which acts on the granulosa cells by stimulating the production of progesterone. This in turn leads to a secretory transformation of the endometrium and prepares it for implantation by thickening and dilating the vessels to facilitate implantation [23,24]. After implantation, the trophoblastic tissue of the placenta secretes HCG, which acts on the ovaries. HCG maintains the corpus luteum and stimulates it to produce estradiol and progesterone, which are necessary for maintaining pregnancy until the placenta begins to produce steroid hormones itself after about seven weeks [25]. In stimulated cycles following ovum pick-up, steroid levels are elevated due to the multiple corpora lutea, which produce more steroids than those produced in a natural cycle. This causes negative feedback on the pituitary gland and consequently lowers LH levels. The result is that luteal phase is shortened (known as premature luteolysis) and the chances of pregnancy are reduced. In summary, premature luteolysis results from high steroid concentrations caused by an increased number of corpora lutea (secondary to controlled ovarian stimulation) during the early luteal phase, which in turn inhibits LH release directly from negative feedback [26–28]. The level of progesterone can be increased directly by administering progesterone, or progesterone and estrogen in combination, or indirectly by administering HCG, which in turn stimulates the secretion of progesterone. HCG or progesterone given during the luteal phase may be associated with higher rates of live births or ongoing pregnancy than placebo or no treatment, but the evidence is inconclusive. Adding GnRH to progesterone appears to improve results [26].

The introduction of GnRH agonists to prevent premature LH surge, premature oocyte maturation, and luteinization had a very favorable effect on IVF outcomes. GnRH agonists have a high affinity for the GnRH receptor, and continuous use leads to desensitization due to clustering and internalization of the pituitary GnRH receptors [29]. Initial GnRH agonist administration is associated with increased FSH and LH secretion, also known as the 'flare' effect. Prolonged administration leads to a downregulation of the pituitary GnRH receptors, which eventually leads to a suppression of FSH and LH secretion [30]. Due to this 'flare' effect, the use of a long suppression protocol with GnRH agonists for ovarian stimulation is time consuming. Undesirable effects inherent to the use of GnRH agonists are the incidental formation of ovarian cysts due to the 'flare' effect, complaints of estrogen deprivation, and the need for increased amounts of exogenous gonadotropins due to ongoing suppression of endogenous gonadotropins [27,28]. In 2004, Tesarik et al. [31] investigated the use of GnRH agonists six days after intra cytoplasmic sperm injection (ICSI) and demonstrated that administration of a single-dose agonist increased the implantation rate without affecting miscarriage and abortion rates. The result was an improvement in the birth rate, but also in multiple pregnancies [31]. Premature luteinization during GnRH antagonist IVF-ET cycles is a frequent event that is associated with lower pregnancy and implantation rates [29,30]. Progesterone elevations are not related to serum LH levels and may reflect the mature granulosa cell response to high FSH exposure [8,24,32–34].

Progesterone in follicular phase

During the controlled ovarian stimulation (COS), the physiology of progesterone secretion is changed. Exogenous administration of gonadotropins, needed to achieve multifollicular development, causes progesterone to rise during the follicular phase. The increased progesterone levels present during the late follicular phase of COS may be attributed to an amplified response of the granulosa cells of multiple follicles to endogenous LH which is called premature luteinization [35].

The GnRH analogues, GnRH agonists and the currently more used GnRH antagonists, are supposed to prevent premature luteinization by downregulation of pituitary GnRH receptors [36–39]. Indeed, the follicular production of progesterone resulting from endogenous LH surge, or premature luteinization, has been successfully eliminated by GnRH agonist administration [40]. However, increase in progesterone during the follicular phase of COS is not always fully eliminated by GnRH analogues [41,42]. Because of the probably different nature of these two phenomena, the Adda-Herzog et al. [43] have proposed to rename the increased progesterone levels observed during COS, as premature progesterone elevation rather than premature luteinization. Yet, studies as recently as 2015 still refer to premature progesterone elevation as the premature luteinization, thus making the research more challenging [11,44]. However, based on known data, premature progesterone elevation is estimated to occur in 5%–38% of IVF cycles [8,45,46].

Few theories for premature progesterone elevation have been postulated. The most probable one is related to number of follicles. Several studies have demonstrated that many follicles present during the COS contribute to the progesterone elevation. Each of the follicles produce a small amount of progesterone. With many follicles, the total level of progesterone increases. The association of follicle number with progesterone levels has been documented in numerous large studies (Table 1) [8–10]. Furthermore, high total FSH dose increases the risk of premature progesterone elevation [11–13]. On the contrary, the addition of LH decreases the risk of premature progesterone elevation [16]. This may be due, at least in part, to additional that LH upregulates 17-hydroxylase to convert progesterone substrate to androgens, which are ultimately aromatized to estradiol [10]. These data support the theory that premature progesterone elevation in GnRH analog cycles is not the result of LH-induced luteinization, but rather a product of FSH-induced progesterone stimulation from a large number of follicles.

According to Venetis et al. [15] and Bosch et al. [8], the number of oocytes appears to be the most influential predictor for progesterone elevation above 1.5 ng/mL on achieving live birth. Papaleo et al. [14] confirmed that other than known risk factors, such as the total dose of FSH administered and estradiol (E_2) level at the time of triggering, a high basal progesterone level (0.45 ng/mL) was also a significant risk factor in late follicular phase progesterone elevation.

When to measure progesterone?

The question, to which many researchers around the world try to answer, is when the best time is to measure progesterone: at the beginning of the cycle or mid cycle? Traditionally, progesterone is measured before HCG administration. Because of lower

implantation rates, in cycles with progesterone above 1.5 ng/mL, embryo transfer is postponed. Little information is available concerning the association of elevated progesterone levels at the beginning of ovarian stimulation with IVF outcome.

The idea of measuring progesterone at the beginning of the stimulation cycle, meaning 2nd or 3rd cycle day, is to predict progesterone rise later in the cycle. Progesterone reaches the lowest levels at menstruation after the regression of the corpus luteum. Elevated baseline progesterone could still occur due to incomplete luteolysis. 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 [47] in contrast with other parameters that have been traditionally proposed, such as patient characteristics and other hormonal measurements (LH, FSH, anti-Müllerian hormone, E_2) or antral follicle count (AFC) [14]. Huang et al. [48] 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. The elevation of progesterone in early follicular phase could appear in ART if a short protocol or GnRH antagonist is used. Long agonist protocol should suppress the pituitary gonadotropins and stimulation should start with normal progesterone. In long GnRH agonist cycles, suppression of gonadotropins results in basal levels of steroid hormones at initiation of stimulation and thus consistently normal progesterone levels [48,49].

Although not many studies have been conducted, elevated basal progesterone levels have been reported in short GnRH agonist cycles [21,22] and GnRH antagonist cycles [17–19]. The incidence of high progesterone levels on cycle day 2 in GnRH antagonist cycles has been shown to be between 4.9% and 13.3% [17–19]. Delaying the administration of gonadotropins in GnRH antagonist cycles could result in normalization of progesterone values. Blockeel et al. [17] suggested that pretreatment with a GnRH antagonist during three consecutive days before ovarian stimulation leads to normalization of progesterone levels, resulting in adequate ovarian stimulation and acceptable pregnancy rates. However, studies have not proven with certainty the elevated progesterone at the beginning is necessarily linked to worse outcome. Kolibianakis et al. [19] were the first to describe the association of elevated progesterone at the beginning of the stimulation cycle and reduced pregnancy rates. In this study, the authors concluded that the elevation on day 2 of the cycle and a progesterone value above 1.6 ng/mL can affect the chance of pregnancy in patients treated with recombinant FSH (rFSH) and GnRH antagonists. The authors delayed the cycle for 1 or 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. obtained similar results [18]. In particular, they concluded that progesterone values > 1.5 ng/mL on day 2 have a negative effect on pregnancy rate. Mutlu et al. [20] 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. [50] did not confirm the clinical value of basal progesterone value before the onset of stimulation with GnRH antagonist (day 3). Tang et al. measured progesterone on day 4 of stimulation. Values above 3 ng/mL were associated with a significant decrease in pregnancy rates [22].

Although knowing the basal progesterone concentration at the beginning of stimulation cycle could carry some benefit, today there is not enough evidence to support routine measurement and even European Society of Human Reproduction and Embryology (ESHRE) in its guidelines advises against this measurement in patients with normal ovarian reserve [51].

The second question still needed to be answered to is what the threshold value of progesterone would be at the beginning and in the middle of cycle. The most often used cut off value before HCG administration is progesterone above 1.5 ng/mL. Indeed, studies by Santos-Ribeiro et al. [52] and Arvis et al. [53] have showed reduced pregnancy rate in such cycles.

Over the past few years, many different cutoff levels for progesterone on the day of HCG in stimulated cycles have been proposed, ranging from 0.8 to 3.0 ng/mL. According to one meta-analysis, progesterone above 0.8 ng/mL was already associated with a significantly reduced pregnancy rate [54]. To date, the most widely used cutoff value is 1.5 ng/mL and seems to be a turning point in the endometrial gene expression profile [55,56].

However, the value on the day 2 or 3 has not been set and, as previously discussed, different authors use different cutoff values.

Effect of elevated progesterone on pregnancy outcome in IVF

Various studies have discussed effect of elevated progesterone on IVF success rates, embryo quality, and endometrial implantation. Among the different studies, however, the results are contradictory [54]. An inconsistency with the results might be associated with the different thresholds used among published studies, the inter-assay variability [57] or changes in progesterone secretion during the daytime [58]. Also, the ovarian response and cause of infertility might play a role [59–63].

Although some studies have suggested there is no effect of elevated progesterone on pregnancy outcome, most studies have observed that in cycles with elevated progesterone levels in late follicular phase, the success rate of ART is less and to date elevated progesterone levels before the ovulation trigger are known to be associated with lower pregnancy rates [15].

According to a meta-analysis that included more than 60,000 IVF cycles, even a progesterone concentration threshold of 0.8 to 1.1 ng/mL on the day of triggering significantly decreases the probability of pregnancy (clinical/ongoing pregnancy or live birth) with an odds ratio (OR) of 0.79 (95% confidence interval [CI]: 0.67–0.95, n ¼ 40 studies) [54].

Aside from the progesterone elevation, the duration of elevated progesterone turns out to play role on success rate [64]. A study of 100 women aged 39 years reported that when hormonal status was checked with regular blood sampling during ovarian stimulation, the area under the curve (AUC) for progesterone was significantly higher for the patients who had achieved an ongoing pregnancy compared with those who did not (AUC = 0.63; 95% CI, 0.53–0.74, $p = .031$). In this study, the AUC for FSH, E_2, LH, and progesterone on the day of triggering did not show a significant difference between the groups [65]. In another study including 1,784 women, after stratifying the duration of the elevated progesterone in the day of HCG (>1 ng/mL) time into three groups as 0, 1 to 2, and 3 days, clinical pregnancy rates appeared to be decreased as the duration of high progesterone exposure increased for every day [66]. Therefore, not only the presence of progesterone elevation, but also the duration of high exposure appears to have a negative impact on IVF outcomes.

The different groups of women based on demographic characteristics or ovarian response during COS have also been put under investigation. According to a retrospective study including over 4,000 cycles, the negative effect of elevated was valid in all age groups of women irrespective of their body mass index

(BMI) and the type of GnRH analog used [8]. In a meta-analysis of six randomized controlled trials, the authors found that in GnRH antagonist cycles, women with 1 to 5, 6 to 9, 10 to 13, and 14 to 18 oocytes all had lower ongoing pregnancy rates when progesterone was reported to be >1.5 ng/mL on the day of HCG administration [67]. However, in contrast with low and normal responder groups, ongoing pregnancy rates were not significantly decreased in high responders (>18 oocytes) when the same threshold of progesterone concentration was used, although evidence was not strong in this group mainly because of small sample size. In a study by Xu et al. [68], that included more than 10,000 cycles, in patients with a high ovarian response as defined by the presence of 20 oocytes, a negative effect of progesterone was observed after exceeding a concentration of 2.25 ng/mL with an OR of 0.47 (0.26–0.85). In the same cohort, the respective thresholds for low (4 oocytes) and normal (5–19 oocytes) responders were 1.5 ng/mL (OR: 0.36; 95% CI: 0.14–0.94) and 1.75 ng/mL (OR: 0.78; 95% CI: 0.65–0.95). Furthermore, the authors found that a period of 3 days was required to observe a negative effect of elevated progesterone (>1 ng/mL) in the high responder group, as defined by having 17 oocytes, while a negative impact was noted even with the very first day of progesterone for low and normal ovarian responders.

Based on these observations in high responders, Bozdag et al. [69] suggested that the negative effect of elevated progesterone is valid in all cases, although it requires higher levels of progesterone or a longer exposure to high levels in patients with hyperovarian response.

The cause for decrease in pregnancy rates are not fully known, however few theories have been postulated. One, and most reasonable explanation, is asynchrony between the endometrium and the embryo implantation. Endometrial biopsies and ultrasound assessment of the endometrium confirmed that elevated progesterone causes premature secretory transformation of the endometrium creating an asynchrony at the embryo-endometrium crosstalk therefore impairing the implantation process [70–74]. Endometrial biopsies have also revealed altered regulation for 140 genes in women with elevated follicular phase progesterone above 1.5 ng/mL leading to altered gene expression [75,76].

Based on these findings, many clinicians decide rather for freezing the embryos and transferring them during a natural cycle, aiming to restore the endometrial receptivity and improve the live birth rates [66,77].

The other explanation would be impaired oocyte quality. Harada et al. [78,79] demonstrated that cycles with premature progesterone elevation yielded fewer embryos beyond the four-cell stage, fewer good quality embryos, and lower implantation rates. 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 [80–84].

Huang et al. [85] in a retrospective study of more than 4,200 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. Vanni et al. [86] found similar results in their study. A retrospective analysis of more than 3,400 ICSI cycles using GnRH antagonist showed increased embryo wastage for cycles with premature progesterone rise that translated in reduced cumulative live birth rates [87].

However, the meta-analysis by Venetis et al. [54] suggested that the adverse impact of progesterone rise on the day of HCG derives from altered endometrial regulation and not the oocyte/embryo quality.

Progesterone levels in follicular phase and pregnancy outcomes in poor responders

A recent meta-analysis showed the estimated pregnancy rate for poor responders was 14.8% compared with 34.5% in normal responders [88]. As previously discussed, the common cause of premature progesterone elevation in GnRH analogue cycles is product of FSH-induced progesterone stimulation from many follicles. Based on this paradigm, poor responders would be expected to have low progesterone elevation, but the available pieces of evidence do not confirm this.

Possible explanation for this discrepancy was evaluated by Beckers et al. [89]. In this study, the authors have noticed that significantly high progesterone levels in the early follicular phase of a spontaneous cycle have been demonstrated in women who had a poor response, possibly caused by continued production by the corpus luteum seen in aging ovaries. Another explanation would be a tendency to give higher doses of gonadotropins, which positively correlate with the occurrence of progesterone elevation.

Trying to explain the consequence of elevated progesterone on IVF outcome, researchers have investigated the effect on different subgroups of women. Some of the investigators amplify the importance of ovarian response when considering the effects of elevated progesterone [68,90,91].

Back in 1997, Fanchin et al. [92] showed a modifying effect of ovarian response on the association between progesterone elevation and the probability of pregnancy: in particular, elevated progesterone level on HCG day adversely affected pregnancy rate only in the poor responder group and not in the women with intermediate and high ovarian response and, later in time, more studies taking into account the ovarian response have been conducted.

In a study by Adda-Herzog et al. [43], the authors found that clinical pregnancy rates were similar in the strong (30% vs. 34%) and intermediate (31% vs. 30%) groups according to ovarian response to COS, irrespective of low or high progesterone levels, whereas in the weak group, progesterone >0.9 ng/mL led to lower pregnancy rates (3.2% vs. 23%). This could be explained by the fact that the poor embryo quality associated with these cycles may not be sufficient to compensate for the alterations in the endometrial receptivity induced by progesterone.

The investigators emphasize the need for more exact definition of progesterone cutoff values considering ovarian response in the different phases of cycle. To date, to our knowledge, just a few research on this topic have been published.

In a study by Arvis et al. [53], the results showed that in poor responders the effect of progesterone elevation is minimal, so cancelations or embryo freezing may be avoided. This corresponds to different studies showing that the freeze-all policy is beneficial in high responders, but not in intermediate and low responders [93]. They have also emphasized the importance of different cutoff values among the groups. In a high responder (15 or more oocytes), the live birth rate is much higher, and the threshold 1.8 ng/mL for these patients corresponds to the same prognosis (around 20%) than a normal responder by using a threshold of 1.5 ng/mL [53]. The question, however, is more concerning for poor responders (three or fewer oocytes), where high values of progesterone on day of hCG seem less harmful than lower values so, for these patients, only a threshold for higher values is not applicable.

However, in a study by Xu et al. [68] the proposed cutoff value was 1.5 ng/mL for the poor responders, whereas a serum progesterone level of >1.75 ng/mL for intermediate group and a progesterone threshold of 2.25 ng/mL for high responders was associated with lower ongoing pregnancy rates.

From this overview, there is no equable standing whether elevated progesterone have the adverse effect on pregnancy outcome in poor responders, and if it does what the cutoff value would be.

As in the normal responder group, in the poor responder group as well there is no clear standing of significance of elevated progesterone at the beginning of the cycle as the predictive factor for pregnancy outcome and for progesterone elevation on the day of HCG. Of note, ESHRE guidelines advice against routine progesterone measurement at the beginning of the cycle, but for the patients above 39 years of age they leave decision under consideration [51,94].

According to a cost-effectiveness analysis of 7,608 IVF cycles with fresh embryo transfer, the fresh embryo transfer cycle was cost-effective when progesterone was 1.5 ng/mL, but 12% of the population had an abnormal test result and a number needed to treat (NNT) of 13 was found [10]. Above those thresholds, elevated progesterone had a negative effect and captured a smaller percentage of patients but with a higher risk for fresh transfer failure, thus making freeze-only a cost-effective treatment option. Similarly, a hypothetical model in a study by Esteves et al. [95] demonstrates that progesterone levels would have to be monitored in 1,000 cycles and intervene in 50–300 cycles with elevated progesterone, to potentially avoid 2–12 implantation failure by applying freeze-all strategy. In the same study, the authors concluded that an individualized approach should be used in cases of elevated progesterone. The recommendation is to proceed with fresh embryo transfer in hyper-responders with low risk of ovarian hyperstimulation syndrome, whereas in normal responders a freeze all strategy might be considered; in poor responders the optimal strategy is yet to be determined.

Conclusion

Despite the literature data that support the negative effect of elevated progesterone on fresh cycles, due to lack of randomized controlled trials, the value of measuring progesterone in daily practice is questionable. Available evidence supports the detrimental effect of elevated progesterone in different subgroups of women, although there is still the need for defining different thresholds and durations of high progesterone exposure. The need for various thresholds for different cohorts of women, the inter-assay variability is making this decision harder. We must also admit that the limitations of our narrative review are due to the fact that this type of work often fails to meet important criteria to avoid bias – often there is a lack of explicit criteria for selecting articles and often there is no evaluation of the selected articles for their validity. However, the greatest strength is that we adhered to the quality standards for narrative reviews as defined and quantified by 'SANRA – a scale for the quality assessment of narrative review articles', included original works that reported specific experiential data on the topic, and used medically relevant databases. In conclusion, there is no uniform approach about the role of progesterone levels in follicular phase of COS, both in normal responders and poor responders, due to a lack of robust data. Further research through well-designed comparative studies and randomized trials are needed to draw conclusions about the role of progesterone levels pregnancy outcome in patients undergoing ART.

Disclosure statement

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