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Review

Effect of progesterone elevation in follicular phase of IVF-cycles on the endometrial receptivity

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KEY MESSAGE

Progesterone rise during the follicular phase of ovarian stimulation for IVF has a negative effect on the pregnancy rate owing to endometrial advancement. The cause of this premature progesterone rise is still unclear; however, recent data suggest that enhanced ovarian stimulation might be a cause.

A B S T R A C T

The premature rise of progesterone during the late follicular phase in stimulated IVF cycles is a frequent event, and emerging evidence shows that premature progesterone rise does negatively affect the outcome of assisted reproductive techniques. The effect of elevated peripheral progesterone levels in the late follicular phase seems to be on the endometrium and the window of implantation, which may lead to asynchrony between the endometrium and the developing embryo. In stimulated cycles, endometrial maturation is advanced on the day of oocyte retrieval, and patients with a progesterone level above 1.5 ng/ml on the day of final oocyte maturation have different endometrial gene expression profiles. This progesterone level seems to represent the critical threshold, at which a negative effect on the ongoing pregnancy rate in fresh IVF cycles can be observed. Moreover, no association exists between progesterone elevation in the fresh cycle, and the probability of pregnancy after transfer of frozen–thawed embryos, originating from that cycle. The causes of premature progesterone elevation during ovarian stimulation are still unclear; however, recent studies point towards enhanced FSH-stimulation as a cause for progesterone elevation.

Introduction

During the pre-GnRH analogue (GnRH-a) period, late follicular phase elevations of serum progesterone throughout ovarian stimulation for IVF occurred as a results of a premature LH elevation and, hence, were correctly defined as 'premature luteinization' (Al-Azemi et al., 2012). With the introduction of GnRH-a in ovarian stimulation protocols for IVF, 'premature luteinization' could be avoided.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
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http://dx.doi.org/10.1016/j.rbmo.2017.01.011
1472-6483/

Nevertheless, the premature rise of progesterone during the late follicular phase in stimulated IVF cycles remains a frequent event, despite the administration of GnRH-a.

In stimulated IVF cycles, a premature elevation of progesterone may occur in up to 38% of cycles, regardless of the stimulation protocols used (Bosch et al., 2003; Ubaldi et al., 1996). The premature progesterone elevation with the presence of normal LH levels and with the administration of GnRH-a is not related to premature luteinization, but is caused by ovarian overstimulation (Lawrenz et al., 2016).

Today, emerging evidence suggests that premature progesterone rise does have a negative effect on the outcome of stimulated cycles (Venetis et al., 2013).

For a pregnancy to occur, a receptive endometrium, a functional embryo at blastocyst developmental stage and synchrony between the embryo and the endometrium is required (Simon et al., 2000). Failure to achieve receptivity and synchrony results in infertility, and is a limiting factor for success in IVF treatment. Endometrial receptivity is driven by time of progesterone exposure after sufficient exposure to oestrogen. The so called 'window of implantation', i.e. the time frame in which the endometrium is receptive and able to support trophoblast–endometrial interactions, is limited in time.

In a natural and idealized 28-day-cycle, it is thought to occur during a time around day 22 to day 24 (Bergh and Navot, 1992). It is assumed, that the window of implantation is constant in time in all women. Displacement of the window of implantation is not a rare cause in women with infertility, especially in women experiencing repeated implantation failure (Ruiz-Alonso et al., 2014). Because of supraphysiological levels of oestradiol and progesterone as a result of the ovarian stimulation for IVF, it could be assumed, that the window of implantation might even be shorter in IVF cycles, compared with a natural cycle (Bourgain and Devroey, 2003).

Over the past few years, many different cut-off levels for elevated progesterone in stimulated cycles have been proposed, ranging from 0.8 to 2.0 ng/ml (Givens et al., 1994; Ubaldi et al., 1995).

The mechanism by which the rise of progesterone during the follicular phase reduces the pregnancy rates is still not fully understood. Elevated peripheral progesterone levels in the late follicular phase do not seem to have any negative effect on the oocyte or embryo quality (Shapiro et al., 2010). Hence, its effect seems to be on the endometrium and the so-called window of implantation, which may lead to asynchrony between the endometrium and the developing embryo (Bourgain et al., 2002).

In this review, data on the possible causes and mechanism of premature progesterone elevation and the influence on endometrial receptivity on the pregnancy rates in IVF treatment are summarized.

Steroid production of the ovary in natural and stimulated cycles

Throughout the menstrual cycle, the ovary produces the steroid hormones oestradiol and progesterone. They are essential for human reproduction, which is demonstrated by the fact, that pregnancies with oocyte donation can be achieved after preparation of the endometrium with oestradiol and progesterone (Devroey and Pados, 1998), even in women without ovaries.

In a natural cycle, oestradiol synthesis increases progressively from the dominant follicle and initiates LH surge. Even before the LH surge, a small increase in progesterone levels is seen, which reflects the increasing LH pulse amplitude and frequency leading up to the surge. An LH surge of 24–36 h is sufficient to initiate the resumption of oocyte meiosis, luteinization of granulosa cells, ovulation, and the initial phase of corpus luteum development. Progesterone and 17a-hydroxyprogesterone (17a-OHP) plasma concentrations increase rapidly after the LH surge or administration of HCG (Christenson and Devoto, 2003), indicating the beginning of granulosa and theca cell luteinization. As well as granulosa cells, the thecal cells produce significant amounts of progesterone.

Progesterone biosynthesis requires two enzymatic steps: first, the conversion of cholesterol to pregnenolone (P5), catalyzed by the enzyme cytochrome P450scc and second its subsequent conversion to progesterone, which is catalyzed by 3β-hydroxy-steroid-dehydrogenase (3βHSD) (Chaffin et al., 2000). Progesterone is further metabolized to androgens by the action of CYP17 in the thecal cells under the influence of LH. This step only takes place in the thecal cell compartment. During the early follicular phase, however, the enzymatic activity necessary to convert 17-OH-progesterone to androstenedione, is absent or very low. Therefore, this process leads to increasing concentrations of progesterone and oestradiol, as the follicular diameter increases (Yding Andersen et al., 2011).

In a cycle without conception, luteolysis occurs owing to a lack of HCG support. The corpus luteum undergoes a process of regression with the loss of functional and structural integrity (Stocco et al., 2007), leading to a decrease in progesterone production.

In a natural cycle with the development of a single dominant follicle, mid-follicular FSH-levels decline towards ovulation (Fleming and Jenkins, 2010); in ovarian stimulation for IVF, multifollicular development is achieved by administration of high daily gonadotrophin concentrations. Stimulation dosage usually remains unchanged throughout the stimulation duration, unless the patient's individual response requires a change in the dosage. Therefore, ovarian stimulation will result in a large number of growing follicles and each follicle will contribute to the progesterone in the systemic circulation.

Progesterone concentration often reflects the number of preovulatory follicles and patients with high oestradiol concentrations have significantly more oocytes and significantly higher progesterone concentrations (Kyrou et al., 2012).

Influence of progesterone on the endometrium in natural and stimulated cycles

The physiologic effects of progesterone are primarily mediated by interaction with the progesterone receptor. There are two classic progesterone receptor isoforms: progesterone receptor A and progesterone receptor B; progesterone receptor A is required for normal ovarian and uterine function (Kastner et al., 1990). They are identical in structure except that the progesterone receptor B isoform contains a 164-amino acid N-terminal sequence, which is lacking in the progesterone receptor A isoform (Wei et al., 1990). After binding of progesterone to the nuclear receptors, steroid receptors activate transcription of their target genes. The mitogenic effect of progesterone in the stroma is also mediated by up-regulation of progesterone receptor A and progesterone receptor B isoforms of the receptor (Salmi et al., 1998; Tseng and Zhu, 1997).

The different histological appearance of the endometrium, depending on the influence of oestrogen or progesterone, have already been studied by Noyes et al. (1950). Although the proliferative phase

under the influence of oestradiol does not allow recognition of subphases other than early, middle or late proliferative phase, progressive changes occur in the endometrium of the secretory phase. Thirty-six to 48 h directly after ovulation, no changes of the endometrium are visible. In addition, under the influence of progesterone, the epithelial glands and vasculature continue to grow and become spiral, whereas the endometrial thickness is relatively unchanged, resulting in a denser endometrium. The morphological changes, observed on histology for each specific day after ovulation, established the classic endometrial dating paradigm that still serves as the gold standard for clinical evaluation of luteal function (Noyes et al., 1975). An endometrial biopsy that shows a difference of more than 2 days between the histologic dating and actual day after ovulation is considered to be 'out of phase' (Wentz, 1980).

Comparison of endometrial steroid receptors and proliferation index between natural cycles and GnRH agonist/HMG-stimulated cycles for IVF have revealed distinct alterations in endometrial maturation. In stimulated cycles, a more advanced secretory endometrial maturation combined with reduced oestrogen receptors and progesterone receptors and a low proliferation index in glands and stroma has been found on the day of oocyte retrieval, compared with endometrial maturation in natural cycles on the day of ovulation.

Endometrial biopsies taken 2 days after oocyte retrieval in stimulated cycles showed a further reduction in steroid receptors and proliferation despite a similar histological maturation compared with biopsies from natural cycles on day 2 after ovulation (Bourgain et al., 2002).

It can be assumed that supraphysiological hormonal levels during stimulation lead to a reduced number of oestrogen and progesterone receptors, and a low proliferation index in glands and stroma. Those functional endometrial alterations might affect the proliferative potential of the endometrium (Bourgain et al., 2002). Solely from the serum progesterone concentrations, the absolute value of serum progesterone increase, or both, however, the exact endometrial development on the day of oocyte retrieval in stimulated cycles cannot be predicted (Ubaldi et al., 1997).

In addition to the aforementioned advancement of endometrial maturation, in patients with a progesterone level above 1.5 ng/ml on the day of HCG administration, differences in endometrial gene expression profile on the day of oocyte retrieval were found, compared with the gene expression pattern below this threshold (Van Vaerenbergh et al., 2011). These changes might explain the impairment of endometrial receptivity in the presence of elevated progesterone, reflected in the lower pregnancy rates reported in the literature (Bosch et al., 2003).

The influence of elevated progesterone levels on the endometrial gene expression pattern was also analysed by Labarta et al. (2011) in a study comparing endometrial dating as well as endometrium gene expression pattern during the window of implantation in 12 healthy oocyte donors. Six patients had progesterone levels above and six patients had levels below the threshold of 1.5 ng/ml. Out of 370 genes, 140 were dysregulated by more than two-fold in women with high serum progesterone levels. A large number of those genes represent biological processes such as cell adhesion, immune system and organ development. Therefore dysregulation of those genes could affect the endometrium and the implantation process.

Interestingly, at day 7 after trigger, no more endometrial advancement was found in the group with elevated progesterone levels on the day of final oocyte maturation. It was shown previously that no pregnancies are achieved in the case of an endometrial advancement of more than 3 days, when the embryo transfer is carried out on day 3 (Kolibianakis et al., 2002; Ubaldi et al., 1997). The detrimental effect of elevated progesterone level on the day of final oocyte maturation, however, subsides when the transfer is delayed until the blastocyst stage (Papanikolaou et al., 2009). This suggests that the endometrium could recover during the window of implantation period.

Causes for progesterone elevation in ovarian stimulation

Increase in serum progesterone levels towards the end of the follicular phase above a randomly chosen threshold have been described in 12–38% of IVF cycles (Bosch et al., 2003; Silverberg et al., 1991; Ubaldi et al., 1996).

Ovarian stimulation before IVF requires the administration of relatively high doses of exogenous gonadotrophins to maintain serum gonadotrophin concentration above the threshold and to support multifollicular growth (Macklon et al., 2006). After each FSH-injection, peak serum FSH levels are reached within 10–12 h and then decline until the next injection. Half-life time of FSH is about 30 h (Mannaerts et al., 1993), leading to steady state levels after 3–5 days. After HMG injections, FSH and LH decline in a biphasic manner. The FSH and LH half-lives in the initial phase are about 4 h and 20 min, and in the terminal phase 40 and 4 h, respectively, and plateaus are reached after 3–4 days (Center for Drug Evaluation and Research, 1999). Because of the relatively short $t_{1/2}$ of FSH and HMG, daily injections are required to prevent serum gonadotrophin levels from dropping below the threshold and subsequent follicular atresia. Consequently, the follicles are being constantly stimulated.

Compared with daily FSH and HMG, corifollitropin alpha (CFA) has a different pharmacokinetic profile, and is characterized by rapid absorption, resulting in peak concentrations 2 days after injection. Thereafter, serum CFA concentrations decrease progressively, although the FSH activity is maintained above the threshold for 1 week. As such, the pharmacokinetic profile mimics a high FSH starting dose, and, a step-down, releasing the pressure on the follicles (Fauser et al., 2009).

In the past few years, several investigators have promoted the idea that premature progesterone rise in stimulated cycles is caused by a lack of HCG and LH activity (Smitz et al., 2007; Werner et al., 2014). Smitz et al. (2007) suggested that HCG and LH activity would have a protective effect, preventing a possible premature progesterone rise, when they compared premature progesterone rise between recombinant FSH and HMG. In that trial, however, patients treated with recombinant FSH, had significantly more follicles at all thresholds according to size (≥10, ≥12, ≥15 and ≥17 mm) compared with the HMG group (Andersen et al., 2006; Smitz et al., 2007). Therefore, these results should be evaluated critically, as intra-follicular progesterone concentrations increase significantly with follicle size (Schneyer et al., 2000) and patients with more oocytes have significantly higher progesterone concentrations (Kyrou et al., 2012).

Furthermore, synthesis of progesterone by preovulatory follicles is stimulated by both FSH and LH, with LH providing the strongest signal (Thuesen et al., 2014; Yong et al., 1992). Although classically it has been proposed that the cause of premature progesterone rise might be enhanced FSH stimulation in assisted reproduction technique cycles (Filicori et al., 2002; Kyrou et al., 2012), a recent single study has suggested that HCG and LH activity even increases the

progesterone production during the follicular phase (Thuesen et al., 2013), rather than preventing it.

The hypothesis of enhanced FSH stimulation being the cause of progesterone elevation is supported by a post-hoc data analysis (Lawrenz et al., 2016) from the previously published ENGAGE (Devroey et al., 2009) and PURSUE study (Boostanfar et al., 2015) on the incidence of progesterone elevation. Patients, who met the criteria for final oocyte maturation after receiving a single injection of CFA had a significantly lower incidence of premature progesterone elevation compared with patients receiving daily recombinant FSH-injections over the same stimulation duration.

It can be assumed that because of the pharmacokinetic profile of CFA, mimicking a step-down protocol, the capacity of the CYP17, catalyzing progesterone in the theca cells, is not overloaded. This results in a significantly lower incidence of premature progesterone rise, compared with stimulation with recombinant FSH.

This finding points clearly towards the fact that enhanced and persistent recombinant FSH stimulation towards the end of the follicular phase is the primary cause of premature progesterone rise.

Effect of progesterone elevation on pregnancy rate

The debate on the effect of elevated progesterone levels during the late follicular phase of ovarian stimulation has been ongoing since the beginning of the 1990s. In 1991, Schoolcraft et al. reported that, in some patients, progesterone concentrations rose above normal follicular-phase concentrations before final oocyte maturation despite the suppression of endogenous LH by GnRH-a (Schoolcraft et al., 1991). As premature elevation of progesterone is not uncommon in ovarian stimulation regardless of the stimulation protocols (Bosch et al., 2003; Silverberg et al., 1991; Ubaldi et al., 1996), the effect of elevated progesterone levels on the pregnancy rate is of utmost importance.

As early as 1997, Ubaldi et al. (1997) evaluated the effect of elevated progesterone levels on the endometrial maturation as well as on the pregnancy rate. They carried out endometrial aspiration biopsies on the day of oocyte retrieval and compared the histological appearances as well as the pregnancy rates of patients with progesterone levels 0.9 ng/ml or less and above 1.0 ng/ml. This study did not reveal a negative effect of a subtle rise in progesterone concentrations on the pregnancy rate. They did not, however, find any pregnancy in patients with an advanced endometrium of more than 3 days.

Meanwhile, several more studies evaluated the effect of progesterone elevation on the pregnancy rate. A meta-analysis, including 12 studies with a total of 2733 patients, was published in 2007 by Venetis et al. (2007). A threshold of more than 0.9 ng/ml was used to define progesterone elevation. They found a tendancy toward lower clinical pregnancy rate in the group with progesterone elevation. The difference, however, was not significant. Limitations of this meta-analysis were the heterogeneity of the studies included, such as arbitrarily defined serum progesterone threshold values using various different assays.

In a prospective study, Bosch et al. (2003) used a cut-off-level of 1.2 ng/ml to define elevated progesterone and found a significantly lower pregnancy rate in the patients with progesterone-levels above 1.2 ng/ml. This study also supports the theory of enhanced FSH-stimulation as a cause of elevated progesterone-levels, as patients with progesterone elevation had a higher dose of FSH and a longer stimulation.

A retrospective analysis of 4032 cycles, carried out as GnRH agonist as well as GnRH-antagonist protocols, clearly demonstrated significantly reduced pregnancy rates in patients with a progesterone level of 1.5 ng/ml or over, independently from the protocol used and from the ovarian response. These findings suggest that serum progesterone concentration of 1.5 ng/ml and above may represent the critical threshold level at which there is a negative effect progesterone on ongoing pregnancy rate (Bosch et al., 2010).

The largest meta-analysis published on this topic included more than 60,000 cycles (Venetis et al., 2013), and the data were stratified according to different progesterone thresholds. Progesterone levels of 0.8 ng/ml and above were already associated with a significant negative correlation between progesterone elevation and pregnancy achievement. The association between elevated progesterone level above 1.5 ng/ml on the day of HCG administration in low, normal, and high responders, and the ongoing pregnancy rates, were analysed in several studies and showed conflicting results in high-responder patients. A meta-analysis (Griesinger et al., 2013) showed a detrimential effect of progesterone elevation above 1.5 ng/ml on the ongoing pregnancy rate in 'low' and 'normal' responders. In high-responder patients, no impairment of the pregnancy rate could be observed. The data from Requena et al. (2014) suggest that a serum progesterone concentration exceeding 1.8 ng/ml may represent the value at which progesterone begins to have a minimum effect on implantation rates in patients with high ovarian response. A significant reduced ongoing pregnancy rate was found in high-responder patients when the progesterone level exceeded 2.25 ng/ml (Xu et al., 2012). So obviously, the progesterone-threshold, having a negative effect on the assisted reproduction technique outcome, depends on the ovarian response and the threshold of 1.5 ng/ml cannot be applied to all patients.

Studies, conducted by Papanikolaou et al. (2009) and Huang et al. (2015) assessed the effect of progesterone elevation on the pregnancy chances in cleavage and in blastocyst transfers. Both studies found decreased pregnancy rates in day-3 embryo transfers, starting from a progesterone elevation of 1.0 ng/ml and getting worse when the progesterone concentration reached 1.5 ng/ml and 0.73 ng/ml, respectively. Results were contradictory, however, for day- 5 embryo transfers. Huang et al. (2015) observed a detrimental effect on day-5 blastocyst-stage transfer only when progesterone concentration reached 1.75 ng/ml, whereas no negative effect was found in the study of Papanikolaou et al. (2009). Out of those results, one might speculate that further developed embryos might counterbalance the endometrial advancement at this stage caused by premature progesterone rise and synchronize with the advanced endometrium.

In patients who underwent a planned single embryo transfer on day 5, decreased ongoing pregnancy rates were seen with increased progesterone levels at the end of stimulation. In patients stimulated with recombinant FSH, the progesterone threshold resulting in a reduced pregnancy rate was lower compared with patients stimulated with highly purified HMG (>4 nmol/l versus >7 nmol/l) (Devroey et al., 2012).

No association was found between progesterone elevation on the day of HCG administration in the fresh cycle and the probability of pregnancy after transfer of frozen–thawed embryos, originating from that cycle. Moreover, since the aforementioned meta-analysis by Venetis et al. (2013), further studies have confirmed that progesterone elevation on the day of final oocyte maturation has no negative effect on the pregnancy rate in a subsequent cryopreserved embryo transfer cycle (Healy et al., 2016; Yang et al., 2015), confirming that the negative effect is on the endometrium and not the oocyte.

Conclusion

A receptive endometrium depends on the interaction of the hormones oestrogen and progesterone, and is crucial to allow embryo implantation. Endometrial receptivity is driven by progesterone exposure after sufficient oestrogen exposure and is obviously at stake when progesterone elevation occurs during late follicular phase of ovarian stimulation for IVF. Progesterone level increases with the size of follicular diameter and in ovarian stimulation for IVF, with a large number of growing follicles, each follicle will contribute to the progesterone in the systemic circulation.

The definition of 'elevated progesterone' is inconsistent, and cut-off-levels are often chosen arbitrarily. Meanwhile, evidence mounts that progesterone levels above 1.5 ng/ml on the day of final oocyte maturation lead to reduced pregnancy rates when the embryo transfer is carried out in the same cycle.

The causes of premature progesterone elevation during ovarian stimulation are still unclear; however, recently published data point towards the fact that enhanced FSH-stimulation towards the end of follicular phase might be the primary cause for progesterone elevation. As FSH induces the expression of LH receptors, further studies should evaluate whether the negative effect of elevated progesterone on the endometrial receptivity occurs after trigger, owing to increased number of LH receptors generated.

Under the influence of progesterone the histological appearance of the endometrium changes. Compared with natural cycles, a more advanced secretory endometrial maturation is found in stimulated cycles and, additionally, using a cut-off-level of 1.5 ng/ml for elevated progesterone levels on the day of HCG administration, an alteration of the endometrial gene expression patterns.

As elevated progesterone does not have an influence on the quality of the oocyte or the embryo, it can be assumed that elevated progesterone levels during ovarian stimulation alter the endometrial receptivity and are therefore the cause of the reduced pregnancy rates in those IVF cycles.

To avoid the negative effect of elevated progesterone levels on the pregnancy rate, different strategies could be considered: first, the incidence of progesterone elevation can be lowered by reducing the stimulation pressure during the late follicular phase of ovarian stimulation (Lawrenz et al., 2016). Until now, no further studies support this hypothesis; therefore, prospective randomized studies are warranted. Second, in the event of progesterone elevation on the day of trigger, fresh embryo transfer should not be carried out and cycle segmentation should be applied. This approach, however, must be applicable according to the fertilization legislation of the country of treatment and to the wishes of the patient. The 'freeze-all'-approach with a subsequent transfer of the embryos in a natural or hormonal-replacement-cycle eliminates the detrimental effect of elevated progesterone levels on the endometrial receptivity (Fatemi and Garcia-Velasco, 2015).

ARTICLE INFO

Article history:
Received 16 September 2016
Received in revised form 17 January 2017
Accepted 17 January 2017
Declaration: The authors report no financial or commercial conflicts of interest.

Keywords:
Endometrial receptivity
IVF
Progesterone elevation

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