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Review

Premature progesterone rise in ART-cycles

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ABSTRACT

Premature rise of progesterone during the late follicular phase in stimulated IVF cycles is a frequent event and its effect on the endometrial receptivity and on the ART (Assisted Reproductive Technique) – outcome has become a matter of intense debate and research. An emerging body of evidence demonstrates that premature progesterone rise does have a negative impact on the outcome of the ART-success. Until now, the exact cause of progesterone elevation is not fully clear, however lately published studies points to the fact, that premature progesterone elevation might be caused by enhanced FSH stimulation. The impact of elevated peripheral progesterone levels seems to be mainly on the endometrium and the window of implantation, leading to an asynchrony between the endometrium and the developing embryo. Hence, new data show additional an influence on the embryo quality. This review aims to summarize the up-to-date knowledge on the causes of premature progesterone rise during hormonal stimulation, on its influence on endometrial receptivity and embryo quality, on the impact on pregnancy and live birth rates as well as on the possible strategies to prevent this event or to deal with premature progesterone elevation in case it could not be avoided.

1. Introduction

Serum progesterone elevation during the follicular phase of ovarian stimulation for IVF treatment and its effect on the endometrial receptivity is a matter of intense debate and research for the last decades.

The first studies demonstrated a possible negative impact of elevated progesterone levels on the day of final oocyte maturation, leading to significantly reduced pregnancy rates in ART-treatments, with the use of arbitrarily chosen progesterone levels above a threshold between 0.9 ng/ml–1,1 ng/ml [1,2]. Later on, different cut-offs have been used to define elevated progesterone during stimulated cycles, ranging from 0.8 to 2.0 ng/ml [3–7]. Finally, the study from Bosch et al. [8] and the metaanalysis of Venetis et al. [9] demonstrated a significant decrease in ongoing pregnancy rates with serum progesterone levels above 1.5 ng/ml on the day of hCG administration.

The herein mentioned studies showed a negative influence on the pregnancy outcome in the case of premature progesterone elevation, using different progesterone levels as cut-off-values. Besides the different cut-off-levels used to define premature progesterone elevation, it has to be kept in mind that different progesterone-assays have been used in those studies and differences in assay performance could have also contributed to the heterogeneous results [10].

2. Mechanism of progesterone elevation during ovarian stimulation

Until now, the exact cause of progesterone elevation towards the end of the follicular phase of ovarian stimulation for IVF is not fully clear. Due to the fact, that the progesterone rise precedes the administration of hCG or GnRH-agonist for final oocyte maturation and is not associated with premature LH surge, it does not reflect a true luteinization event.

The administration of relatively high doses of exogenous FSH is required to achieve multi-follicular growth [11] and data from several studies point to the fact that premature progesterone elevation might be caused by enhanced FSH stimulation [12–14].

Those data are supported by a recently published in-vitro-study on human ovarian cortical samples and a non-luteinizing FSH-responsive human mitotic granulosa cell line [15]. It was demonstrated, that FSH stimulates the expression of 3β-hydroxysteriod dehydrogenoase (3β-HSD) and progesterone biosynthesis in these cells in addition to its stimulatory effect on the expression of other steroidogenic enzymes, required for estrogen synthesis. FSH has a direct stimulatory effect on the enzymatic activity of 3β-HSD and therefore increased the conversion of pregnenolone to progesterone. This lead, in a dose-dependent fashion, to an enhanced progesterone and estradiol output from the samples stimulated with FSH. The findings of this study also support the

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two-cell–two-gonadotropin theory in humans [16]. According to this theory, pregnenolone and progesterone produced by granulosa cells must enter the theca cells in order to be converted into androgens. In the absence of LH support the activity of 17α-hydroxylase cannot be enhanced with FSH stimulation only and 17-alpha-hydroxylase does not respond to FSH stimulation in human granulosa cell. In the event of ovarian stimulation by continuously elevated FSH-levels, the amount of precursor steroids generated may exceed the ability of the ovary to effectively convert them into estrogen pathway. This may delay the conversion of progesterone into androgens in theca cells leading to their accumulation and leak into systemic circulation and provides a plausible explanation why FSH stimulation promotes P output from granulosa cells without luteinization.

Daily injections with recombinant FSH are necessary to prevent serum FSH levels from dropping below the threshold which is required for follicle growth as recombinant FSH has a half-life of about 30 h [17]. Consequently, the follicles are under continues FSH stimulus until the final oocyte maturation.

Lately it has been demonstrated, that ovarian stimulation with corifollitropin alpha (CFA) only leads to a significantly reduced incidence of premature progesterone elevation on the day of final oocyte maturation [14]. CFA is characterized by a rapid absorption which results in peak concentrations two days after the injection. Thereafter, serum CFA-concentrations decrease progressively, although the FSH activity is retained above the threshold for one week. The pharmacokinetic profile of mimics a high FSH starting dose and a step-down protocol, releasing the pressure on the follicles [18]. Following the idea that reduction of FSH-dosage will lead to a lower incidence of progesterone rise, a step-down protocol can be applied in order to avoid progesterone elevation. However future studies will have to proof the effectiveness of this approach.

Besides enhanced FSH stimulation, prolongation of ovarian stimulation leads also to significantly higher progesterone levels on the day of final oocyte maturation [19,20].

Other authors promoted the idea that premature progesterone rise in ovarian stimulation cycles is caused by a lack of hCG/LH activity [21,22] and suggested that hCG/LH activity has a protective effect and could prevent premature progesterone rise [22]. To support their theory they compared premature progesterone rise between rFSH and HMG used for ovarian stimulation. However, those data have to be evaluated critically as the patients, stimulated with rFSH, had significantly more follicles at all sizes (≥10, ≥12, ≥15 and ≥17 mm) as compared to the HMG group [17]. Already previously it has been shown, that intra-follicular progesterone concentrations increase significantly with follicle size [23] and therefore patients with more oocytes have significantly higher progesterone concentrations [24]. Also the data of the study from Thuesen et al. [25] suggested that hCG/LH activity even increases the P production during the folicular phase rather than preventing it.

3. Premature progesterone elevation and endometrial receptivity

Endometrial receptivity depends on the duration of progesterone exposure after sufficient estrogen exposition. The morphological changes of the endometrium under the influence of progesterone had been described by Noyes et al. [26] for each specific day after ovulation, establishing the classic endometrial dating paradigm for the clinical evaluation of the luteal function. An endometrial biopsy that shows a difference of more than 2 days between the histologic dating and the actual day after ovulation is considered to be “out of phase” [27].

Supraphysiological hormonal levels during ovarian stimulation for IVF might jeopardize the endometrial receptivity by premature progesterone elevation during the follicular phase [28]. Ubaldi et al. [2] carried out endometrial biopsies on the day of oocyte retrieval and compared the histological appearance with the pregnancy rates in patients with elevated progesterone levels. No pregnancy could be achieved in patients with an “out of phase” endometrium and an endometrial advancement of more than 3 days. It is assumed that the endometrial advancement leads to an asynchrony between the endometrium and the developing embryo [29]. The finding of differences in gene expression profiles in the endometrium between patients with progesterone serum concentrations above or below a threshold of 1.5 ng/ml on the day of hCG administration support the idea, that premature progesterone elevation has a negative impact on the endometrial receptivity [28,30]. Lately it was shown, that progesterone levels above 1.7 ng/ml on the day of hCG-administration for final oocyte maturation affect the epigenetic modification in three compartments of endometrium in the peri-implantation period. It was suggested, that the altered epigenetic modification status in the endometrium in women with high progesterone on the day of final oocyte maturation may disrupt the endometrial receptivity and lead to reduce pregnancy rates [31]. The same group of authors also investigated the influence of progesterone levels on the expression profile of genes involved in natural killer cell mediated cytotoxicity pathway in the endometrium. They could demonstrate, that high progesterone levels affect this pathway by gen-dysregulation in patients with high progesterone levels not only on the day of trigger but also on the day after trigger. It was suggested, that alteration of this pathway provides the molecular basis of how high progesterone alters gene expression in the endometrium at the time of implantation [32].

4. Premature progesterone elevation and embryo quality

Besides the negative impact of elevated progesterone levels on the endometrial receptivity, recently published data point towards the fact, that there is also a correlation between the progesterone level on the day of final oocyte maturation and the rate of “top embryo quality” (TEQ). This is contradictory to the previous findings that elevated peripheral progesterone levels in the late follicular phase do not seem to have any negative impact on the oocyte or embryo quality [33,34]. It seems that patients with an elevated progesterone level during the follicular phase are at risk for the absence of top quality blastocysts [35,36] and the TQE rate was significantly different between serum progesterone levels < 2.0 ng/ml and > 2.0 ng/ml. Obviously, elevated progesterone levels above 2.0 ng/ml before oocyte maturation are detrimental to the oocyte [37]. However, the data of relationship between human oocyte quality and elevated progesterone levels is limited and only based on findings in animal studies. According to those findings it seems that, besides other factors, lower and consistent progesterone concentrations promote oocyte competence [38].

5. Impact of progesterone elevation on the pregnancy rate

Since premature elevation of progesterone is not uncommon in COS regardless of the stimulation protocols [2,39], the impact of elevated progesterone levels on the pregnancy rate is of utmost importance and several studies have been done on this topic.

The largest metaanalysis on this topic included more than 60.000 cycles [9] and the data were stratified according to different progesterone thresholds. A significant negative correlation between progesterone elevation and pregnancy achievement could already been demonstrated from progesterone levels of 0.8 ng/ml and above.

The association between progesterone-levels above 1.5 ng/ml on the day of hCG administration and the ongoing pregnancy rates in different responders (low, normal and high) was analysed by Griesinger et al. [40] who performed a *meta*-analysis, including 6 studies with a total of 1866 patients. Whereas a detrimental effect of progesterone elevation above 1.5 ng/ml was demonstrated on the ongoing pregnancy rate in “low” and “normal” responders, no impairment of the pregnancy rate could be observed in high responder patients.

However, the data from Requena et al. [41] suggest, that serum