Quick Response Code

To transfer or not to transfer: That is the question

About the Author

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INTRODUCTION

Luteinization, the process by which the mature follicle is transformed into the corpus luteum, is mainly induced by a luteinizing hormone (LH) surge.[1] In contrast, the subtle and gradual increase in progesterone levels observed during the last day of ovarian stimulation reflects only the total amount of progesterone secreted by maturing follicles in the absence of any premature uncontrolled LH surge.

The frequency of rise in serum progesterone (P) on or before the day of human chorionic gonadotropin (hCG) administration, and its incidence varies among different down-regulation protocols in controlled ovarian stimulation (COS); the frequency has been reported as being as high as 35% (5-35%) in gonadotropin-releasing hormone (GnRH) agonist cycles and as high as 38% (9-38%) in GnRH antagonist cycles.[2-6]

The issue of serum progesterone rise on the day of hCG administration (serum *P* hCG) during COS is still a matter of debate. As emphasized above, serum *P* rise observed during the final stages of COS cannot really be called premature luteinization because it takes place in patients whose endogenous reproductive hormones are suppressed with GnRH analogs, which fully control any consequent LH surge. However, it should be noted that despite pituitary down-regulation, luteinization and premature ovulation could occur in GnRH agonist (GnRHa) cycles due to the discontinuous manner of administration (missed injections or nasal spray applications). In addition, premature LH peaks have been reported in antagonist cycles during ovarian stimulation,[7] as well in modified natural cycles[8] and natural cycles.[9]

An elevated serum *P* concentration on the day of hCG administration has previously been reported to affect adversely *in vitro* fertilization (IVF) pregnancy outcomes.[10-12] A more recent publication[13] has also shown that high serum *P* on the day of hCG administration (serum *P* hCG) had detrimental effects on the pregnancy rate of IVF after using a GnRHa/recombinant follicle-stimulating hormone (FSH) (225 IU/day) short protocol. However, other studies have not found that probability of pregnancy decreased significantly when serum progesterone was above a threshold concentration on the day of hCG administration.[14-16] Other groups[17-18] observed no significant differences in pregnancy rates in patients undergoing IVF with high or low progesterone concentrations on the day of hCG administration and in patients who received oocytes from women with high or low progesterone concentrations.

DISCUSSION

During COS, premature luteinization, as detected by an elevated serum P, is traditionally prevented by suppression of LH secretion with GnRH analogs.[19] An inadvertent

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marked increase of *P* levels before final oocyte maturation with hCG would lead to cancellation of IVF cycles in the majority of cases. Despite the use of GnRH analogs, a subtle rise in serum *P* levels is observed in a subgroup of women, particularly at the end of the stimulation cycle. An excess number of follicles, with each one producing a normal amount of *P* consistent with the late follicular phase rather than excessive amounts of *P* being produced by granulosa cells as part of early luteinization, has been suggested to account for this observation.[5,20]

There is strong evidence from histologic observations and expression analysis of implantation window markers that ovarian hyperstimulation in IVF cycles profoundly alters the luteal-phase endometrium.[21] Patients with elevated *P* levels >1.5 ng/mL on the day of hCG administration display a significantly different gene expression profile of the endometrium as early as 36 h later when compared with patients with *P* levels <1.5 ng/mL.[22] Similar effects were observed 7 days after hCG administration, corresponding to the window of implantation, when a total of 370 analyzed genes were dysregulated by more than twofold in patients with *P* levels >1.5 ng/mL.[23] Both studies support the concept of endometrial impairment in the presence of elevated *P* and accordingly lower ongoing pregnancy rates.[5,24,25] Consistent with these observations, elevated *P* levels >0.9 ng/mL on the day of hCG administration are associated with an accelerated increase of the endometrial echogenicity during the early luteal-phase of controlled ovarian hyperstimulation cycles.[26]

The influence of LH on serum progesterone rise during gonadotropin stimulation is a matter of debate. Hugues *et al*.[27] assessed the relationship between endogenous LH serum levels after GnRH analog administration and serum *P* elevation on the day of hCG administration in a retrospective study of 708 patients undergoing a GnRHa or antagonist protocol for IVF/ICSI cycles. Serum *P* on day of hCG administration values were significantly lower following the GnRH antagonist than agonist protocol. The lower serum *P* levels on hCG administration day following the GnRH antagonist protocol are mainly explained by lower granulosa cell steroidogenic activity. The correlation of *P* levels with serum LH on day of hCG was positive in the GnRHa-treated group.

The purpose of a recent analysis by Hugues[28] was to assess the impact of supplementation with "LH activity" products on serum progesterone changes before hCG administration in GnRH analog-treated women. A computerized literature search was performed to identify studies comparing FSH treatment alone to those that provided supplementation with "LH activity" using hMG, recombinant rLH or hCG in GnRH analog protocols. Data regarding stimulation regimens were extracted from those that reported serum progesterone levels at the time of hCG in order to assess the specific role of LH activity products. Serum progesterone determination at the time of hCG administration was performed in 34 out of 108 studies comparing the effects of FSH alone or in combination with LH activity products. In a vast majority, no significant difference in serum progesterone could be found between stimulation regimens. However, in four studies where LH activity (three hMG and one rLH) was administered from the beginning of ovarian stimulation, serum *P* values were significantly decreased. In contrast, in two studies where LH activity (hCG) was provided during the late follicular phase, serum *P* values were significantly increased. Analysis of confounding factors showed that the intensity of ovarian stimulation is the most important determining factor to explain serum progesterone elevation at the time of hCG administration. This systematic review showed that providing LH activity supplementation in combination with FSH during ovarian stimulation does not have a consistent effect on serum progesterone concentrations at the time of hCG administration. However, these data also suggest that, in accordance with physiological concepts, the timing of LH activity administration could influence the impact on serum progesterone changes.

Many questions have been raised regarding the incidence of progesterone elevation in GnRH-analog-controlled cycles specifically on the impact on cycle IVF outcome. A meta-analysis[20] concluded that there was a lack of evidence for a negative impact of high *P* values on implantation rates. However, this conclusion has recently been challenged[29-32] for several reasons: Results confounded by the use of different GnRH analog protocols, methodological flaws such as the unreliability of commercial nonextraction assays,[33] arbitrary choice of defined threshold (0.9 ng/ml) where the use of a receiver operator characteristics curve might have been more appropriate. Using this approach, Bosch *et al*.[5] reported a negative impact of serum progesterone increase with a threshold value of 1.5 ng/ml in a large single-center study where GnRHa and antagonist cycles were analyzed separately. This threshold value has been proposed in a recent study that additionally emphasizes the predictive value of progesterone/estradiol (E2) ratio.[34] Furthermore, the consequences of serum progesterone rise on IVF outcome might be drastically different depending on whether it occurs in women with a strong or weak response to COS. Indeed, a low clinical pregnancy rate was mainly observed when the response to

COS was weak.[35] Therefore, confounding factors such as patients' ovarian reserve, oocyte and embryo quality need to be also considered when assessing the consequences of serum progesterone rise on cycle outcome following COS.[29,36]

It has also been recently suggested that the duration of the follicular phase could be an important determining factor in the occurrence of serum progesterone rise and, therefore, in the risk of cycle failure.[32] Indeed, increasing the duration of stimulation could result in a larger number of follicles and higher E2 levels, which could negatively impact cycle outcome throughout an earlier expression of progesterone receptors.[37-39] In accordance with this concept, it has been suggested that adjustment of the timing of hCG administration according to serum progesterone concentrations might improve cycle outcome.[40]

Sharma *et al*.[41] and Silverberg *et al*.[3] suggested that the mechanism of a deleterious effect of an elevated *P* was abnormal acceleration of endometrial maturation leading to impaired endometrial receptivity. COS may advance endometrial maturation and elevated *P* may hasten the closure of the implantation window.[17,42] Therefore, the placement of the embryo in an asynchronous endometrium results in failure of establishing the embryo-endometrial cross-dialog, and in turn, embryo demise and failure of implantation.

However, several clinical trials have been performed in which *P* supplementation for the luteal-phase support was started on the day of hCG administration, without any negative impact on pregnancy rates due to the deleterious effect on the endometrium, suggesting that there is no negative impact of high *P* levels on IVF outcome.[43-45]

Several strategies have been suggested to allow for endometrial recovery before transfer, such as extended embryo culture. There have been two studies that sought to determine whether prolonged embryo culture and blastocyst transfer would mitigate the adverse effect of elevated *P* that is seen on the day of hCG administration.[46,47] Papanikolaou *et al.* showed a significant negative effect on pregnancy outcome when a *P* threshold of 1.5 ng/mL was encountered on the day of hCG trigger and cleavage-stage embryos were subsequently transferred.[46] Importantly, no negative effect was seen when using the same *P* threshold and subsequent blastocyst transfer, suggesting that the deleterious effect is at the level of the endometrium.

In recent times, Corti *et al.* explored this question using the same *P* threshold on the day of trigger, however, they did not find that extended embryo culture lessened the negative endometrial effect on pregnancy outcome; this may be partially explained by the overall younger and potentially better prognosis patient population in the former study.[47] Due to these conflicting findings, further larger studies are required in the future to determine whether extended culture or embryo freezing is the preferred route for managing patients with elevated Polotsky *et al*.[48] and Shapiro *et al*.,[49] demonstrated that in cycles with elevated preovulatory progesterone, the probabilities of implantation and ongoing pregnancy are increased if all 2-pronuclear oocytes are cryopreserved and subsequently thawed and cultured to the blastocyst stage before transfer.

Kyrou *et al*.[38] demonstrated that patients with high estradiol concentrations have significantly higher progesterone concentrations and significantly more oocytes. The association of high estradiol and progesterone elevation suggests that at least one of the mechanisms that play a role in progesterone rise is linked to the high response of the ovary to ovarian stimulation. An excess number of follicles, and consequently an excess of proliferating granulosa cells, can lead to increased progesterone production. Recently, Al-Azemi *et al*.[50] demonstrated that by measuring the estradiol concentrations and number of follicles, one could anticipate the risk of premature progesterone rise. Based on the above finding, it seems that an upcoming progesterone rise could be prevented by modification of the protocol and timing of triggering of final oocyte maturation. Although progesterone rise is often seen in women displaying a good response to ovarian stimulation and is associated with more cumulus-oocyte-complexes retrieved and higher estradiol concentrations, it can also take place in women whose ovarian responses to ovarian stimulation are weak. In those cases, a per follicle increase in progesterone production is seen.[51] The nature of this latter phenomenon could be explained by the fact that these patients need longer stimulation and thus a significantly higher total FSH dose. Furthermore it could be considered as an indirect sign of ovarian ageing.[35]

The risk of premature progesterone rise appears to be associated with the number and the size of follicles and the intensity of FSH stimulation. It might be preferable, for example, to trigger earlier in high responders than normal and poor responders to avoid premature progesterone rise and consequently poor outcome. Jones *et al*.[52] investigated the association between follicular fluid volume (follicle size) and oocyte morphology in follicles stimulated by hMG. The authors evaluated this in terms of oocyte maturity, which is responsible for the establishment of pregnancy after single-embryo transfer (ET). Their findings revealed

that mature oocytes can be obtained from follicles as small as 11 mm in diameter. This was also reported by Edwards[53] who reported 69% recovery of mature oocytes from follicles 10-17.5 mm in size. These data suggest that an earlier trigger in high responders in order to avoid premature progesterone elevation is feasible.[32,54] Another preventive measure is to adopt mild stimulation protocols. This approach will prevent high estradiol concentrations, which are associated with progesterone rise in the follicular phase.[38]

Higher hormone concentrations might affect tubal peristalsis and the egg or zygote transport. Progesterone was shown to contribute to uterine quiescence.[55] Increasing uterine contractility might allow for decreased implantation within the uterine cavity and favor migration of the embryos into the Fallopian tubes. In IVF cycles, supra-physiological progesterone concentrations could exceed the concentration of normal conception cycles and may result in more uterine relaxation during the ET. Also, high estradiol concentrations in IVF cycles affected tubal peristalsis through the control of tubal smooth muscle contractility and ciliary activity.[56] Paltieli *et al*.[57] found that, after the addition of progesterone to the culture medium, higher concentrations of progesterone caused a significant decrease in the ciliary beat frequency, estradiol-induced a slight increase in frequency, and gonadotropins did not affect ciliary motility, which suggested that higher concentrations of progesterone caused ciliary dysfunction and subsequently might be a cause of possible ectopic pregnancy.

CONCLUSIONS

Several studies have evaluated the impact of elevated *P* at the time of hCG trigger in GnRHa down-regulated cycles, with conflicting results; while several have supported the notion that elevated *P* negatively impacts pregnancy rates, other investigators have been unable to substantiate this finding. Endometrial receptivity is tightly linked to the hormonal milieu present at the time of ET in an IVF cycle. During COS, excessive follicular development and supra-physiologic serum concentrations of E2 can lead to a premature rise of *P* in the late follicular phase, resulting in asynchrony associated with implantation failure. Additional hypotheses that have been considered to explain this phenomenon include the elevation of follicular LH levels secondary to incomplete desensitization to GnRHas, serum accumulation of hCG from hMG, increased LH receptor sensitivity of the granulosa cells, poor ovarian response with increased LH sensitivity, and the disruption of signaling in the ovarian granulosa cells. Although the mechanism remains unclear, most investigators favor a cumulative deleterious effect on the endometrium.

The negative effect of an elevated *P* at the time of oocyte retrieval appears to be limited to the endometrium, as no effect on oocyte maturation or fertilization rate was detected; this has been corroborated by previous studies in donor-recipient IVF cycles as well as in frozen embryo cycles[17-18,31,39-41,58,59] Therefore, a simple solution may be vitrification of embryos when *P* levels exceed this threshold. The advantages of a frozen-thawed vitrified ET over a fresh ET have been described in the literature, particularly as pregnancy success rates are much better than fresh ETs in many IVF labs.[60-63]

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