Elevated P level on the day of hCG administration is related to FSH dose: is it the whole truth?

Sir,

I read with much interest the article by Bosch et al. (2010) published recently in the Human Reproduction. In a retrospective analysis, the authors examined the relationship between serum progesterone (P) level on the day of hCG administration (hCG day) and the probability of ongoing pregnancy, in an unselected population of women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction technologies (ART) treatment. They found that elevated serum P level is associated with reduced ongoing pregnancy rate. Furthermore, they showed that daily FSH dose, number of oocytes and E2 value on hCG day were positively associated with P levels. The authors concluded that their results support the notion that the mechanism responsible for this occurrence seems to be directly related to the total FSH dose used during COH and the number of oocytes obtained.

Since the introduction of GnRH analogues and their routine use into ART cycles the topic of elevated P level on hCG day has become one of the most controversial and debated topics in modern reproductive endocrinology. While some investigators linked this phenomenon to low pregnancy rate (Silverberg et al., 1991), others did not find a negative influence (Givens et al., 1994) and yet others have found a favorable effect (Legro et al., 1993) on ART outcome. This debate has started almost 20 years ago and it is ongoing to the present days (Venetis et al., 2007) and the pathophysiology of this phenomenon is still in question.

In this letter, it is not my intention to contradict the conclusions raised by Bosch et al., but to try and clarify the mechanism underlying elevated P level on hCG day. I agree that one of the mechanisms responsible for the elevated P level on hCG day is high FSH dosage when it causes an excessive ovarian steroidogenic activity. This hypothesis is supported by the results of the Merit study, a prospective trial showing that during COH, P peaks higher when FSH rather than hMG is employed in young normogonadotropic women (Andersen et al., 2006). In this setting, high FSH dose will recruit a large number of growing follicles leading to an increased ovarian steroidogenic activity that will produce and secrete more P. LH activity in such a non-luteinized environment may act to reduce circulating P, by promoting its conversion to androgens, which are then further metabolized to estrogens by the granulosa cells (Fleming, 2008). However, whether this is the whole truth or only part of it remains to be seen. Whether the same explanation can be introduced in the low ovarian reserve women undergoing ART treatment is in doubt.

Although both E2 level on hCG day and number of oocytes are typical signs of multiple follicular development and increased ovarian steroidogenic activity, the daily FSH concentration does not always indicate either of these. The common practice of a reasonable ART specialist is to reduce the daily dose of FSH dosage to prevent ovarian hyperstimulation syndrome development. High FSH administration is only used for women with low ovarian response or reserve. Indeed, in the retrospective analysis performed by Bosch et al., 28.4% of women in the study were with low ovarian reserve as the main infertility cause. In another 11.1% the main cause was unexplained infertility, which is also considered to be a risk factor for low ovarian reserve (Nikolaou and Templeton, 2003). These patients with low ovarian reserve were a priori excluded when the Merit study was conducted (Andersen et al., 2006).

Moreover, the results of the multivariate analysis in the Bosch showed that the factor most related to serum P elevation was a higher daily FSH dose with an OR of 1.44, compared only to 1.063 for the number of oocytes achieved and 1.0004 for E2 level on hCG day.

High FSH administration does not necessarily cause the development of high number of follicles. Women with low ovarian reserve who are treated with high doses of FSH achieve a small number of developing follicles, which does not lead to considerable ovarian steroidogenic activity. It is therefore not reasonable to relate the elevated P level on hCG day to an increased ovarian steroidogenic activity. Other mechanisms should be searched for and explored.

Elevated P level on hCG day, measured by adequate assays, has been previously shown to be an early manifestation of low ovarian reserve in non-GnRH analogue as well as GnRH analogue cycles (Younis et al., 1998, 2001). In these studies the P/E2 ratio on hCG day was presented in order to control for the ovarian response of each patient. Accordingly, a P/E2 ratio of >1 was related to low ovarian reserve and associated with reduced clinical pregnancy rate.

Moreover, in a previous study by Fanchin et al. (1997), elevated P level on hCG day adversely affected pregnancy rate only in the weak responder group. In women with intermediate and strong ovarian response, elevated P level on hCG day had no negative impact on IVF results.

Taken together, it seems that elevated P level on hCG day during COH for ART treatment in young normogonadotropic women is related to multiple follicular development and increased ovarian steroidogenic activity leading to P accumulation. Whether the same mechanism for the elevated P level could be employed for the low ovarian reserve patients is in question and other mechanisms should be explored.

Having said that, this raises the question as to whether the decreased pregnancy rate found in several reports and linked to elevated P level on hCG day, is due to the phenomenon itself or is it linked to the ovarian reserve of the patients studied. In other words, is it always the result of untimely P elevation causing asynchrony.
between embryo and endometrial dating adversely affecting endometrial receptivity? What is the role of embryo quality in these cases? Obviously, in low ovarian reserve infertile women that develop elevated P level on hCG day, their embryo quality does reduce pregnancy rate. Is it possible that the non-linear relationship between ongoing pregnancy rate and P level on hCG day, found by Bosch et al., is the result of a dual effect on pregnancy rate? One related to endometrial receptivity and the other to embryo quality.

Only conducting properly designed prospective targeted studies, that take into account all factors including ovarian response and type of gonadotrophin employed (with or without LH activity), could provide clear answers regarding elevated P level on hCG day and its influence on ART outcome. It is my opinion the time has come to do so.

References


Reply: Elevated P level on the day of hCG administration is related to FSH dose: is it the whole truth?

Sir,

We are grateful for Dr Younis’ letter supporting our view that an elevated progesterone (P) level on the day of hCG administration is detrimental to ART outcomes, despite conflicting prior reports in the literature (Bosch et al., 2010; Younis et al., 2010). We fully agree with him that there is a need for more research to understand the underlying mechanisms. More specifically, in Dr Younis’ letter the mechanism behind P elevation at the end of the follicular phase, and the influence of the ovarian response on the relationship between P levels and ongoing pregnancy rate, are discussed. Dr Younis further suggests that the elevated P levels may have a dual influence on pregnancy rate, one related to endometrial receptivity and the other to embryo quality.

With regards to the first issue, it seems clear that high dosages of FSH during stimulation are related to high P levels. This has not only been our observation in this study, but has also been shown before (Bosch et al., 2003) and by other authors (Adonakis et al., 1998; Filicori, 2002). Several authors have suggested that the negative impact of high P levels on cycle outcome is only relevant in poor responders (Fanchin et al., 1997) and poor responders require higher FSH dosages. In order to avoid any confusion on this relationship, we performed a stratified analysis according to ovarian response in terms of both number of oocytes collected, and serum E2. As shown in Fig. 3 of our manuscript, high P levels affected ongoing pregnancy rate in all ovarian response intervals. Obviously, patients with low response (one to five oocytes) showed a poorer outcome than the rest, but also good responders had a different outcome according to P. This means that, regardless of whether total P is a result of many follicles producing low amounts of P, or of just a few of them producing high amounts each, an elevated serum P affects cycle outcome. It is very probable that patients with a low response and high P (increased P/E2 ratio) have the poorest outcome because they have two bad prognosis factors, but supplemental Fig. 5 of our paper shows a lower pregnancy rate with higher P levels on the day of hCG irrespective of serum E2 levels (pg/ml).

Factors other than high dosages of FSH will contribute to P rise during ovarian stimulation (Fleming and Jenkins, 2010). If we analyse carefully the follicular steroidogenesis, we see that, while in the presence of LH the metabolism of pregnenolone (precursor of P) is promoted to androgens for later aromatization to estrogens, in the