## Pre-hCG elevation of plasma progesterone: good, bad or otherwise

Sir,

In the pre-GnRH analogue (GnRH-a) era, late follicular phase elevation of progesterone in IVF was taken as evidence of premature LH elevation and hence, correctly named 'premature luteinization'. The advent of GnRH-a, rapidly adopted in all IVF centres, allowed reliable suppression of LH throughout controlled ovarian hyperstimulation (COH) and thus, prevented premature luteinization. In the mind of all therefore, GnRH-a had definitively erased the pitfalls of pre-hCG progesterone elevation and its adverse consequences on IVF outcome. The reprieve, however, was going to be short-lived.

In 1991, a report from Schoolcraft *et al.* (1991) drew attention to the fact that in certain patients, progesterone still rose above normal follicular phase levels prior to hCG administration in spite of gonadotropin suppression by GnRH-a. In their patients, this was associated with an ominous prediction of IVF outcome. Soon, however, other reports came out with different conclusions on this issue, which created vast confusion. Attempting to separate the wheat from the chaff in the lingering debate over the consequences of pre-hCG progesterone elevation, Venetis *et al.* (2007) conducted a meta-analysis of published data. From their results, pre-hCG progesterone elevation did not adversely affect IVF outcome. We do not intend to minimize the value of this report but yet, we agree with the arguments voiced by Bosch (2007) and Fleming (2008) in Human Reproduction Update about the limitations of this meta-analysis.

Bosch (2008) alleges that a relationship between progesterone elevation and FSH administration likely exists and contends that it could have been identified had a multivariate analysis been conducted. Hence, FSH would be a confounding factor for the observed link between pre-hCG progesterone and E2 levels. This concept is supported by the results of a prospective trial showing that in COH, progesterone peaks higher when FSH rather than hMG is used (Smitz *et al.*, 2007).

Likewise, we concur with the methodological concerns raised by Fleming (2008). His comment in Venetis *et al.* (2007) meta-analysis rightfully stresses the fact that the assays used for measuring progesterone in the studies retained in the meta-analysis were neither conceived nor validated for measuring low levels of progesterone in the follicular phase. Fleming's own data showing that assay precision varied depending on whether a petrol-ether extraction step was used or not eloquently supports this methodological concern. This, therefore, emphasizes the weakness of the methodological grounds on which rest all the publications retained in the meta-analysis. Specifically, Fleming provides methodological evidence supporting the possibility that progesterone measurements at the end of COH treatments could have been flawed by patient-specific matrix effects (Fleming, 2008, in press).

To these concerns, we would like to add one more of our own in an effort to thoroughly review all the facets of this clinically relevant albeit puzzling hormonal maze. In previous work, we observed that pre-hCG progesterone elevation was associated with drastically different consequences on IVF outcome depending on whether it occurred in women whose COH yielded strong or weak responses, based on E2 and follicle data (Fanchin *et al.*, 1997). Our study was not retained in Venetis' meta-analysis, probably because of eligibility issues, something we do not intend to challenge here. Regardless of whether our study was included, we believe our conclusion that the consequences of pre-hCG progesterone elevation are COH-response dependant should be a part of the debate. Indeed, our observation of a link between the impact of pre-hCG progesterone elevation on IVF outcome and the type of COH-response (strong or weak) has not been challenged in $>10$ years. In a field in which contradiction looms large, this buttresses the likelihood that our finding is real.

Considering that the consequences of pre-hCG progesterone elevation on IVF outcome are COH-response related, we find that Venetis' report of higher $E_2$ levels in the high-progesterone group actually explains the lack of impact on IVF outcome. It indicates that in the high pre-hCG progesterone group, the poor responders to COH were diluted out by a larger number of high-COH responders. In this case, therefore, our own observation (Fanchin *et al.*, 1997) would have also predicted the no harm conclusions of the Venetis *et al.* (2007) meta-analysis.

Taken together, our comments and those of Bosch (2007) and Fleming (2008) concur in tempering the Venetis *et al.* (2007) conclusion that pre-hCG progesterone elevation bears no adverse consequences on IVF outcome. We indeed see two important limitations to this conclusion: (i) there is evidence of methodological flaws in the late follicular phase measurements of progesterone, which may have affected the results of an unknown number of studies retained in their meta-analysis and therefore impacted on the conclusions of the meta-analysis itself; (ii) until proven otherwise, the clinical consequence of pre-hCG progesterone elevation should be analyzed within the context of the ovarian response to COH in which it is encountered. When pre-hCG elevation is observed in case of a weak response to COH, we persist in thinking that it means a poor prognosis.

### References


Bosch E. Comment on: is progesterone elevation on the day of human chorionic gonadotrophin administration associated with the probability of pregnancy in in vitro fertilization? A systematic review and meta-analysis. By Venetis et al (2007). *Hum Reprod Update* 2008;**14**:194–195.

Fanchin R, Righini C, Olivennes F, Ferreira AL, de Ziegler D, Frydman R. Consequences of premature progesterone elevation on the outcome of in vitro fertilization: insights into a controversy. *Fertil Steril* 1997;**68**:799–805.

Fleming. *Hum Reprod Update* 2008;**14**:391–392.

Schoolcraft W, Sinton E, Schlenker T, Huynh D, Hamilton F, Meldrum DR. Lower pregnancy rate with premature luteinization during pituitary suppression with leuprolide acetate. *Fertil Steril* 1991;**55**:563–566.

Smitz J, Andersen AN, Devroey P, Arce JC; MERIT Group. Endocrine profile in serum and follicular fluid differs after ovarian stimulation with HP-hMG or recombinant FSH in IVF patients. *Hum Reprod* 2007;**22**:676–687.

Venetis CA, Kolibianakis EM, Papanikolaou E, Bontis J, Devroey P, Tarlatzis BC. Is progesterone elevation on the day of human chorionic gonadotrophin administration associated with the probability of pregnancy in in vitro fertilization? A systematic review and meta-analysis. *Hum Reprod Update* 2007;**13**:343–355.



D. de Ziegler[1], G. Bijaoui and C. Chapron

*Université Paris Descartes*
*Service de Gynécologie Obstétrique II et Médecine de la Reproduction*
*CHU Cochin Saint Vincent de Paul Paris, France*

[1]Correspondence address. E-mail: france.ddeziegler@bluewin.ch



doi:10.1093/humupd/dmn020
Advance Access publication June 2, 2008