Is it time to abandon progesterone supplementation of early pregnancy after IVF?

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It is estimated that a million couples receive IVF treatment globally every year (ICMART, 2009). The majority of women who become pregnant after IVF receive progesterone during the first trimester. A study conducted by Kyrou et al. published in the present issue of Human Reproduction challenges this concept for GnRH-antagonist treatment cycles and thereby adds to the growing concern that progesterone supplementation of early pregnancy after IVF might overall be unnecessary.

The scientific evidence on which progesterone supplementation of early pregnancy was introduced to the field is unfortunately weak and stems from only a single randomized study (Prietl et al., 1992) on 120 subjects. IVF patients who received a combination of intra-muscular estrogen and progesterone supplementation until 12 weeks of pregnancy had an ongoing pregnancy rate of 89% compared with only 59% in the group with no supplementation. Although these data may not pass rigorous re-assessment, they have formed the basis for a treatment standard, namely continuation of progesterone administration in early pregnancy after IVF. Accordingly, Crinone®, a vaginal progesterone formulation licensed for luteal phase support by the European Medicine Agency (EMEA), has on its label to continue administration ‘for 30 days if there is laboratory evidence of pregnancy’. The US Food and Drug Administration (FDA) label for the same product reads: ’If pregnancy occurs, treatment may be continued until placental autonomy is achieved, up to 10–12 weeks’. The same is in the posology for Utrogestan®, which is supposed to be administered until 12 weeks of gestation. Another vaginal progesterone preparation for use in IVF, Endometrin®, is supposed to start the ‘day after oocyte retrieval and continuing for up to 10 weeks total duration’ according to FDA labeling.

In this setting, clinicians now need to have a high level of confidence of not doing harm when routinely withdrawing early pregnancy progesterone supplementation from their patients. In other words, a conclusive ‘non-inferiority trial’ is required for that purpose (EMEA, 2006). In contrast to a superiority trial, the null hypothesis of the non-inferiority trial is that a difference of at least $\Delta x$ exists between two treatments. The trial is targeted at disproving this in favor of the alternative that no difference exists.

Thus, the task now is to prove that stopping progesterone with a positive pregnancy test is non-inferior to continuing progesterone in terms of live birth achievement. But what does ‘proving of non-inferiority’ mean in clinical and statistical terms?

In order to demonstrate non-inferiority, the recommended approach is to pre-specify a margin of non-inferiority in the protocol (which was $-7\%$ difference in live-birth rate in the trial by Kyrou et al., 2011). After study completion, a one-sided 97.5% interval for the true difference between the two treatments is constructed. This interval should lie entirely on the positive side of the non-inferiority margin with special note on the lower limit of the confidence interval, which represents the degree of inferiority to the reference that can be excluded (with an acceptable low chance of error) based on the data presented.

Figure I Power analyses for non-inferiority trials designed to detect non-inferiority margins from $-2\%$ to $-10\%$ (under the assumption that the reference group with early pregnancy progesterone administration achieves 80% live-birth rate; single-sided $z$-test, $\alpha = 0.025$, $\beta = 0.20$).
However, it can be assumed that even a much smaller $\Delta x$ (e.g. $-2$ to $-3\%$) would justify the use of progesterone in the eyes of the majority of clinicians given the effort of producing these pregnancies by IVF, and given that vaginal progesterone is comparatively cheap, safe and easy to administer. Moreover, a non-inferiority trial on live-birth rates requires a large number of participants to show that cessation of progesterone in early pregnancy is indeed not worse than the comparator by more than the pre-specified, small amount. Figure 1 depicts the necessary sample sizes to detect non-inferiority margin differences from $-2\%$ to $-10\%$. It can be seen that in order to reject the null hypothesis of, for example, a difference of $-4\%$ or larger from a live-birth rate of $80\%$, a sample size of $2140$ women with a positive pregnancy test after IVF would be required.

A number of retrospective studies have indicated that early pregnancy progesterone supplementation might not be necessary (Stovall et al., 1998; Stelling et al., 1999; Schmidt et al., 2001; Proctor et al., 2006). However, only a single randomized trial on IVF patients after ovarian stimulation in a long GnRH-agonist protocol (Nyboe-Andersen et al., 2002), as well as the present trial on GnRH-antagonist-treated patients (Kyrou et al., 2011) are available. In both studies, vaginal progesterone $3 \times 200$ mg/day was either discontinued with a positive pregnancy test or continued for 3–5 weeks. Figure 2 depicts absolute differences in live-birth rate or ongoing pregnancy rate with $95\%$ confidence intervals for the two trials. It can be seen that the lower bound confidence interval of the difference is $-3\%$ for the trial in GnRH-antagonist-treated patients, yet it is $-13\%$ for the trial in long GnRH-agonist-treated patients.

So is it time to abandon early pregnancy progesterone supplementation in IVF? The answer is: not yet. First, studies with larger sample sizes are necessary to clearly establish non-inferiority for both GnRH-agonist and GnRH-antagonist protocols. In this context clinicians need to decide on a minimally important effect size (the $\Delta x$), or in other words: ‘how many women would we be prepared to unnecessarily treat with progesterone to save one pregnancy from aborting?’ Secondly, subsequent studies should include patients of advanced age, polycystic ovary syndrome, patients with inadequate hCG rise, early bleeding or endometriosis (these patient categories have been excluded in either trials by Kyrou et al. or Andersen et al., respectively), and stratify the outcome for these patient groups. Thirdly, in subsequent studies a placebo control group should be established (or patient compliance with allocation should be monitored). Finally, other routes of administration, doses and formulation of progesterone are employed for early pregnancy supplementation and care should be taken to not unduly extrapolate the findings from studies with vaginal administration of progesterone.

However, Nyboe-Andersen et al. and Kyrou et al. have to be highly credited for having conducted these studies, which may ultimately mark the beginning of the end of early pregnancy progesterone supplementation in IVF. Taking the sheer number of globally performed IVF cycles and the associated discomfort and costs of progesterone treatment into account, further studies are urgently needed. The data that we have by now provides a well-founded basis for designing future trials and will facilitate patient recruitment into such trials.

### References


