

### Endogenous LH surge detection versus administration of HCG to correctly time intrauterine insemination: which provides a better pregnancy rate?

Dear Sir,

We have read with great interest the paper by Awonuga and Govindbhai (1999), investigating in a retrospective design whether or not waiting for a spontaneous LH before administering HCG in the presence of mature follicle(s) provided a higher probability of pregnancy. In their study, the authors did not find any difference in the pregnancy rate among the three different forms studied to time the artificial insemination: (i) endogenous LH surge; (ii) HCG administered after the LH surge was detected; and (iii) HCG given before the LH surge was observed.

Their study provides further data to the continuing debate on the best method available for ovulation prediction and detection for optimal timing of artificial insemination in order to achieve an optimal pregnancy rate. However, some methodological questions are raised. Urinary LH monitoring has its limitations, and false-negative results can occur if peak LH concentrations are <40 IU/l, something that may occur in up to 35% of ovulatory cycles (Arici *et al.*, 1992). When LH kits alone were used to time intrauterine insemination (IUI), 36% of inseminations were timed incorrectly (Lloyd and Coulman, 1989). Furthermore, some women may ovulate before LH can be detected in the urine (Irons and Singh, 1994). On the other hand, the follicular size detected by ultrasound does not predict ovulation because of the wide variability in preovulatory follicle size (Vermesh *et al.*, 1987). In addition, the interval between HCG injection and follicle rupture assessed by transvaginal ultrasonography is highly

variable, in the range 34–46 h (Andersen *et al.*, 1995). Thus a combined approach may prove of benefit, although the results published by Awonuga and Govindbhai (1999) do not support this hypothesis, probably due to their study design.

The authors themselves state that the retrospective design of their study may bias the results. Indeed, a retrospective study is less likely to have clearly defined criteria for patient inclusion, the quality of the recorded data is inferior, and non-randomized trials have the potential to provide a very distorted view of the problem. There are already several retrospective studies in the literature showing no statistically significant differences in pregnancy rate between these two methods of ovulation monitoring. A much stronger evidence of any scientific hypothesis is provided by prospective, randomized, controlled studies.

We recently published the first prospective, randomized, cross-over study in the literature to our knowledge that evaluates the benefit of HCG-timed versus LH-timed IUI in clomiphene citrate-stimulated cycles (Zreik *et al.*, 1999). This study showed no statistically significant differences in the pregnancy rate with the use of HCG induction versus LH monitoring to time of IUI (4.22 versus 4.29% respectively). However, we should remember that failure to show a statistically significant difference does not mean that there is no difference. If the results of all well-designed studies are published, future systematic reviews and meta-analysis will include these data from small randomized trials, and then we will definitely know if one of these two monitoring methods (or the combination of both) provides any advantage.

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Dear Sir,

We thank Garcia-Velasco *et al.* for their interest in our paper (Awonuga and Govindbhai, 1999) regarding the benefit or otherwise of waiting for a spontaneous LH surge before administering HCG in the presence of a mature follicle in intrauterine insemination (IUI). Our study listed the reasons why this strategy might lead to a better pregnancy rate in IUI. The potential benefit of such an approach was the reason for its introduction as an option for timing insemination in our IUI programme. However, the findings from our study did not support this hypothesis.

We concur with Garcia-Velasco *et al.* that failure to show a statistically significant difference does not mean there is no difference. Indeed, we devoted the last paragraph of our paper to the shortcomings of our retrospective design. Only one study to date (Fuh *et al.*, 1997) has suggested that a better pregnancy rate is achieved when HCG is given following the demonstration of an LH surge in artificial insemination. This study also used a retrospective design, which represents inferior evidence. It is well known, that studies in which treatment is allocated by methods other than randomization tend to show larger treatment effect than do randomized trials (Sacks *et al.*, 1983).

We are familiar with the paper by Zreike *et al.* (1999). In a prospective, randomized, cross-over study (which is not without its limitations; Khan *et al.*, 1996), they compared HCG timed to urinary LH timed IUI in clomiphene citrate-stimulated cycles. Their conclusion (the same as in our own study) is that timing IUI with ultrasound monitoring and HCG induction of ovulation does not appear to produce an increased pregnancy rate over urinary LH monitoring of ovulation. In the light of available data, there is no evidence that a combined approach using ultrasound and HCG is of benefit over ultrasound and LH surge. We went further in our paper and unlike the finding by Fuh *et al.*, (1997), found that even when all the three modes of timing ovulation are combined (ultrasound monitoring, urinary detection of LH surge and HCG administration) for IUI, pregnancy rate is not necessarily improved.

We agree that urinary LH monitoring does have its limitations. Two retrospective studies (Brook *et al.*, 1994; Horne *et al.*, 1998), reached conflicting conclusions when insemination cycles were monitored by serum compared with urine LH assay. Whether serum LH monitoring will improve the pregnancy rate over and above that offered by urinary home LH testing remains to be confirmed by a well-controlled study. We believe that until the advantage of serum over urine LH testing is proven, the benefits of home urine LH testing kits should not be dismissed lightly. Apart from the invasive nature of serum LH testing, there is the inconvenience and the cost of travelling to the clinic together with the need for trained personnel. Another obvious disadvantage of blood measurements arises in the case of hormones displaying pulsatile secretion, as is the case with oestradiol and LH, where a single measurement may not be representative of the prevailing secretion rate. Urinary LH sampling, on the other hand, will integrate any episodic variation in secretion. It is also pertinent to realise that whether blood or urine testing is

used, timing the exact onset of the LH surge requires the collection of urine or blood samples every few hours over a period of 2–3 days which is not practical with blood samples.

Certainly, more prospective randomized controlled studies followed by meta-analysis of these studies will be required to determine whether in the presence of a mature follicle there is any benefit in waiting for the LH surge before administering HCG in patients having IUI. Such studies need to take into consideration all of the confounding variables that are likely to affect the pregnancy outcome.

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