fertility clinics. The authors correctly point out that the delivery rates reported from a number of countries are unrealistically low. First of all, we are pleased that the authors appreciate the difficulties encountered in many clinics and registers regarding adequate follow-up of the outcome of pregnancies. Even though it may be difficult, we can only define the optimal end-point in ART, the birth rate, through complete and accurate reporting on deliveries. The concern is how to report in an appropriate way on birth rates in a world with incomplete follow-up on pregnancies. As this problem is likely to be consistent, at least for several years to come, it is appropriate to discuss how we should report on deliveries after ART.

The authors provide four examples. The extreme is the Netherlands, where no births were reported following treatment in 2005. The reason is that the National ART Register in the Netherlands has so far not included recording of any data on deliveries. We have not stated that it was 0, but we have simply left the spaces open in Tables VI and VII. Indeed, we could have made a footnote and stated this more explicitly, or indicated ‘NA’ for not available.

Regarding the data from the other three countries: Italy, Spain and Turkey, it is also correct that the decline from the reported number of pregnancies to number of deliveries is huge. If we look at the ICSI data in Table VII, deliveries accounted for 43% (Italy), 44% (Spain) and 22% (Turkey) of the reported pregnancies. Evidently, this is underreporting of deliveries. The ideal would of course be to have complete recording of deliveries, or at least to have data on the number of pregnancies "lost for follow-up". However, neither is recorded adequately in the registers at the present time.

In the EIM, we could provide estimations on the number of deliveries. From Table VII, we could select 12 countries (Belgium, Czech Rep, Denmark, Finland, France, Germany, Norway, Portugal, Slovenia, Sweden, Switzerland and the UK) as a reference, because these ART registers have consistently reporting delivery rates for several years. These countries reported 26 980 ICSI pregnancies which resulted in 20 465 (76%) deliveries. It thus seems that around 76% of the pregnancies will result in birth, but the variability is not negligible, as it ranged from 64% in Germany to 89% in the UK. In Germany, the documented number of miscarriages does not cover the difference between pregnancy and delivery rates, as almost 1000 pregnancies are true lost for follow-up. Therefore, the accurate figure on deliveries is undoubtedly higher. The calculations illustrate, however, that it will remain difficult to provide a reliable estimation of the true number of deliveries.

In both Tables VI and VII, a footnote is included stating that the recording of deliveries is incomplete. I presume that most professionals will realise this, but as Dr Ata and Urman stated, it is important because the data should be disclosed to the public, and misinterpretations may occur. We therefore agree with them that we should have addressed this issue more clearly.

In the EIM, we could simply have omitted all data on deliveries. We have discussed this option, but indeed both among professionals and patients, deliveries are the objective of ART and remain our gold standard in relation to defining efficacy. We therefore feel that the reporting of deliveries should be included—also in order to stress the importance of this key parameter.

A third possibility is to censor the reporting and only report on deliveries in those countries where we believe that the reporting is rather accurate. The problem here will of course be how to define the threshold for the lowest acceptable level of incompleteness of reporting. It could be easy if only one-third of all pregnancies resulted in a reported delivery, but what about for instance Russia where the number of deliveries reported was 59% of the recorded pregnancies in 2005. Should we then report deliveries from Russia or just delete the number available?

Our suggestion is that both National and Regional registers like the EIM continue to report on deliveries, but that we try to be more explicit in order to explain the inadequacy of the reporting on deliveries. Finally, we would like to use this correspondence to stress the importance of establishing statutory registers, where recording of deliveries is compulsory and where data are validated.

### Reference


Baris Ata1,2 and Bülent Urman1,3

1Department of Obstetrics and Gynecology, The Assisted Reproduction Unit of the American Hospital of Istanbul, Guzelbahce Sokak No.20, Nisantasi Istanbul 34365, Turkish Republic

2Present address: McGill Reproductive Centre, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, McGill University Health Centre, Montreal, Canada

3Correspondence address: E-mail: burman@superonline.com
doi:10.1093/humrep/dep388

Advanced Access publication on December 4, 2009

### Reply: ART register data on delivery rates

Sir,

We would like to thank Dr Ata and Dr Urman for their interest in the reporting on delivery rates by the European IVF Monitoring (EIM) consortium of ESHRE (Nyboe Andersen et al., 2009).

The authors correctly point out that the delivery rates reported from a number of countries are unrealistically low. First of all, we are pleased that the authors appreciate the difficulties encountered in many clinics and registers regarding adequate follow-up of the outcome of pregnancies. Even though it may be difficult, we can only define the optimal end-point in ART, the birth rate, through complete and accurate reporting on deliveries. The concern is how to report in an appropriate way on birth rates in a world with incomplete follow-up on pregnancies. As this problem is likely to be consistent, at least for several years to come, it is appropriate to discuss how we should report on deliveries after ART.
Reply: GnRHa to trigger final oocyte maturation: a time to reconsider

Sir

We are pleased by the feed-back from Dr Youssef et al., regarding our latest review on the most recent clinical trials employing a GnRH agonist (GnRHa) to trigger final oocyte maturation (Humaidan et al., 2009c). In this review we conclude, from our own published results and the results of other trials, that GnRHa triggering of final oocyte maturation is now a valid alternative to hCG triggering, taking into account that additional luteal phase support in terms of LH activity supplementation is mandatory.

In our review we, among others, refer to the results of the largest RCT (302 patients) until now on GnRHa triggering of final oocyte maturation (Humaidan et al., 2009a), reporting a non-significant difference in live birth rate between GnRHa triggering and hCG triggering (24 versus 31%, respectively). These results thus corroborate the results of a previous pilot study (Humaidan et al., 2006), showing that supplementation with a small bolus of 1500 IU hCG on the day of oocyte aspiration, rescues the luteal phase and secures the reproductive outcome when GnRHa is used to trigger final oocyte maturation.

We have thus come a very long way since the disappointing reports from the first RCTs focusing on the reproductive outcome when GnRHa was used to trigger final oocyte maturation (Humaidan et al., 2005; Kolibianakis et al., 2005). In these studies an extremely low ongoing pregnancy rate (6%) and an unacceptably high early pregnancy loss rate (80%) was reported, despite standard luteal phase support with vaginal progesterone and estradiol.

As we discuss in our review, the reason for the low reproductive outcome seen previously when GnRHa was used to trigger final oocyte maturation, seems to be an LH depleted luteal phase, induced not only by differences in the profile and duration of the surge of gonadotropines, elicited by a bolus of GnRHa (Gonen et al., 1990; Itskovitz et al., 1991), but also by the supraphysiological steroid level (estradiol and progesterone), exerting a negative feedback on LH secretion by the pituitary (Tavaniotou et al., 2001; Tavaniotou and Devroey, 2006).

With the latest research, adding LH activity to the luteal phase after GnRHa triggering in addition to the standard luteal phase support with estradiol and progesterone, it thus seems that we have detected the problems of the luteal phase insufficiency previously seen.

Youssef et al. (2009) refer to their Cochrane review, presented at this years ESHRE meeting. This review includes a total of 713 patients randomized to either GnRHa or hCG for triggering of final oocyte maturation. The authors conclude that although GnRHa triggering significantly reduces moderate/severe OHSS, ‘GnRHa triggering results in significantly lower birth rate and ongoing pregnancy likelihood— and should, therefore, not be used in general practise for final oocyte maturation’.

We, like others, believe in the strength and relevance of meta-analyses. However, the relevance of a meta-analysis including 713 cycles only, should be critically questioned, especially if studies included also have employed different modes of luteal phase support. In addition, although moderate/severe OHSS has a low incidence after ovarian stimulation, it still represents the main morbidity and mortality cause in IVF. In this context, GnRHa triggering is of paramount importance in high responder patients (Griesinger et al., 2007; Humaidan et al., 2009b).

Moreover, the fact, that the implantation rate after hCG triggering in IVF is approximately 30% at its best, indicates that the luteal phase is probably the last black box in ART, irrespective of the mode of triggering. Therefore, the understanding of the luteal phase is of immense importance for the improvement of our results to the benefit of the patient.

GnRHa triggering of final oocyte maturation has taught us that the commonly used luteal phase support in IVF does not secure a functional endometrium. Instead of meta-analyzing studies employing different luteal phase support schemes, lessons from the luteal phase support from GnRHa triggering, should be extended to luteal phase support after hCG triggering in order to find the most appropriate protocol for luteal phase support.

In conclusion, we have only just started to understand the problems concerning the luteal phase insufficiency seen after GnRHa triggering. The results of the largest RCT, using a supplementary bolus of 1500 IU hCG on the day of oocyte aspiration in addition to a standard luteal phase support, now show a non-significant difference in live birth rate (24 versus 31%). We are thus on the right path. Moreover, the fact that no OHSS was seen and that more MII oocytes were retrieved in the GnRHa group further encourages us to refine the GnRHa triggering protocol. This could eventually lead to a paradigm shift from hCG triggering to GnRHa triggering, coinciding with the increasing use of GnRH antagonist protocols.

References


A. Nyboe Andersen1, J de Mouzon and KG Nygren. On behalf of The European IVF Monitoring (EIM) Consortium ESHRE.

1Correspondence address. E-mail: anders.nyboe.andersen@rh.regionh.dk

doi:10.1093/humrep/dep389 Advanced Access publication on December 5, 2009

Reference