Clinical relevance for the fact that GnRH antagonists do not down-regulate the GnRH receptor

Sir,

It has been more than 10 years since safe and effective gonadotrophin-releasing hormone (GnRH) antagonists became available for use in controlled ovarian stimulation (COS) cycles. In 2000, we noted that there was an inconsistency with how researchers in this field describe the mechanism of action of GnRH antagonists (Mannaerts and Gordon, 2000). Unfortunately, there is continued misuse of terminology describing the differences in the mechanism of action of the two classes of GnRH analogues in articles published in Human Reproduction and Fertility and Sterility (Huang et al., 2012; Youssef et al., 2012). References to ‘GnRH antagonist down-regulated cycles’ or ‘pituitaries desensitized to GnRH antagonists’ are inaccurate and lead to confusion.

GnRH agonists have been used clinically since the mid-1980s to prevent the occurrence of a surge in LH, which may occur prematurely before the leading follicle reaches the optimum diameter for triggering ovulation with human chorionic gonadotrophin (Gordon and Hodgen, 1991). GnRH agonists reduce the incidence of a premature LH surge by suppressing gonadotrophin levels via pituitary desensitization and down-regulation following an initial short period of gonadotrophin hypersecretion (Conn and Crowley, 1991). Unlike GnRH agonists, GnRH antagonists cause an immediate and rapid inhibition of LH release by competitively blocking GnRH receptors in the anterior pituitary gland and thereby preventing endogenous GnRH from inducing LH and FSH release from the pituitary cells (Gordon and Hodgen, 1991). GnRH antagonists have the formal regulatory indication of prevention (inhibition in the USA) of premature LH surges in women undergoing COS prior to IVF/ICSI in most countries.

The fundamental mechanistic difference between GnRH agonists and antagonists has gained clinical significance as it has become apparent that ovarian hyperstimulation syndrome can largely be avoided by using a GnRH agonist bolus to trigger an endogenous LH/FSH surge to produce final oocyte maturation (Ron-El et al., 2000; Humaidan et al., 2010; Devroey et al., 2011). Importantly, this can only be achieved in a GnRH antagonist protocol as an LH/FSH surge cannot be induced with a GnRH agonist if the pituitary is down-regulated and/or desensitized.

Hence, in an attempt to simplify things moving forward we propose that the terms ‘pituitary inhibition’ or ‘pituitary suppression’ are used to signify the actions of GnRH antagonists and the terms ‘down-regulation’ and ‘desensitization’ are used to define the actions of GnRH agonists.

References


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Elective single-embryo transfer in older women

Sir,

We thank Dr Gleicher for his commentary concerning our article ‘Elective single-embryo transfer in women aged 40–44 years’ (Niinimäki et al., 2012; Gleicher, 2012). We understand that in many countries the reimbursement system makes the implementation of the elective single-embryo transfer (eSET) into clinical practice very difficult. However, in the opinion article there are some misinterpretations of our findings, which we would like to correct.

The aim of our retrospective study was to look at the effect of eSET on pregnancy and live birth rates in women 40 years or older, as this embryo transfer strategy has not yet been studied in older patient population (Niinimäki et al., 2012). To evaluate the usefulness of eSET, it is essential to calculate the cumulative pregnancy rate including both fresh and frozen embryo transfers of one oocyte collection,
because only these figures show the real efficiency of the program (Veleva et al., 2009).

One of the main findings in the present study was that even among older women there is a wide variation in the prognosis of the treatment (Niinimäki et al., 2012). As well as in any other age group, it is possible to select good prognosis women for eSET and at the same time maintain a good pregnancy rate as well as low multiple pregnancy rate. In our opinion, it is very important to maintain a low risk of multiple pregnancies among women over 40 years of age as women in advanced age have clearly increased risk of pre-eclampsia, impaired glucose tolerance and obesity than younger women (Lamminpää et al., 2012). We find that it would be irrational, or even unethical, to accept higher multiple birth rate among older women, if it is avoidable.

We want to emphasize that our study was not randomized, and the two groups [eSET and double-embryo transfer (DET)] were highly selected by design. Therefore, the two study groups were not equal regarding the prognostic factors. Hence, the low number of twins in the DET group only indicated that the criteria for eSET or DET were feasible in the clinical practice, and not that DET would be a good option in all women in that age group.

At our clinic all couples were carefully counselled by an experienced doctor on the benefits and risks concerning SET and DET in their particular situation. The opinion of the patients was taken into account and DET was performed if this was the wish of the couple and there were no medical contraindication for a twin pregnancy. We disagree with Gleicher (2012), that our patients’ preferences would have been ignored for the sake of eSET policy.

As stated in our paper, eSET should not be recommended to all IVF patients. The proportion of women suitable for eSET is lower among older age groups, as was also shown in this study. However, if the aim is to decrease risks and thus the number of multiple births, the advantages of eSET have been shown in many countries. By allowing two or even more high-quality embryos to be transferred among older women would expose many women to excessive risk of multiple birth and possible pregnancy complications.

During the last 10 years eSET policy has been adopted in many countries. As far as we know nowhere a drop of overall success rate has been reported while the safety of the treatment, including perinatal outcome, has been significantly improved.

Our study shows that the same criteria as for performing eSET in younger women can also be applied to women older than 40, which could encourage clinics to expand their indications for eSET. We look forward to see if our experience will be confirmed by other investigators. By sharing experiences of different treatment policies it is possible to find the optimal treatment mode in this challenging patient population.

**References**

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**Risks of untreated depression outweigh any risks of SSRIs**

Sir,

A recently published article (Domar et al., 2013) is misleading and harmful. We belong to a worldwide network of professionals who treat psychiatric illness in pregnancy and post-partum and we conclude that, aside from a possible slightly increased risk of miscarriage, selective serotonin re-uptake inhibitors (SSRIs) are relatively safe for use in pregnancy and post-partum (Einarson et al., 2009a,b).

SSRI use in pregnancy is usually considered in the setting of a moderate–severe depressive disorder, not in the context of depressive symptoms associated with infertility. The risk of relapse of depression for those who stop using psychotropic medication during pregnancy is 68% (Cohen et al., 2006). Prenatal depression can lead to missed obstetric appointments, poor diet and sleep, substance abuse and an increased risk of suicide. Women with untreated depression during pregnancy have an increase in preterm births and low birthweight babies due to the depression itself (Wisner et al., 2009). Grote et al. (2010) found delivery dates of 38.5 weeks for those on SSRIs versus 39.4 weeks for depressed women not taking medication and 39.7 weeks for controls, a finding of questionable clinical significance. Therefore, untreated prenatal depression is not beneficial for either the mother or baby.

Concerning the ‘neonatal syndrome’ found in some newborns taking SSRIs, Moses-Kolko et al. (2005) found 10–30% of neonates exposed to SSRIs in utero experienced increased muscle tone, tremulousness, jitteriness, and feeding and sleep problems as well as respiratory difficulties. However, the majority of the infants experienced transient, mild effects that required only supportive care and spontaneously resolved by 2 weeks of age, far better than the infant being cared for by a woman with a severe post-partum depression.

Pulmonary hypertension of the newborn (PHHN) is a serious but rare disorder. The study by Chambers et al. (2006) that first indicated an association between third trimester use of SSRIs study included only 14 cases and 6 controls and relied on after-the-fact patient interviews and incomplete records. 99.5% of the case