Reply to: Are laparoscopic ovarian diathermy and gonadotropin administration the only therapeutic second-steps in clomiphene-citrate resistant women with polycystic ovary syndrome?

Sir,

We would like to thank Dr Palomba and colleagues for their interest in our paper (van Wely et al., 2004). In Western Europe, recombinant FSH is most commonly used for ovulation induction in women with polycystic ovary syndrome (PCOS) that does not respond to clomiphene citrate (CC). Urinary FSH is practically not used anymore in The Netherlands. The only alternative gonadotrophin to rFSH that is available on the market is human menopausal gonadotrophin (hMG). We agree with Dr Palomba and colleagues that there is no evidence of a difference in effectiveness and safety between rFSH and hMG for this indication (van Wely et al., 2003; Bayram et al., 2004). However, we chose to compare a laparoscopic electrocautery strategy with rFSH, as ovulation induction with rFSH best represents current practice in the Netherlands.

In their response, Dr Palomba and colleagues also emphasize the role of metformin. At the time of designing our study, both laparoscopic electrocautery strategy and rFSH were established therapies, while metformin was not yet being used in PCOS. During the last few years it has become common practice to use metformin, generally as co-treatment, for ovulation induction in women with polycystic ovary syndrome. In a recently published Cochrane review, metformin and CC were shown to result in a higher ovulation rate than clomiphene citrate combined with a placebo in women with CC-resistant PCOS (risk rate using a random effect model: 2.31, 95% CI 1.08–4.96; Lord et al., 2004). This result was based on five trials, with a total number of only 71 versus 70 clomiphene citrate resistant women.

Following these results, it can be concluded that metformin may be of value for ovulation induction in women with polycystic ovary syndrome. Given the small numbers, we feel there is not enough ground for drawing definitive conclusions in favour of metformin. Although metformin seems to be a relatively safe medication, it should not be forgotten that metformin is associated with a high incidence of nausea, vomiting and other gastrointestinal disturbance (Lord et al., 2004).

Furthermore, although there are indications that metformin can improve ongoing pregnancy rates, data regarding metformin safety during pregnancy are very limited (Glueck et al., 2001; Jakubowicz et al., 2002; Heard et al., 2002). Therefore, we should not prescribe metformin during pregnancy before large randomized controlled trials have been performed in which the safety and benefit is proven.

We look forward to the publication of the randomized trial by Palomba et al. (2004) in which metformin is compared with laparoscopic electrocautery in CC-resistant women with PCOS.

References


Madelon van Wely1,3, Neriman Bayram1, Fulco van der Veen1 and Patrick M.M. Bossuyt2

1Center for Reproductive Medicine, Department of Obstetrics and Gynaecology and 2Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

3To whom correspondence should be addressed.

E-mail: M.vanWely@amc.uva.nl

doi:10.1093/humrep/deh469

Mechanisms regulating the expression of indoleamine 2,3-dioxygenase during decidualization of human endometrium

Sir,

The recent interesting work of Kudo et al. (2004) prompted us to comment on the presented data regarding indoleamine 2,3-dioxygenase (IDO) expression. The authors performed an investigation evaluating IDO mRNA levels in non-pregnant endometrium, decidua as well as in decidualized endometrium from ectopic pregnancies.

Using RT–PCR, the authors found IDO mRNA expression to be higher during decidualization of human endometrium...
as compared with non-pregnant endometrium, which may point to a possible significance of IDO for gestation. The authors suggest that the measured mRNA results from decidual stromal cells, but they do not describe the purification of stromal cells prior to RNA extraction. Endometrial samples always consist of a mixture of cells including a variety of immune cells (Starkey et al., 1991). IDO is known to be expressed in immune cells, such as activated dendritic cells (Hwu et al., 2000). These cells can be found both in endometrium and in decidua, and therefore it is difficult to determine whether the detected IDO mRNA originates from immune cells or from stromal cells. The experiments were not designed to discriminate which cell type is the source of IDO expression.

Some of the immunohistochemical results of Kudo et al. (2004) may raise doubts. We evaluated the monoclonal and polyclonal antibodies by Chemicon as well as the monoclonal antibody used by Kudo et al. The polyclonal antibody was first described by Munn et al. (2002) who demonstrated its application in immunohistochemistry. When testing the monoclonal antibody as used by Kudo et al., we achieved results which resembled those which are presented in their paper. It was mainly the cells with high concentrations of Fc-receptors that have the capacity to bind antibodies specifically on their surface, such as syncytiotrophoblast, endothelia and mast cells which were stained positive. In contrast, the use of the polyclonal antibody led to clear and reproducible staining results. We mainly found specific IDO expression in the extravillous trophoblast (Honig et al., 2004).

On account of the contradictory results obtained with the two antibodies, we compared their ability to detect IDO in interferon-γ (IFN-γ)-stimulated mature dendritic cells, which are known to express this enzyme extensively (Hwu et al., 2000). While reliable results in terms of IDO detection were gained with the polyclonal antibody, the monoclonal antibody only led to a faint staining of the cells.

Furthermore, Kudo et al. (2004) used a secondary antibody system that usually enhances the signal. This enhancement is caused by the multiple phosphatases bound to the secondary antibody which lead to rather strong signals. When taking that into consideration, the visualization in the presented immunohistochemical figures appears rather weak.

The authors describe two opposing factors that influence IDO expression. IFN-γ stimulates and progesterone suppresses IDO expression. Drawing conclusions from a cell culture system for the decidualization in vivo is difficult. Levels of IFN-γ and progesterone might not be the same, and other factors for IDO regulation could be missing (Carlin et al., 1987).

As IDO has been gaining increasing scientific attention, future experiments might show how significant its expression is for human gestation.

References


A. Honig, L. Riger, J. Dietl and U. Kämmerer
Department of Obstetrics and Gynaecology,
University of Würzburg, Josef-Schneider str.4,
D-97080 Wuerzburg, Germany

E-mail: FRAK057@mail.uni-wuerzburg.de
doi:10.1093/humrep/deh477