Associate editor’s commentary on ‘Beneficial effect of luteal-phase GnRH agonist administration on embryo implantation after ICSI in both GnRH agonist- and antagonist-treated ovarian stimulation cycles’ by Tesarik et al.

GnRH agonist for luteal support in IVF? Setting the balance between enthusiasm and caution

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GnRH induces LH and FSH secretion by the pituitary gonadotroph cells in an orderly way, which is crucial for the control of gonadal function. Sustained stimulation of the pituitary with GnRH itself or with a GnRH agonist causes desensitization resulting in partial chemical reversible hypophysectomy that has become one of GnRH agonist applications as the cornerstone adjuvant medical treatment for disseminated prostate cancer and as an important tool in medical treatment of other sex steroid-dependent disorders such as leiomyomata and endometriosis.

However, nowadays, the most widely used application is with hormonal treatment protocols for women undergoing IVF. Although the first IVF treatments ever performed were in a natural cycle, it became clear that more success was obtained if more than one oocyte could be retrieved at a time, and thus, ovarian stimulation with gonadotrophins was introduced but with one important disadvantage namely the not infrequent premature luteinization due to the untimely occurrence of an LH surge. Confronted with this problem, Porter et al. (1984) published for the first time in this context, based on the brilliant idea of Fleming et al. (1982) to apply GnRH agonist for blockade of the pituitary LH (and FSH) surge by desensitization of the gonadotroph cells. Subsequently, Fleming et al. (1985) reported the success of this strategy in ovulation induction for polycystic ovary syndrome. Within no time, this application became part of the standard procedure and was shown to be highly beneficial in terms of outcome of IVF (Hughes et al., 1992). Remarkably, the rapid and widespread adoption of this strategy took place before the availability of any proper dose-finding studies, and safety data were available. For practical reasons, daily GnRH agonist dosages known to effectively block gonadotroph secretion in cancer patients were used. It took 16 years before the first (and only) placebo-controlled dose-finding study of ‘long protocol’ GnRH agonist was published that showed (i) premature luteinization occurs in about 25% of IVF cycles and (ii) that a much lower than usual dose was just as effective in preventing this (Janssens et al., 2000).

Nowadays, application of the GnRH agonist in preventing premature luteinization is not alone in the field as the use of a GnRH antagonist enables instant prevention of the surge. Fortunately, as a lesson from the past, introduction of these antagonists was preceded by necessary strenuous dose-finding and safety studies (Albano et al., 1997; The ganirelix dose-finding study group, 1998; Huirne et al., 2004).

With regard to safety, greatest concern existed about possible adverse effects on oocytes and, more importantly, the embryo. Until today, there are no data that indicate that application of GnRH agonist and antagonist for prevention of premature luteinization in IVF harms the embryo. The assurance that today’s safe use is warranted is partly based on the notion that administration takes place before embryo transfer thus minimizing the chance of embryonic exposure. In addition, the relative assurance that human embryonic exposure will not be harmful is based on series of individual case reports about accidental administration to pregnant women (Golan et al., 1990; Isherwood et al., 1990; Ron-El et al., 1990; Smizt et al., 1991; Jackson et al., 1992; Balasch et al., 1993; Elefant et al., 1993; Har-Toov et al., 1993; Weissman and Shoham, 1993; Wilshire et al., 1993; Young et al., 1993; Gartner et al., 1997).

This potted history becomes of relevance in the light of recent new developments. Over the past several years, there has been continuous concern with regard to luteal phase deficiency as a particular problem of the IVF-stimulated cycle (Macklon and Fauser, 2000), and various ways are practised to prevent this such as by giving hCG, progesterone and sometimes estradiol (E2). Recently, several investigators have reported independently on the potential use of the GnRH agonist in the luteal phase for support (Tesarik et al., 2004; Pirard et al., 2005; Hugues et al., 2006; Pirard et al., 2006; Tesarik et al., 2006).
The first was the report by Tesarik et al. (2004). They envisaged luteal administration as a voluntary therapeutic action to enhance implantation based on the impression that the inadvertent GnRH agonist administered in the luteal phase supported rather than compromised implantation (Golan et al., 1990; Isherwood et al., 1990; Ron-El et al., 1990; Smits et al., 1991; Jackson et al., 1992; Balasch et al., 1993; Elefant et al., 1993; Har-Toov et al., 1993; Weissman and Shoham, 1993; Wilshire et al., 1993; Young et al., 1993; Gartner et al., 1997). In a prospective randomized manner in an oocyte donor programme, two recipients received either a single injection of GnRH agonist (triptorelin) 6 days after ICSI or a placebo sharing the oocytes from a single donor (Tesarik et al., 2004). Implantation rate and birth rate were substantially higher after luteal phase agonist administration with, in particular, more twin pregnancies and deliveries. Pirard and co-workers reported on the use of intranasal GnRH agonist buserelin for induction of final oocyte maturation and support of the luteal phase in IUI and IVF patients (Pirard et al., 2005, 2006) and concluded that this scenario could be effective in particular in GnRH antagonist-treated IVF patients.

In this issue of Human Reproduction, Tesarik and co-workers (2006) now present a large trial (600 participants) in which GnRH agonist or antagonist pre-treated-IVF patients who received hCG for final oocyte maturation were thereafter randomly assigned to receive a single injection of 100 μg triptorelin or placebo 6 days after ICSI. They observed that the luteal phase administration of agonist improves implantation rate and live birth rate per embryo and ongoing pregnancy rate. The administration of a single dose of agonist yielded increased hCG levels 15 days after ICSI in the conception cycles.

In this study, they now report the remarkable observation that the luteal phase administration of a single dose of agonist strongly improves pregnancy rates in patients who received antagonist for pituitary suppression. At this moment, it is difficult to explain this significant effect. Theoretically, the effect has to take place either through (i) improvement of the function of the corpus luteum, (ii) improved function of the endometrium or (iii) a direct effect on the embryos or through some combination of these possibilities. The authors suggest possible direct effects on the embryo, because (i) optimal administration of the conventional hormones hCG, P and E₂ to ensure maximal corpus luteum and endometrium support was given and (2) that the higher hCG levels in the conception cycles reflect an embryonic effect. So far it seems far from clear what is happening. Unfortunately, the study by Tesarik does not provide detailed luteal phase endocrine data, but Hugues et al. (2006) in a preliminary report of an ongoing similar trial do not observe any substantial differences in hormonal data during the luteal phase. At this stage, a direct effect of the agonist on the endometrium mediated through locally present GnRH receptors can certainly not be ruled out.

On the basis of the available data, it may seem attractive to consider administration of a GnRH agonist in the IVF luteal phase to improve pregnancy rates by perhaps 10%. In our view however, it is too early to adopt this step wholesale despite the apparent attraction that the drug can be easily prescribed—it is only one injection and the effect seems impressive.

Much more work needs to be done. In the first place, the results need to be replicated. Second, we need to know more about the possible mechanism of action, and, as learnt from history, detailed knowledge has to be gained with regard to an optimal (minimally effective dose and timing) way to treat. This is even more important than with any other indication using GnRH agonists, because in this particular situation, the administration of this unnatural hormone takes place explicitly when embryos will be present. If, as suggested (Tesarik et al., 2006), the effect is indeed on the embryo, then we are dealing with the unique situation that early intrauterine embryos are the drug targets. It is obvious that in this case the highest standards of safety for these embryos are required, and it is our duty to carefully weigh the balance here between the benefits of some improvement of pregnancy rates at a presently unknown possible cost of long-term health of the resulting children.

These comments in no way detract from these possibly highly important findings that may well turn out to provide a significant breakthrough in the improvement of IVF outcome. We merely point out that further properly conducted trials should be the order of the day before wholesale adoption of this idea, inviting as it may be, directly into the, commercial and competitive world of IVF.

References


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