OPINION

Can GnRH agonists act directly on the ovary and contribute to cyst formation?

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Pituitary desensitization with gonadotrophin-releasing hormone (GnRH) agonists prior to ovarian stimulation is now a routine part of most in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) procedures. The two criteria which are used to determine whether pituitary desensitization has occurred are: (i) serum oestradiol concentrations of <50 pg/ml and (ii) the absence of any ovarian cysts with a diameter >15–20 mm (Ron-El et al., 1989; Sampaio et al., 1991; Jenkins et al., 1993; Tarlatzis et al., 1994; Keltz et al., 1995). It takes ~10–15 days for this effect of GnRH agonist to manifest on the ovary, irrespective of the phase of the cycle (early follicular phase or mid-luteal phase) in which the GnRH agonist is started, the type of GnRH agonist used (long-acting triptorelin or short-acting buserelin or leuprolide acetate) and the mode of administration (nasal spray, i.m. administration of long-acting preparations or s.c. administration) (Sampaio et al. 1991; Parinaud et al., 1992; Jenkins et al., 1993).

There have been several reports on the presence of ovarian cysts while the women are still undergoing treatment with GnRH agonists (Feldberg et al., 1989; Ron-El et al., 1989; Sampaio et al., 1991; Jenkins et al., 1992; Parinaud et al., 1992; Stewart et al., 1992; Jenkins et al., 1993; Tarlatzis et al., 1994; Keltz et al., 1995; Weissman et al., 1998). The elevated concentrations of serum oestradiol and the high concentration of oestradiol in the fluids aspirated from these cysts indicate that these cysts originate from the ovarian follicles and have been termed as ‘functional follicular cysts’ (Jenkins et al., 1993). Some of these cysts may also be endometriomata (Yanushpolsky et al., 1998).

The incidence of formation of such cysts is reported to be 2–40% (Feldberg et al., 1989; Ron-El et al., 1989; Parinaud et al., 1992; Jenkins et al., 1993; Tarlatzis et al., 1994). There are some reports that the incidence is higher in older women (Keltz et al., 1995); in those in whom GnRH agonists have been started in the follicular phase, compared with those in whom it is started in the mid-luteal phase (Ben-Rafael et al., 1990); and in those having higher basal (day 2) values of follicle stimulating hormone (FSH) in the pre-treatment cycle (Keltz et al., 1995). The reasons for the formation of such cysts remains unclear. Three hypotheses have been proposed to explain this phenomenon:

Hypothesis I

Commencement of GnRH agonist, either as a single dose of the long-acting form or as daily s.c. doses, results in an initial transient ‘flare-up effect’ on the pituitary leading to a surge of circulating gonadotrophins. It is postulated that this surge triggers the growth of the primordial follicles. The absence of a subsequent luteinizing hormone (LH) surge prevents the rupture or luteinization of the follicles which then get converted into cystic structures. This hypothesis was first proposed to explain the presence of ovarian cysts after GnRH agonist administration (Feldberg et al., 1989) and then later by most other investigators reporting on the presence of ovarian cysts after administration of GnRH agonists (Herman et al., 1990; Ron-El et al., 1990; Stewart et al., 1992; Jenkins et al., 1993; Tarlatzis et al., 1994).

The incidence of ovarian cyst formation following GnRH agonist treatment in IVF cycles is related to the serum progesterone concentrations on the day of GnRH agonist treatment initiation (Marqalioth et al., 1991) and is lower when progesterone is administered prior to starting GnRH agonist treatment (Aston et al., 1995). This is attributed to the ability of progesterone to decrease gonadotrophin release in response to GnRH agonist (Araki et al., 1985), therefore the initial transient ‘flare-up effect’ of GnRH agonist becomes subdued and subsequently the formation of cysts. This hypothesis explains the presence or formation of ovarian cysts after GnRH agonist administration, but fails to explain how these ‘cysts’ continue growing and secreting oestradiol in the absence of any endogenous or exogenous gonadotrophin stimulation for a prolonged period of time.

Several authors (Ron-El et al., 1989; Herman et al., 1990) have clearly demonstrated that there is a sharp rise in the serum FSH and LH concentrations within the first 48 h of GnRH agonist administration with a concomitant rise in oestradiol concentrations. Daily administration of buserelin or leuprolide acetate for 4 days after the administration of long-acting GnRH agonist results in a decrease in both serum gonadotrophin and oestradiol values. In cases where these cysts have been observed, the gonadotrophin concentrations decrease but the diameter of the cysts and circulating oestradiol concentrations are maintained or increase (Herman et al., 1990).

According to this hypothesis, if it is the ‘flare-up’ effect of the GnRH agonist which triggers the rise in gonadotrophin...
values in the first 48 h which results in primordial follicle development and oestradiol production; then, once the gonadotrophin concentrations drop in circulation, the oestradiol concentrations should also drop over the next few days. However, this does not occur. Oestradiol production by these ‘cysts’ continues. It may be possible that these cysts act as a reservoir for oestradiol and could be responsible for maintaining serum oestradiol concentrations, despite a lack of FSH stimulation. However, this still does not explain why the diameter of these cysts continues to increase, suggesting that there is another mechanism which results in the formation and growth of cysts during GnRH agonist administration.

Even in women who are at a risk of ovarian hyperstimulation syndrome (OHSS) because of extremely high concentrations of oestradiol in serum, after pituitary desensitization followed by ovarian stimulation, a period of ‘coasting’ where gonadotrophins are discontinued but GnRH agonists are continued, results in a drop in oestradiol concentrations after 48 h of coasting (Sher et al., 1995; Tortoriello et al., 1998).

There have even been reports on the occurrence of severe OHSS following the administration of GnRH agonists alone (Weissman et al., 1998). This hypothesis, which can explain the occurrence or formation of cysts following GnRH agonists, thus fails to explain how these follicular cysts continue growing and the presence of high circulating concentrations of oestradiol after prolonged use of GnRH agonists.

Hypothesis II

Pituitary desensitization may take >15 days in some women. In some of the reports on the presence of ‘functional ovarian cysts’ and serum oestradiol values of >50 pg/ml, the authors have not reported on the concentration of FSH and LH in serum at that point in time (Sampaio et al., 1991; Jenkins et al., 1992; Stewart et al., 1992; Tarlatzis et al., 1994). It is probable that the circulating gonadotrophin concentrations may not have dropped down to that of a ‘hypophysecomized stage’. This also explains why in some women, continuation of GnRH agonist for a few more days prior to starting stimulation brings about both a drop in the serum oestradiol concentrations and the size of the cysts (Sampaio et al., 1991; Parinaud et al., 1992).

However, this cannot be the only explanation for the occurrence of ovarian cysts while women are on GnRH agonists because ‘functional cysts’ are reported, despite achieving pituitary desensitization as evidenced by low concentrations of FSH and LH (Feldberg et al., 1989; Jenkins et al., 1994; Weissman et al., 1998).

Hypothesis III

It has also been postulated that GnRH agonists may have a direct effect on the ovaries and steroidogenesis (Sampaio et al., 1991; Parinaud et al., 1992). This hypothesis is primarily based on two premises: (i) reports on the presence of GnRH receptors on the ovary (Latoche et al., 1989; Namiki et al., 1990); and (ii) reports of GnRH agonist-induced steroidogenesis by cultured human granulosa cells (Parinaud et al., 1992; Bussenot et al., 1993).

The detection of receptors for GnRH in the ovary is not definitive evidence of direct action of GnRH on the ovary. The second premise (on which this hypothesis is based) is itself questionable. The granulosa cells obtained for this study were from gonadotrophin-stimulated women undergoing follicular aspiration for IVF. These cells were therefore already primed with gonadotrophins. GnRH agonist-induced steroidogenesis by these cells is, therefore, not a clear indication of direct action by GnRH on the ovaries.

There is one more report on ‘direct action’ of GnRH agonist on the monkey granulosa cells which has not been cited by any of the previous publications reporting on the formation of cysts during GnRH agonist treatment: (i) the GnRH agonist exerted a direct dose-dependent stimulative effect on the aromatase activity and progesterone production in cultured monkey granulosa cells; (ii) the stimulative effect on steroidogenesis can be completely blocked by concomitant treatment with a GnRH antagonist, suggesting that the actions of GnRH are mediated through stringent stereo-specific recognition sites; (iii) in addition to the stimulative effect, the GnRH agonist in the presence of gonadotrophins also exerts an inhibitory effect, even though the peptide by itself is more effective in the stimulation of steroidogenesis, and the stimulation of gonadotrophin on steroidogenesis could be gradually restored by decreasing the concentration of the GnRH agonist in the culture (Liu et al., 1991).

We had also observed a case where a woman developed an ovarian cyst 2.5 cm in diameter while on 500 µg GnRH agonist (buserelin) s.c for 14 days. This 21 year old woman, undergoing IVF with embryo transfer, had a history of two ectopic pregnancies. One of the Fallopian tubes had been removed while the other was blocked. Pituitary desensitization was achieved as indicated by the very low values of FSH and LH (<1.5 IU/ml) 14 days after starting GnRH agonist. Despite pituitary desensitization, the ovaries were active as indicated by the increase in the diameter of the follicular cyst (1–2.5 cm), the number of follicles (there was only one follicle, >0.5 cm, at the time of starting the GnRH agonist but after 14 days there were three more follicles with a diameter of 0.9 cm); serum oestradiol concentrations after 14 days were 146 pg/ml; and the thickness of the endometrium increased from 0.5 mm on the day of starting GnRH agonist to 1.05 cm after 14 days. Ovarian stimulation with human menopausal gonadotrophin (HMG) was commenced after 14 days of GnRH agonist and the dose of GnRH agonist was decreased from 500 to 100 µg. The diameter of the cyst did not change. A total of 13 oocytes were aspirated and fertilized in vitro. Eight embryos developed and three 4-cell embryos were transferred on day 2 after IVF. No pregnancy resulted.

Thus our observation is similar to the earlier reports. The cyst may have been formed as proposed in hypothesis one; as the serum FSH and LH concentrations were first measured after 14 days of GnRH agonist, it remains unclear whether pituitary FSH and LH concentrations may have changed over the next few days. However, as the values of FSH and LH were very low, it is more likely that this case along with earlier reports (Liu et al. 1991; Weissman et al., 1998) supports the hypothesis that GnRH agonists have a direct effect on the ovarian steroidogenesis which is independent of its action on the pituitary. More in-
vivo and in-vitro studies need to be carried out to demonstrate a direct effect of GnRH agonists on the ovary. If GnRH receptors are found to be functionally active in the ovary, then this must be considered when designing IVF stimulation protocols using GnRH antagonists.

Addendum

Subsequent to the submission of this manuscript, the patient whose case was reported here underwent another attempt at ovarian stimulation for IVF/embryo transfer. GnRHα (500 μg per day s.c) was started in the mid-luteal phase (Day 21) of the pretreatment cycle. 10 days after GnRH agonist treatment, the serum oestradiol concentrations were 70 pg/ml while there was an ovarian cyst measuring 1.5 cm. GnRH agonist was continued and on day 14 of GnRH agonist treatment, 3 ovarian cysts were present measuring 2.2, 1.5 and 1.0 cm each; the serum oestradiol concentrations had increased to 330 pg/ml while the serum FSH and LH levels were 1.2 mIU/ml and <1 mIU/ml respectively.

The increase in the number and size of cysts, the rise in the serum oestradiol concentrations when the serum gonadotrophin values were very low further supports the third hypothesis that GnRH agonist has direct effect on ovarian steroidogenesis which is independent of its action on the pituitary.

References


