Regimen of ovarian stimulation affects oocyte and therefore embryo quality

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Without any doubt the regimen used to mature multiple capable oocytes for IVF impacts IVF outcomes. Studies have indicated that the inclusion of LH activity, adjuvant agents such as growth hormone (GH), and regimens providing for simultaneous action of both LH and FSH during final oocyte maturation may have beneficial effects on IVF outcomes. Because of the difficulty in improving IVF outcomes in poor responders, the studies on GH are of particular interest. As pointed out in this review, the apparent beneficial effects of GH on oocyte competence may also apply to older women or to normal responders with reduced embryo quality. A much more difficult question is whether and how much ovarian stimulation impacts on oocyte competence. Paradoxically it seems that there are not demonstrated differences between the stimulated and the natural unstimulated cycle, whereas studies in laboratory animals and IVF patients have shown deleterious effects of higher compared with lower doses of gonadotropins. Recent studies suggest that the use of high doses of gonadotropins as an independent factor correlates negatively with the probability of live birth, whereas a high ovarian response per se is associated with better cumulative pregnancy rates, owing to the availability of more euploid and good-quality embryos. Although adjunctive use of androgens has not been discussed here, it is briefly covered in the first review of this series. (Fertil Steril® 2016;105: 560–70. ©2016 by American Society for Reproductive Medicine.)

Key Words: Ovarian stimulation, oocyte quality, gonadotropins, growth hormone

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Follicular development and oocyte maturation are two intimately related processes. Although the oocyte was previously considered only a passive recipient of signals for maturation from the granulosa cells, it is now well known that communication between oocytes and granulosa cells is bidirectional (1). Moreover, this interplay is essential for both follicular differentiation but also for the production of an oocyte competent to undergo fertilization and embryogenesis.

The communication between granulosa cells and the oocyte is controlled by gonadotropins and the oocyte itself. Both gonadotropins influence oocyte competence through the two main local growth factor systems: the bone morphogenetic system and the insulin-like growth factors (IGF) system. It has been observed in the animal model that modification of these systems influences ovulation rates, oocyte competence, and resulting embryo quality (2).

Inevitably, controlled ovarian stimulation (COS) for IVF entails variations in theca and granulosa cell functions that may affect oocyte quality. Multiple follicular development causes the growth of follicles of different sizes and functional activity that will contain oocytes at different maturation stages (3). On the other hand, success of IVF is clearly dependent on the size and quality of the oocyte cohort (4–6). Today the therapeutic arsenal for COS includes many possibilities, depending on the type of gonadotrophins given, their doses, the regimen of pituitary suppression used, and the administration or not of adjuvant agents (7). The effects of each

Received November 13, 2015; revised January 9, 2016; accepted January 19, 2016; published online January 27, 2016.
E.B. has received honoraria for speaking bureaus and advisory boards from Ferring Pharmaceuticals, Merck Serono, MSD, Unify, OvaScience, Glycotope, HRT Pharma, Finox, and TocopheRx. E.L. has nothing to disclose. E.K. has nothing to disclose. M.R. has nothing to disclose. D.M. has nothing to disclose.
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Fertility and Sterility® Vol. 105, No. 3, March 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.01.022

of these combinations on follicular growth and oocyte maturation may be different.

The impact of ovarian stimulation on oocyte and embryo quality is still unclear. Most of the studies performed in animals show a deleterious effect of ovarian stimulation on oocyte quality and embryo development throughout different stages. Although in humans this issue has not been thoroughly studied owing to ethical reasons, pregnancy rates are still lower in stimulated IVF cycles than one might predict, and the proportion of embryo loss is more than desired. It has been hypothesized that ovarian stimulation treatments could explain these findings, but also high ovarian response after the use of gonadotropins.

OVARIAN STIMULATION PROTOCOL AND OOCYTE QUALITY: THE ROLE OF GnRH ANALOGUES AND GONADOTROPINS

The use of GnRH agonists (GnRHas) in IVF practice led to lower cancellation rates, an increased number of oocytes, and higher pregnancy rates (8). Later the introduction of GnRH antagonists, which cause profound and immediate pituitary suppression (9), allowed for less aggressive and more individualized protocols and also avoided the initial flare-up and subsequent estrogen deprivation symptoms (10). Initial trials comparing GnRHa and GnRH antagonist cycles reported slightly but consistently lower pregnancy rates when antagonists were used (11). The action of antagonists inhibiting the cellular cycle via the decrease of growth factors was suggested as a putative cause of this poorer outcome (12). However, to date it has been clearly shown that GnRH antagonist cycles obtain similar live birth rates compared with the GnRHa long protocol (13), and therefore no impact on oocyte quality has been observed. Nevertheless, patients with endometriosis (14), or those with accelerated folliculogenesis, could benefit from a GnRHa long protocol, owing to the better control of endogenous gonadotropins (15).

Although the physiologic role of LH during the follicular phase of a natural cycle is unquestionable (16, 17), its impact during a COS cycle remains controversial.

The administration of LH activity in COS induces several differences in the synthesis of follicular steroids, which may have an impact on oocyte maturation and competence. Using recombinant LH, our group has shown that there is an LH-dose-dependent increase of follicular fluid E_2, androstenedione (A), and T (18). Metaphase I oocytes were obtained from follicles that had significantly lower E_2 concentrations and higher T and A levels, whereas oocytes with multiple anomalies were recovered from follicles with significantly higher LH levels. Together, this suggests there is an optimal level of LH action on the follicle through which the oocyte achieves adequate maturation and maximal competence. These findings of steroids in follicular fluid are consistent with those observed in the MERIT study (19), in which patients who received highly purified hMG for stimulation showed higher concentrations of E_2, A, and T than those who were stimulated with recombinant FSH (rFSH). Interestingly, more good-quality embryos were observed in the highly purfied (hp)-hMG group, although pregnancy rates were comparable.

These studies suggest that the action of LH may be helpful for patients with low serum androgen levels. It has been shown that serum androgens decline steeply with age, with a decrease from menarche to menopause that ranges from 49% for free T to 77% DHEAS (20). Moreover, it has been demonstrated that whereas the synthesis of E_2 in response to rFSH stimulation is preserved in older women, there is a significant decrease in the synthesis of A when rFSH alone is given for stimulation (21). Indeed, in a prospective, randomized study we observed that in patients with basal T below the mean (0.45 ng/mL), there was a strong trend toward a better ongoing pregnancy rate when LH was added to rFSH, compared with rFSH alone in a GnRHa long protocol (22), whereas no differences were observed when both protocols were compared in women with T above the mean. No other differences were observed with respect to other androgen serum levels. Together, this supports a potential benefit of LH administration in older women, in whom basal androgens and their synthesis in response to rFSH in the absence of LH are diminished.

Controlled Ovarian Stimulation in Normogonadotrophic Patients

To date there seems to be no clear benefit obtained by combining LH and FSH in unselected normogonadotrophic patients (23, 24). On the other hand, the potential benefit of LH administration in patients of advanced reproductive age (i.e., >35 years) has been evaluated in a systematic review and meta-analysis (25). In that group of women it was clearly shown that LH administration led to significantly better implantation and clinical pregnancy rates than rFSH alone. Moreover, it was demonstrated that although rFSH led to a higher oocyte yield, there were no differences in metaphase II oocytes, and the fertilization rate was better in patients receiving LH. These were also our findings in an age-adjusted randomized, controlled trial performed in normogonadotrophic patients after COS using a GnRH antagonist protocol (26). It was observed that whereas in patients under 35 year old, results were virtually the same in both stimulation groups (rFSH vs. rFSH + recombinant LH [rLH]), the implantation rate was significantly higher in women receiving rFSH and rLH in the 36–39-year-old group, with a clinically relevant increase in ongoing pregnancy rate.

These findings seem to conflict with those published more recently in a similar trial in which patients aged 35 years or more were stimulated with the GnRH antagonist protocol and randomized to receive either rFSH alone across the cycle, together with 150 IU of rLH from day 6 of stimulation (27). In this study no benefits of rLH administration were observed. Nevertheless, an analysis of the differences between the studies allows drawing interesting and complementary conclusions about the possible role of LH in the treatment of this particular population (28). In our study we used a contraceptive pill (CP) the cycle before stimulation, and we substituted 75 IU of rFSH per day with 75 IU of rLH from stimulation day 1 in the study group. Although in our study hormonal determinations before starting stimulation are not available, it is very likely that after a cycle of CP, hormone values (E_2, FSH, LH, P, and T) were lower than in the