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Exogenous LH supplementation in controlled ovarian stimulation: why, when and to whom?

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Follicle stimulating hormone (FSH) and luteinizing hormone (LH) play an important role in assisted reproductive technology during ovarian stimulation[1]. These hormones execute different but complementary functions in the control of ovarian folliculogenesis and steroidogenesis, but while the role of FSH is well understood, the need for LH supplementation in controlled ovarian stimulation (COS) is still debated and controversial. Several confounding factors (e.g. different exogenous LH formulations, different stimulation protocols, different study populations, difficulty in identifying a threshold value below which an LH add-back could be beneficial) contribute to the continuous uncertainty reported in literature concerning exogenous LH supplementation, despite the large number of trials that have been published.

LH is produced by the anterior pituitary gland and its synthesis and secretion are controlled by gonadotropin-releasing hormone (GnRH). LH is required for follicular growth, ovulation, luteinization of the dominant follicle and progesterone production after ovulation. LH receptors (LHCGR) are mainly located on theca cells of human antral follicles. According to the classical "two cell – two gonadotropin" theory, LH is responsible for the production of androgens precursors, which are essential for estradiol biosynthesis ruled by FSH in granulosa cells[2]. During COS patients undergo daily injection of GnRH analogues (GnRH agonist or GnRH antagonist) in order to prevent a premature LH surge. It is important to underline that with the long GnRH agonist protocol a complete pituitary desensitization is obtained only after 2-3 weeks of treatment and that it is preceded by an initial production of gonadotropins (flare up effect). On the other hand, during downregulation with GnRH antagonist LH secretion remains present, although reduced due to the supra-physiological levels of estradiol related to FSH administration, and it is completely blocked during the periovulatory phase for 3-5 days following GnRH antagonist injections[3,4].

Until few years ago, the only available form of exogenous LH have been human menopausal gonadotropins (HMG). HMG are urinary derived gonadotropins that contain FHS, LH and human chorionic gonadotropin (hCG), showing biological activity of FSH and LH in a 1:1 ratio. Despite their widespread use, the administration of these compounds has shown several limitations related to the extraction processing (protein contamination, wide fluctuation in LH concentration and activity)[5]. Different studies have compared the use of HMG and recombinant FSH (rFSH) to rFSH-only cycles reporting an increase in live birth rate (3% to 4%), especially when using the long GnRH agonist protocol, with fewer ampoules of rFSH administered to the patient[6,7]. Recently, new highly purified HMG preparations have been developed and have shown comparable results in terms of safety and efficacy[8], but despite the encouraging results, the available evidence is too limited to make definitive conclusions. Recombinant LH (rLH) has been introduced in clinical practice since its approval in 1994. rLH structure and functionality are analogous to human endogenous LH, with higher purity and precision of dosing, similar volume of distribution and half-life when compared to urinary products.

According to the threshold theory, optimal folliculogenesis requires a minimal amount of LH for adequate steroidogenesis (<1% of RLH should be occupied), but on the other hand excessive LH could inhibit cell growth and suppress granulosa aromatase activity[9]. However, the identification of a minimal threshold LH value below which LH supplementation during COS could be beneficial in terms of treatment outcomes still remains a matter of concern. Several studies investigating GnRH agonist and GnRH antagonist protocols have employed sporadic single serum LH dosage on different days during ovarian stimulation (e.g. day 1-3 after agonists initiation, day of hCG administration, day 8 in antagonist protocols) in order to justify LH supplementation to increase pregnancy outcomes with inconsistent results. Other authors suggest that it is not the absolute LH value that affects the final outcome, but it is rather the dynamic decrease (≥ 50%) in LH level following GnRH analogues administration that impacts the ultimate live birth rates the most[10]. In

addition to that, in some cases similar LH levels or comparable LH dynamic changes do not correspond to similar patient's response during COS. The differences in ovarian response may be related to different LH isoforms or to LHCGR polymorphisms, which expression varies from an individual to another[11,12].

Identifying those patients who could beneficiate from exogenous LH replacement is another topic of debate. Indeed, not all patients undergoing COS will require LH add-back. Women with deep LH deficiency due to hypogonadotropic hypogonadism (WHO class I) undergoing COS clearly benefit from rLH supplementation[13]. In poor responders or in patients at risk of hyporesponse during ovarian stimulation (suboptimal ovarian response or prior poor response) there is a chance to optimize the final reproductive outcome through the addition of exogenous LH[14]; however, despite some studies reported better cumulative implantation rate and cumulative pregnancy rate[15-17], others concluded that there is still insufficient evidence to encourage stimulation regimens that include exogenous LH supplementation in these groups of patients[18]. The inclusion of rLH to rFSH stimulation could enhance ongoing pregnancy rate also in patients older than 35 years. With age, modifications in LHCGR of theca cells decreases ovarian sensitivity to LH. In addition, serum androgens levels decline abruptly and so does the response to FSH stimulation. Several authors support the inclusion of rLH to stimulation protocols in advanced aged patients given the fact that different studies report higher clinical pregnancy rate and implantation rate[7,19], but others conclude that there is still insufficient evidence to determine a possible positive effect in term of clinical outcome[20].

Since international guidelines (European Society of Human Reproduction and Embryology, American Society for Reproductive Medicine, National Institute for Health and Care Excellence) do not specify any particular stimulation protocol as regimen of first choice for COS, the recently updated Cochrane review on the use of rLH and rFSH for ovarian stimulation acquires a lot of importance in the field[17]. The authors considered 36 randomized controlled trials with a total of 8125 women undergoing in vitro fertilization (IVF) or intracytoplasmatic sperm injection (ICSI). Of the 36 studies, 25 analyzed the effect of rFSH combined or not with rLH in GnRH agonist downregulated cycles and 11 studies compared the use of rFSH alone or combined with rLH in GnRH antagonist downregulated cycles. Live birth rate and incidence of ovarian hyperstimulation syndrome (OHSS) were considered primary endpoints, whether ongoing pregnancy rate, clinical pregnancy rate, miscarriage rate and cancellation rate (due to low response or to imminent OHSS) were measured as secondary outcomes. Even if the quality of the evidence was reported to range from moderate to low due to high risk of bias mainly related to poor reporting methods, no difference was found in risk of OHSS, miscarriage rate and cancellation rate when comparing rLH combined with rFHS versus rFSH-only cycles. A probable improvement in ongoing pregnancy rate was found (21% in rFSH-only cycles versus 21-27% in rFSH + rLH cycles), especially in patients identified as poor responders, regardless the type of GnRH analogue used and the age of the patient. The evidence was too limited to determine if rLH add-back could improve live birth rate.

In conclusion, up to now there is still insufficient evidence to support the use of stimulation protocols that include LH supplementation. Further studies are needed in order to identify patient tailored treatments that take into account individual variations and polymorphisms and their effect on LH dynamic changes during COS.

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