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Review Article

Use of recombinant luteinizing hormone for controlled ovarian hyperstimulation in infertile patients

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ABSTRACT

Controlled ovarian stimulation has become an integral part of a high complexity infertility treatment. Treatment options with recombinant gonadotrophins add more to knowledge on folliculogenesis and ovarian steroidogenesis. Therefore, a literature search was conducted in the following data bases: Medline, Scielo and PubMed. The descriptors/key words used were ovarian stimulation, in vitro fertilization, recombinant luteinizing hormone, supplementation LH. The aim of this study was to review the available literature and to assess the benefits of using recombinant luteinizing hormone associated with recombinant follicle stimulating hormone in different populations who have undergone assisted reproduction procedures.

Keywords: ovarian stimulation, in vitro fertilization, supplementation LH

INTRODUCTION

Reproduction treatment for infertile couples has evolved rapidly since the birth of Louise Brown, the first baby born from in vitro fertilization (IVF) (Steptoe & Edwards, 1978).

To choose the ovarian stimulation scheme that produces the best follicular response in the most physiological way possible is a very important step in this process. The ovarian stimulation regimens have been enhanced through the use of new therapeutic options (Macklon *et al*., 2006).

The recombinant luteinizing hormone (rLH) has become available by recombinant DNA technology and is now a new option in ovarian stimulation treatment protocols. It enables us to develop new strategies of ovulation induction, in order to achieve a better control of folliculogenesis. The use of rLH supplementation in IVF is controversial in patients undergoing ovarian stimulation and has been widely debated (Ramachandra *et al*., 2014; Hill *et al*., 2012).

Since 1993, rLH has been available for clinical trials and, more recently (2001), it has been registered for therapeutic use. Pharmacokinetic studies with rhLH were undertaken to compare its actions to pituitary and urinary LH. The mean concentration time curve, clearance, and volume distribution at steady states were similar for the three sources of human LH. The distribution half-lives were approximately 0.7 hours, and the terminal half-lives were approximately 10 hours (Porchet *et al*., 1995).

Specific populations that have been suggested to benefit include patients older than 35 years of age (Bosch *et al*., 2011), suboptimal responders to ovarian stimulation (Mochtar *et al*., 2007) and those undergoing a specific GnRH antagonist cycle (Baruffi *et al*., 2007) or GnRH agonist cycle (Franco *et al*., 2009).

The aim of this study was to review the available literature and to assess the benefits of using rLH associated with recombinant follicle stimulating hormone (rFSH) in different populations who have undergone assisted reproduction procedures, and the results in number of oocytes retrieved, implantation rate, live birth rate and pregnancy rate.

MATERIALS AND METHODS

The papers retrieved were those published in the Medline, Scielo and PubMed data bases between the years of 1978 and 2015. The descriptors/key words used were ovarian stimulation, in vitro fertilization and LH supplementation. The words were searched both in Portuguese and English.

The inclusion criteria were: papers published in Portuguese or English between the years of 1978 and 2015; papers with key words pre-established in the titles and/or abstract; studies carried out with human beings. The exclusion criteria were: papers that did not have the pre-established key words in the title and/or abstract. The papers were preselected after the reading of the titles and abstracts. After the papers that fit the criteria were spotted, they were read thoroughly.

RESULTS

Recombinant LH administration in patients with poor ovarian response

The definition of poor ovarian response (POR) in a simple and reproducible manner: it usually indicates a reduction in follicular response, resulting in a reduced number of retrieved oocytes (Ferraretti *et al*., 2011).

After the introduction of ovarian hyperstimulation in IVF, it soon became clear that ovarian response differs between women. Already in 1983, the first study that described women with poor response was published (Garcia *et al*., 1983). Poor response is often related to women with advanced age, in whom the low response to gonadotrophins reflects a physiologic decline in ovarian reserve of primordial follicles (Lawson *et al*., 2003).

A pathologic decline in number and quality of primordial follicles may also occur in young women. Poor reserve is a common clinical problem, with up to 26% of IVF cycles resulting in poor response (Keay *et al*., 1997). In the future this percentage is likely to increase as women continue to postpone childbearing. The diagnosis of poor ovarian reserve is based upon the ovarian response in an IVF treatment cycle and/or patient characteristics such as age, basal FSH, anti-Müllerian hormone (AMH) and/or basal antral follicle count (Sallam *et al*., 2005).

In women with poor ovarian reserve, the number of mature follicles that develop during stimulation is frequently considered to be insufficient for a successful treatment, leading to cycle cancellation. A Cochrane review suggested that the addition of rLH to controlled ovarian hyperstimulation (COH) with rFSH increases ongoing pregnancy rates in women with poor ovarian reserve [odd ratio (OR) 1.85, 95% confidence interval (CI) 1.10–3.11] (Mochtar *et al*., 2007).

Before considering the addition of rLH to IVF stimulation for women with poor ovarian reserve, its costs should be balanced against its potential benefits it will bring in terms of pregnancy (Musters *et al.*, 2012).

Three databases (Medline, Embase and Central) were

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searched (from 1990 to 2011) and included 6433 patients aged 18-45 years. The co-primary endpoints were number of oocytes retrieved and clinical pregnancy rates. Analyses were carried out for the overall population and patients with poor ovarian response. No significant difference in the number of oocytes retrieved was found between the rFSH plus rLH and rFSH alone groups. However, in poor responders, significantly more oocytes were retrieved with rFSH plus rLH. These data suggest that there is a relative increase in the clinical pregnancy rates of 9% in the overall population and 30% in poor responders (Lehert *et al*., 2014).

Recombinant LH administration in hypogonadotropic hypogonadism

Hypogonadotropic hypogonadism (HH) is a neuroendocrine dysfunction presenting with arrested folliculogenesis due to reduced hypothalamic or pituitary activity. In women with HH, successful induction of ovulation can be achieved with pulsatile GnRH therapy, which supplies pulsatile release of gonadotrophins from the pituitary (Filicori *et al*., 1994).

The exclusive use of FSH in these patients results in fewer developed follicles and lower estradiol levels. In such cases, the addition of LH increases estradiol levels, follicular recruitment and pregnancy rates (European Recombinant LH - Study Group, 1998).

Even though there is no question that rLH administration is necessary in patients with HH, it is still controversial whether its use could enable follicular growth during ovarian stimulation. Although both gonadotropins are necessary for normal follicular development and appropriate steroidogenesis, it has been documented that FSH plays an important role in ovarian stimulation protocols; small amounts of LH are needed to promote a suitable secretion of estradiol and also enable the follicle to undergo final maturation when exposed to hCG (human chorionic gonadotropin). On the other hand, it is known that elevated concentrations of LH in the follicular phase may affect folliculogenesis, resulting in the ovulation of post-mature oocytes (Balasch *et al*., 1995).

The first randomized clinical study using rLH in HH patients (28 with primary and 10 with secondary HH) was carried out with 38 patients by administering different doses of rLH (placebo, 25, 75 and 225 IU/day) in combination with a fixed dose of rFSH (150 IU/day) (European Recombinant LH Study Group, 1998). Serum estradiol concentrations increased proportionally with increasing rLH and a similar correlation was found in endometrial thickness in rLH up to 75 IU/day dose. Follicular growth was reported in 79% of patients receiving 75 or 225 IU/day of rLH, while this rate was 27% in the placebo or 25 IU/day among the rLH receiving group.

This prospective controlled nonrandomized pilot study was designed to investigate whether split daily doses of rLH is more efficacious than the single daily dose in supporting follicular development and ovulation in primary HH. Twenty-seven women with HH received a 150 IU fixed daily subcutaneous dose of rFSH, supplemented by 75 IU daily dose of rLH administered either as a single dose (n=9; single-dose group) or four equally divided doses (n=18; split-dose group). Women in the split-dose group achieved higher serum estradiol concentrations per follicle, endometrial thickness measurements and numbers of follicles than in the single-dose group (not statistically significant). The OR for ovulation rate was 2.08 (not statistically significant). This study concluded that administering rLH in split daily doses could provide superior results compared to the traditional single daily dose (Awwad *et al*., 2013).

Recombinant LH administration in older assisted reproduction patients

A possible mechanism behind the beneficial effect of exogenous LH supplementation for women with less sensitive ovaries relates to the decreasing numbers of functional LH receptors with increasing age. In addition, ovarian androgen secretion, i.e. estrogen precursor secretion capacity, starts to decline as early as before the age of 30 years, again suggesting a diminished capacity of the ovary to respond to LH stimulus with age (Piltonen *et al*., 2003).

A randomized controlled multicentric study compared rLH supplementation to rFSH in 253 patients aged between 35 and 43 years in a protocol with GnRH antagonist. Of 253 subjects randomized, 125 received both rFSH and rLH and 128 received rFSH only. The objectives were to analyze: clinical pregnancy rates, implantation rates, cancellation rates, number of follicles > 15 mm on the day of hCG administration and number of oocytes obtained. There were no demographic or clinical differences between the groups. They concluded that LH supplementation has no benefit on ongoing pregnancy rates in women of 35 years or older (König *et al*., 2013).

Vuong *et al*. (2015), through a randomized controlled trial evaluated a total of 240 women aged ≥ 35 years undergoing IVF received ovarian stimulation through a GnRH antagonist protocol. Of the 240 patients randomized to treatment, 120 received rFSH/rLH and 120 received rFSH. Their live birth rates, number of oocytes retrieved, implantation rates, miscarriage rates and clinical pregnancy rates did not differ significantly ($P > 0.05$) between rFSH + rLH and rFSH.

Bosch *et al.* (2011) analyzed the impact of LH administration on cycle outcome in ovarian stimulation with GnRH antagonists. The patients evaluated were under 35 years old (n= 380) and those aged 36 to 39 years (n= 340). They compared rFSH versus rFSH + rLH administration. Recombinant LH administration significantly increased the implantation rate in patients aged 36 to 39 years. A clinically relevant better ongoing rate per started cycle was found, although the difference was not statistically significant. Patients younger than 36 years did not obtain any benefit from rLH administration.

Recombinant LH administration in normogonadotropic patients

The issue of both LH supplementation and endogenous LH concentrations in GnRH antagonist, as well as GnRH agonist stimulation protocols in normogonadotropic women remains controversial, although a large number of studies on this issue are available. Kol (2005) suggests that the need for exogenous LH could possibly be predicted by the dynamics of endogenous LH levels during stimulation. Rigorous studies with the GnRH agonist GnRH antagonist in multiple dose protocols failed to find an association between endogenous LH and ongoing pregnancy likelihood (Kolibianakis *et al*., 2006).

A study evaluated the use of rLH supplementation in an unselected group of IVF patients undergoing follicular stimulation with rFSH after pituitary down-regulation. Group A comprised 122 cycles of rFSH and rLH administered, while group B included 331 cycles using rFSH only, during the same period of treatment. There was no significant difference in any of the endocrine, embryological and outcome parameters measured. The implantation rate of 14.2% for group A compared with 9.8% for group B showed a positive trend ($P = 0.055$) (Lisi, 2002).

A total of 244 patients without ovulatory dysfunction, aged < 40 years and at the first ICSI cycle were divided into two groups matched by age according to an ovarian stimulation scheme: Group I (n = 122): Down-regulation with GnRH agonist + rFSH and Group II (n = 122):

Down-regulation with GnRH agonist + rFSH and rLH (beginning simultaneously). The number of oocytes collected, the number of oocytes in metaphase II, fertilization rates, the mean number of embryos produced per cycle, the mean number of frozen embryos per cycle and cumulative implantation rate were significantly lower in the Group I than in Group II. This study demonstrated the potential benefits with the use of rLH (Franco *et al.*, 2009).

Thus, no consensus has been reached regarding the benefits of adding rLH to this group of patients.

CONCLUSIONS

There are controversies about the rLH supplementation to FSH during controlled ovarian stimulation. Further comparative studies will be needed to explore and substantiate a proposed beneficial effect of LH supplementation in special patient populations or under certain circumstances, before LH supplementation can routinely be implemented in such situations. It is possible that rLH find its place in ovarian stimulation when nominations are clearly defined and success rates offset the cost of treatment.

CONFLICT OF INTERESTS

No conflict of interest have been declared.

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