

Research Article

Is there any Benefit in Adding LH Activity to the FSH Stimulation in Poor Responders?

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The aim of this study is to evaluate if there is any benefit in adding LH activity to the ovarian stimulation regime in poor responders. It is a retrospective study where all the IVF/ICSI cycles with poor response in 2012-2013 were analysed. The primary outcomes were clinical pregnancy rate per embryo transfer (CPR/ET) and live birth rate per embryo transfer (LBR/ET). The secondary outcomes were number of mature follicles, oocyte/follicle retrieval rate, endometrial thickness, failed fertilisation rate, implantation rate (IR). 9% of cycles in this period were deemed to have poor ovarian response. In 52 cycles, rFSH (group1), and in 25, hMG (group2) were used. There were no significant differences in mean age, AMH levels, sub fertility factors, and semen quality between the groups. There were no significant differences in the dose of FSH, duration of stimulation, protocols, number of mature follicles, endometrial thickness, oocyte retrieval rate/follicle and failed fertilisation rate between the groups. There were no significant differences in IR (19.5 versus 11.1, $p=0.7$), CPR/ET (14.6 versus 11.1, $p=1$), and LBR/ET (14.6 versus 0, $p=0.16$) between the 2 groups. We detected no significant differences in the primary or secondary outcomes with the use of rFSH or hMG in poor responders.

Keywords: Ovarian stimulation; Poor ovarian response; LH activity**Abbreviations**

E2: Estradiol; FSH: Follicle Stimulating Hormone; ESHRE: European Society of Human Reproduction and Embryology; POR: Poor Ovarian Response; IVF: In Vitro Fertilisation; hMG: Human Menopausal Gonadotropin; LH: Luteinising Hormone; rFSH: Recombinant Follicle Stimulating Hormone; rLH: Recombinant Luteinising Hormone; ICSI: Intra Cytoplasmic Sperm Injection; AMH: Anti Mullerian Hormone; GnRHa: Gonadotropin Releasing Hormone Agonist; s.c.: Sub Cutaneous; rhcg: Recombinant Human Chorionic Gonadotropin; CPR: Clinical Pregnancy Rate; LBR: Live Birth Rate; SPSS: Software Package for Statistical Analysis; IBM: International Business Management Corporation; MERIT: Menotrophin versus Recombinant FSH in vitro Fertilisation Trial

Units: Standard International system of units has been used in this article.

Introduction

Dealing with poor ovarian response poses a clinical challenge in assisted reproduction. Clinicians have been striving to overcome this problem by innovating various treatment strategies, with an aim to reduce the risks of cycle cancellation and poor pregnancy rates in this group [1-4].

Regarding the incidence of poor ovarian response, there is a wide range (5-24%) quoted in the literature [5-6].

The definition of poor ovarian response also varies in the literature. As reported by Pandian et al [7], there has been a wide range of definition of poor response used in various studies, including less than 2 to 5 follicles, less than 3 to 6 oocytes retrieved, maximum

E2 levels attained during stimulation (100-660 pg/ml), total dose and duration of gonadotropin used; in a background of known markers of poor ovarian response, such as 40 years or older, and high serum FSH [8]. The ESHRE consensus group has defined poor ovarian response, when at least two of the following three features are present: (i) advanced maternal age or any other risk factor for POR; (ii) a previous POR; and (iii) an abnormal ovarian reserve test; or two previous episodes of POR despite maximal stimulation [9].

Regarding the optimum stimulation regime in IVF in general (i.e. not specifically in poor responders), there is longstanding debate and controversy regarding whether use of hMG, or supplementing LH to rFSH, confers any benefit in ovarian stimulation cycles [10-12]. The Cochrane review in 2003 [13], a subsequent meta-analysis [14], and the BFS Practice Committee recommendation [15] suggest that there is no significant difference in clinical outcome in terms of oocyte numbers, pregnancy and live birth rates, with hMG and rFSH use. Similarly, no significant difference in ongoing pregnancy or live birth rates with use of hMG or rFSH was noted in a more recent meta-analysis [16]. Coomarasamy et al [17] showed in their meta-analysis however that hMG use in comparison to rFSH, was associated with significant increase in live birth rates in down regulation protocol. On the other hand, the meta-analysis by Leheret et al [18] gave evidence of fewer oocytes retrieved and higher dose of gonadotropin required, when hMG is used, in comparison to rFSH. However, there were comparable pregnancy rates in both the groups. Similarly, Anderson et al found lower number of oocytes retrieved, but higher level of E2 with use of hMG in comparison to rFSH, but no significant difference in ongoing pregnancy rates in the 2 groups [19].

Specifically for ovarian stimulation for poor responders,

there is some suggestion in the literature that using hMG instead of recombinant FSH, or LH supplementation in the stimulation protocol, is associated with better ovarian response and higher live birth rates in group of women poorly responding to FSH alone [20-22, 15]. However, this claim is also fraught with conflicting evidence as other studies or reviewers performing meta-analysis found no significant differences following LH supplementation to rFSH, use of hMG in comparison to rFSH [2, 23, 5, 24]. Bosch et al found a significant increase in implantation rates and on-going pregnancy rates with rLH supplementation to FSH in the 36-39 years age group of women, in comparison to rFSH use alone, but there was no such benefit noted in the younger age group [25].

Therefore, it seems that the evidence in the literature of clinical outcome following the use of hMG versus rFSH, or following LH supplementation to rFSH during controlled ovarian stimulation is conflicting, not only in an unselected population, but also in the poor responder category of women.

A Cochrane review in 2010 concluded that there is insufficient evidence to support the use any particular intervention of ovarian stimulation or adjuvant therapy in poor response, and more robust data were needed [7]. A more contemporary meta-analysis regarding the supplementation of rLH in poor responders was also inconclusive for dearth of consistent definition of poor response used in the studies, and the limited number of studies included in the meta-analysis [5].

In the light of this evidence, we embarked on this study on our local population, aiming to evaluate if there is any difference in clinical outcome with the use of hMG (Menopur), which has both FSH and LH activity, versus rFSH (Gonal F) in our poor responders. It is acknowledged that hMG exerts LH activity and being a urinary derivative, is contaminated with other impurities as well; and hence this study does not reflect a direct translation of efficacy of LH per se.

Materials and Methods

It is a retrospective study where all the IVF/ICSI cycles in the two years period from January 2012 to December 2013 in a tertiary care hospital were analysed. In this study, the definition of poor ovarian response was taken as the yield of less than 4 oocytes, following the use of 3000 or more units of FSH, as described by Kailasam et al [26]. The inclusion criteria included all the cycles in this time period that reached oocyte retrieval, where 0 to 3 oocytes were retrieved following use of a total of 3000 or more units of FSH. Egg donor cycles and embryo freezing cycles with no fresh transfer were excluded. The type of ovarian stimulation protocol and the type of gonadotropin used depended on the discretion of the individual clinical practitioners.

The poor responder women were identified from the electronic database, and the relevant information regarding the patients and the IVF/ICSI cycles, were obtained from the database. The confounding factors potentially impacting the clinical outcome including age, cause of infertility, AMH level were noted.

The types of intervention during the IVF/ICSI cycles were noted; including the type of ovarian stimulation protocol used (down regulation/ flare / antagonist), type of gonadotropin used, total dose and duration of stimulation, type of ovulation trigger used, semen quality, IVF/ ICSI procedure, any difficulty during embryo transfer, number of embryos transferred, type of luteal phase support.

The cycles were analysed in 2 groups, depending on the use of Gonal F (group 1) or Menopur (group 2), and the confounding factors were compared, in order to ascribe any difference in clinical outcome, related to the use of rFSH or hMG.

The primary outcomes analysed were CPR and LBR, and the secondary outcomes analysed were number of mature pre-ovulatory follicles (≥ 17 mm), highest E2 level, number of oocytes retrieved, fertilisation and failed fertilisation rates, endometrial thickness achieved, implantation rates, miscarriage rates and frozen embryo rates.

Analysis was performed using SPSS 21 (IBM software). Normality of data was tested using Shapiro Wilk, and Kolmogorov Smirnov tests for the 2 groups as appropriate, and parametric or non-parametric test were done as necessary. Comparison of continuous variables was made by using Independent sample T test. Pearson's chi squared test was used in case of nominal variables.

Results

In the down regulation protocol, GnRHa, Buserelin acetate 0.5 mg was used s.c. from day 21 to achieve down regulation, and the same was started in the early follicular phase for the flare protocol. In the antagonist cycles, Cetrorelix 0.25 mg (Cetrotide, Merck Serono) was used subcutaneously from day 5/6 to prevent endogenous LH surge. Ovarian stimulation was achieved using either hMG (Menopur, Ferring), or rFSH (Gonal F, Merck Serono), administered by daily s.c. injections and the doses were altered depending on the serial USS and serum E2 levels. Ovulation was triggered when the leading follicles reached 18mm, using rhcg injection (Ovitrelle, Merck Serono), and 250 mcg. Luteal phase support was provided using Progesterone vaginal pessaries, 400 mg twice a day (Cyclogest, Actavis).

In the 2 year period, there were 851 IVF/ICSI cycles in this unit, 77 (9%) of which were deemed to have POR, by the criteria used. In 52 cycles, rFSH (group1) was used, and in 25 cycles, hMG (group2) was used for ovarian stimulation.

There were no significant differences in the variables including the mean age, AMH levels, sub fertility factors ($p=0.16$), and semen quality on the treatment day ($p=0.21$) in the 2 groups, as shown in Table 1. None of these women had a history of previous live birth. (22)42.3% cycles in group 1 were antagonist using Cetrorelix, (21)40.3% were long down regulation and (9)17.3% were agonist flare protocols. This was not statistically different ($p=0.16$) to that in group 2, where (21)84% were antagonist cycles, and the rest (4), 16% long down regulation. Ovulation trigger and luteal phase support were identical in the 2 groups. The proportion of cycles treated by ICSI was comparable in the 2 groups, with slightly more ICSI treatments in group 2 (13 ICSI out of 25 in group 2, versus 22 out of 52 in group 1) although it was not statistically significant.

Table 1 confirms that there were no significant differences in the median dose of gonadotropin used, and the duration of stimulation days in the 2 groups. There were no significant differences in the number of mature follicles, endometrial thickness, and mature oocyte retrieval/follicle rate, number of mature oocytes retrieved, fertilisation rates and failed or abnormal fertilisation rates in the 2 groups.

41 cycles in group 1 and 18 in group 2 progressed to embryo

Table 1: Demonstrates the characteristics, interventions and outcome comparisons in the 2 groups.

| | rFSH (group 1) | hMG (group 2) | p |
|------------------------------------------------|--------------------|-----------------|------|
| Mean age | 39.3(S.D.4.43) | 38.7(S.D. 3.82) | 0.6 |
| Median AMH | 2.9 (S.D 4.66) | 2 (S.D 1.36) | 0.29 |
| Median dose of FSH units | 4,500 (S.D 1277.9) | 4500(S.D1498.7) | 0.9 |
| Median duration of stimulation days | 12 (S.D 2.96) | 12 (S.D 3.69) | 0.9 |
| ICSI % | 42.3 | 52 | 0.47 |
| Median no. of mature follicles (= \geq 17mm) | 2 (S.D 1.53) | 3 (S.D 1.45) | 0.38 |
| Endometrial thickness mm | 10 (S.D 2.47) | 10.5 (S.D 2.04) | 0.36 |
| Median no. of mature oocytes | 2 (S.D 0.74) | 2 (S.D 0.71) | 0.74 |
| Mature oocyte retrieval rate/ follicle % | 100 | 66.6 | 0.7 |
| Fertilisation rate % | 100 | 66.6 | 0.7 |
| No. of embryos transferred | 1(S.D 0.85) | 1 (S.D 0.89) | 0.9 |
| IR% | 19.5 (8/41) | 11.1 (2/18) | 0.7 |
| CPR/ET% | 14.6 (6/41) | 11.1 (2/18) | 1 |
| LBR/ET% | 14.6 (6/41) | 0 (0/18) | 0.16 |
| Failed/abnormal fertilisation rate% | 21.2 (11/52) | 28 (7/25) | 0.57 |
| Embryo freezing rate% | 2.44 (1/41) | 5.55 (1/18) | 0.5 |

transfer, with 9.8% (4/41) difficult transfers in group 1, and 5.6% (1/18) difficult transfers in group 2, which was not statistically significant ($p=1$).

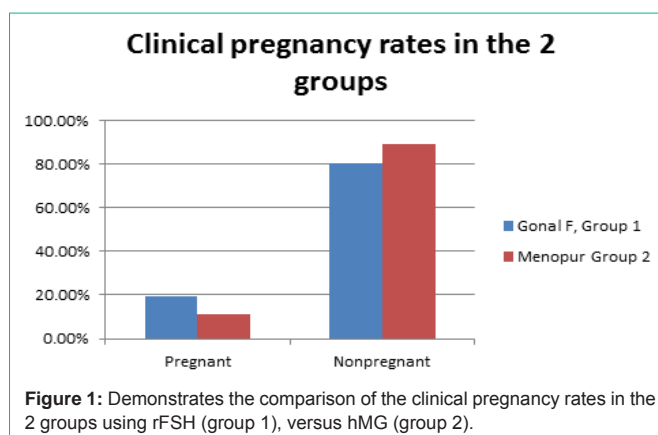
There were 8 and 2 implantations, 6 and 2 clinical pregnancies, and 6 and 0 live births in the 2 groups respectively. There was 11.1% (2/18) miscarriage rate per embryo transfer in group 2, and none in group 1, and no difference in embryo freezing rate in the 2 groups.

Thus, in this study there was no significant difference in either the primary, or the secondary outcomes with the use of rFSH or hMG in poor responders.

Figure 1 depicts the comparison of clinical pregnancy rates in the 2 groups.

Discussion

The main strengths of this study are that: i) a validated evidence based definition of poor ovarian response has been used based on the criteria of Kailasam et al [26], where poor ovarian response was taken as the yield of less than 4 oocytes, following the use of 3000 or more units of FSH. In this retrospective analysis, this patient population also fulfil the ESHRE criteria of poor responders in having a previous poor response, and low AMH, as a marker of reduced ovarian reserve [9]. This is important, since one of the main weaknesses of recent meta-analysis was inconsistency in the definitions used for poor response in the various studies [5]; ii) In the previous studies and meta-analyses comparing the clinical outcome following the use of rFSH versus hMG, either solely GnRH agonist down regulation protocol [24], GnRH flare protocol [11], GnRH agonist down regulation and flare protocols [5], or only GnRH antagonist protocol [23] have been used. This study reports the outcome following GnRH agonist down regulation protocol, flare protocol, as well as GnRH antagonist protocol, and shows that there was no significant

**Figure 1:** Demonstrates the comparison of the clinical pregnancy rates in the 2 groups using rFSH (group 1), versus hMG (group 2).

difference in clinical outcome with either rFSH or hMG. This finding is significant as it had been postulated that the drastic inhibition of LH secretion in antagonist cycles would necessitate exogenous LH supplementation [23, 27]. There is also report of lower number of oocytes and reduced fertility rates following the use of rFSH devoid of LH activity, in GnRH α down regulation cycles [23,28]. However, this claim is also fraught with controversy, as there are reports that in down regulated cycles, the level of endogenous LH activity is sufficient to maintain follicular development and pregnancy [29,23,5]. The argument for using gonadotropin with LH activity stems from the two cell-two gonadotropin hypothesis, which emphasises that both FSH and LH are synergistically important in folliculogenesis. FSH acts by promoting aromatase activity to convert androgen to 17 β E2 in granulosa cells, and LH drives the theca cells to produce the substrate for the aromatase activity, androgens [2, 30-32]. The validity of this hypothesis is clearly demonstrated when inducing ovulation in the gonadotropin deficient World Health Organisation Type 1 anovulatory population. It was proposed that supplementation of LH in poor responders would be beneficial effect on oocyte quality and fertilisation [5, 33]. Ferraretti et al [21] had hypothesised that in poor responders, rLH supplementation was required to restore the diminished oocyte competence, as opposed to simply increasing the dosage of FSH alone, to improve IR and CPRs. In the Cochrane review, Mochtar et al [2004] also propounded that poor responders with a higher risk of miscarriages may benefit from rLH supplementation, related to reduction of early pregnancy miscarriages. On the contrary, inappropriate high levels of LH during folliculogenesis could potentially lead to follicular atresia and impaired oocyte development [5, 35, 36].

However, in this study we selected women who responded poorly but had egg collections, which was our end point. Starting from this, we went back to see which women had been on FSH Alone and which had been on FSH and LH-activity. We found that women who responded poorly were just as likely to have used FSH alone or FSH and LH activity together.

There was no significant difference in the primary outcome, LBR, with the use of rFSH or hMG in this study. In comparison to the reported studies, this is similar to the findings of other studies or meta-analyses which reported comparable LBR/ ongoing pregnancy rates with the use of rFSH versus hMG, or with LH supplementation to rFSH [5,14, 18]. The MERIT group established non-inferiority of

hMG in producing on-going pregnancy rates, although its superiority over rFSH was not established [19]. Our findings were different to that of the results of the meta-analysis by Coomarasami et al [17], who found a 4% increase in LBR with the use of hMG in agonist down regulation cycles.

This study did not find any significant difference in CPR and IR between the 2 groups; and this was corroborated by other studies [2, 23].

There was no significant difference in the oocyte numbers between the 2 groups; which was similar to the findings in other studies reporting their experience in poor responders [2, 23, 5]. In contrast, Leher et al and the MERIT trial reported more oocyte numbers in the rFSH group [18, 19]. Interestingly, the increased oocyte numbers in the rFSH group in the MERIT trial was not associated with improved oocyte quality in that group. On the contrary, they found more number of top quality embryos in the hMG group. It has been proposed that improved oocyte quality is mediated by the LH activity of hMG, mediated by action on cumulus cells [19, 37]. In this study however, there was no difference in the maturity of the oocytes in the 2 groups.

Barranetxea et al [2] reported no difference in serum E2 levels in the 2 groups, in a population of poor responders; which is similar to the findings of this study. On the contrary, Anderson et al [19] had reported achievement of higher serum level of E2 in the rFSH group. They however did not find any difference in the endometrial thickness, and in the proportion of women with triple layer structure of the endometrium; which was corroborating with the findings of this study, with no difference in the endometrial thickness in the 2 groups. The MERIT group [19] although found an association of hyper echogenic endometrium in women treated with rFSH, which they hypothesised, could be relevant in treatment outcome.

Leher et al [18] found higher total dose of Gonadotropin required in the hMG group, unlike the findings of this study. However, Chung et al [23] reported no difference in the cumulative dosage of FSH requirement, or the duration of stimulation needed to attain follicle maturity in between the 2 groups of poor responders <40 years old. A few other papers have also reported no difference in the duration of stimulation in between the 2 groups, which was similar to the findings of this study [2, 5].

Conclusion

Thus in this study, the two groups of women with poor response, who used FSH-stimulation only versus FSH and LH-activity combined, were similar with comparable AMH levels, identical demographic features including similar age groups, sub-fertility factors and no previous live births. Both the groups had IVF/ ICSI treatments with GnRHa down regulation protocol, flare protocol or antagonist protocol, using rFSH or hMG. All the confounding factors and interventions being comparable, there were no significant differences in the IR, CPR, LBR, as well as in the mature follicle and oocyte numbers, embryo freezing rates, endometrial thickness and maximum serum E2 achieved, or in the dose and duration of FSH stimulation required. Accepting the main drawback of the inherent limitation associated with a retrospective study, the main strengths of this study lie in the use of validated definition of POR, and the

simultaneous reporting of the outcome of the commonly used treatment protocols.

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