

Comparison of Human Menopausal Gonadotropin with Recombinant Follicle Stimulating Hormone in Ovulation Stimulation During Intrauterine Insemination

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Abstract: Fecundability increases when ovulation induction was conducted before starting intrauterine insemination procedure (IUI). Human Menopausal gonadotrophin (HMG) and recombinant follicle stimulating hormone (rFSH) are gonadotropin hormones that are widely used in the stimulation of ovulation in infertile patients. Although comparison of gonadotropin preparations have been carried out in IVF, but comparison of rFSH preparations and HMG on IUI was still lacking. The aim of this study was to compare rFSH and HMG, each was combined with clomiphene citrate in infertile women undergone intrauterine insemination (IUI). This study was a retrospective study in the Department of Obstetrics and Gynecology Wahidin Sudirohusodo. Samples were infertile patients who meet these following criteria: women aged 20-45 years, infertility of unknown cause for approximately 12 months, had a history of induced ovulation for approximately 6 cycles without IUI, IVF or ICSI, patent tubes examined with hysterosalpingography, and normal semen analysis according to 1999 WHO criteria. A total of 78 patients consisted of 30 patients using clomiphene citrate + rFSH and 48 other patients using clomiphene citrate + HMG. In two groups, total dosage, duration of gonadotropin administration, follicle count, mean size of follicles, endometrial line size and pregnancy were compared. Statistical test using Levene T and unpaired t test was conducted using SPSS 16 for Windows version. There was no statistically significant difference among total dosage, duration of gonadotropins administration, follicle counts, mean size of follicles, and endometrial line size. The mean number of pregnancy was higher in patients treated with clomiphene citrate + hMG but this difference was not statistically significant. hMG and rFSH was equally effective in stimulating ovulation in intrauterine insemination.

Keywords: Ovulation Stimulation, Intrauterine Insemination, HMG, rFSH

1. Introduction

Infertility is defined as 1 year of unprotected intercourse without pregnancy. This condition may be further classified as *primary infertility*, in which no previous pregnancies have occurred, and *secondary infertility*, in which a prior pregnancy, although not necessarily a live birth, has occurred. The main causes of infertility include male factor, decreased ovarian reserve, ovulatory disorders (ovulatory factor), tubal injury, blockage, or paratubal adhesions (including endometriosis with evidence of tubal or peritoneal adhesions), uterine factors, systemic conditions (including infections or chronic diseases such as autoimmune conditions

or chronic renal failure), cervical and immunologic factors, and unexplained factors (including endometriosis with no evidence of tubal or peritoneal adhesions). The basic investigations that should be performed before starting any infertility treatment are semen analysis, confirmation of ovulation, and the documentation of tubal patency. [1] Male factor is the only cause of infertility in 20% of infertile couples, but it may be a contributing factor in as many as 30% to 40% of cases. Treatment of reversible endocrine or infectious causes of subfertility, such as sexually transmitted diseases and thyroid disorders, tends to be effective.

Intrauterine insemination (IUI) is the best studied and most widely practiced of all the insemination techniques. Intracytoplasmic sperm injection (ICSI) has allowed couples with male factor infertility to achieve assisted reproductive technology (ART) pregnancy outcomes that are comparable with those of couples with non-male factor infertility using conventional *in vitro* fertilization (IVF) treatment.

Ovarian stimulation is being used in the majority of assisted reproduction units in order to improve the success rate by increasing the number of oocytes and thus the number of embryos to be replaced.[2] FSH is the key gonadotropic hormone during the follicular phase and only minute amounts of LH are needed in different stages of follicular development. In IUI, if the cycle is normal, exogenous gonadotropine stimulation can improve the success rate of IUI especially when induction with clomiphene fails or a woman reaches the age of over 35 years.[3] In recent years, induction of ovulation has shown major advances, with multiple products commercially available and the focus of ovarian stimulation has shifted from trying to obtain the maximum possible number of oocytes to trying to obtain an adequate cohort of good quality of embryos from quantity to quality.[4] Urinary products include human menopausal gonadotropins (hMG), urinary FSH (uFSH), and human Chorionic Gonadotropin (hCG). Human menopausal Gonadotropin (hMG) containing 75 IU FSH and 75 IU LH is excreted from the urine of postmenopausal women and is of low purity as 95% of the proteins are contaminants. The urinary proteins may have negative effects on follicular recruitment and development. [5] More recently, recombinant FSH (r-FSH) and recombinant luteinizing hormone (rLH) have entered the market. Recombinant human FSH (rFSH) is produced by a Chinese hamster ovary cell line, transfected with the genes encoding for the two FSH subunits. The results in an almost totally pure FSH preparation. Finally highly purified (HP)-hMG in which the purification process allows its administration via the subcutaneous route, is the latest addition to this family of infertility drugs. HP-hMG and rFSH have been widely and successfully used for ovarian stimulation in infertile women undergoing treatment for invitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) and embryo transfer.

It is well known that the quantitative aspects can be modulated by the doses of gonadotropins, the type of gonadotropin used, and by the endocrine environment associated with stimulation. Randomized controlled trials comparing gonadotropin preparations have primarily focused on clinical aspects and have been designed to evaluate the number of oocytes retrieved or, to a lesser extent, pregnancy rates. [6-9]

Several studies comparing the outcome of r-FSH and hMG have been reported, most of which were performed in women undergoing pituitary downregulation with a GnRH agonist long protocol. [10-13] Recent meta analysis have demonstrated that hMG was not inferior to r-FSH with regard to pregnancy and live birth rates. [14-15] Van Wely et al. found a borderline significant difference of a 5% higher clinical pregnancy rate in women stimulated with

menotropins (27%) compared with r-FSH (22%). [16] Recently, it was confirmed that a better outcome in terms of the live birth rate was obtained when HP-hMG was used for ovarian stimulation as compared with r-FSH in the GnRH agonist long protocol. [17]

A comparison of gonadotropin preparations have been conducted on IVF, but the comparison of using rFSH preparation and HMG on IUI is still rarely. [18] The aim of this research is to compare the effectiveness between the two preparations gonadotropine (HMG and rFSH) that are combined with clomiphene citrate in infertile women using IUI.

2. Methods

This research was a retrospective observation in the Obstetrics and Gynecology Department of Wahidin Sudirohusodo Hospital. Samples are infertile patients as many as 78 people who have met the following criteria: female aged between 20-45 years old, unexplained infertility for at least 24 months, history of at least 6 cycles of previous induction ovulation but no IUI, IVF or ICSI attempts, patent fallopian tubes documented by hysterosalpingography (HSG), normal semen analysis according to the 1999 WHO criteria. [19] Patient were excluded if there were history of previous assisted reproduction attempts by IUI, IVF or ICSI, endometriosis (classification stage III and IV of the American Infertility Society), contraindication to one of the investigated drugs, persistent ovarian cyst (larger than 30 mm and there have been more than 2 months). [18] Samples were divided into two groups. The stimulation of ovulation in Group A was begun with an administration of 50 mg clomiphene citrate daily from the third day until the seventh day of the menstrual cycle, then the patients were given 75 IU of rFSH on the seventh day to ninth day. The method applied in Group B is the same method as group A but the administration of rFSH was replaced with 75 IU hMG. At the tenth day, each sample in both groups are tested on transvaginal ultrasound. All patients were monitored from the tenth day until they reach the dominant follicle (>17 mm diameter). Then, they were injected with 5000 IU hCG intramuscularly and the next 24-36 hours IUI procedure was performed. Levene T and unpaired t-Test was conducted using SPSS 16 for Windows version.

3. Results

Table 1. Sample characteristics of this research are valued according to some variables.

	Group A (rFSH)	Group B (HMG)	p
Age	34.233±5.210	35.188±5.8260	0.500
Duration of infertility	7.00±3.789	6.25±4.783	0.266

The table reveals that variables of sample characteristics which are valued have no significant difference between group A (Clomiphene Citrate + rFSH) and group B (Clomiphene Citrate + HMG).

Table 2. Comparisons of pregnancy and characteristics between group A (Clomiphene Citrate + rFSH) and B (Clomiphene Citrate + HMG).

	Group A (rFSH)	Group B (HMG)	p
Duration of gonadotropin therapy	5.33±1.446	5.17±1.521	0.633
Total doses of gonadotropin	405.83±112.319	403.125±121.4523	0.922
A number of dominant follicles (>17mm) injected with HCG	1.933±0.868	2.208±1.0711	0.240
The average diameter of follicles injected with HCG (mm)	19.739±1.268	20.224±2.208	0.277
Thickness of endometrium injected with HCG (mm)	7.27±1.403	7.71±1.1419	0.181
Total pregnancy	5 (16.66%)	7 (14.5%)	0.522

According to the calculation, total doses of gonadotropin in group A (rFSH) and B (HMG) (405.83±112.319 vs 403.125±121.4523; $p=0.922$) and durations of therapy (5.33±1.446 vs 5.17±1.521; $p=0.633$) have no significant difference. However, in a research of Rashidi et al stated that duration of gonadotropin therapy is shorter in Clomiphene Citrate+ rFSH group than Clomiphene Citrate +HMG's group.[18] Likewise, with total doses of gonadotropin given to Clomiphene Citrate+ rFSH patients is obtained less than those receiving Clomiphene Citrate+HMG. [17] In this research, both of that doses are insignificant.

In addition, the average of dominant follicles in group A and group B is insignificant and statistically have no significant difference (1.933±0.868 vs 2.208±0.9732; $p=0.404$). The average of follicle diameter in group B is larger than that of group A, however, they statistically have no extremely difference (19.7390 ±1.268 vs 20.224±2.208 $p=0.277$). The thickness of endometrium in group B is greater than that of group A (7.27±1.403 vs 7.71±1.1419; $p=0.181$). In group B, there were seven pregnancies (14.5%) and group A were five pregnancies (16.66%), but this comparisons have no considerable significance ($p=0.522$).

4. Discussions

Until the recent introduction of rFSH, urinary gonadotropin was used for ovulation induction since the early 1960s and ovarian stimulation since the early 1980s. Besides the difficulty in collecting urine, urinary gonadotropins have a lot of disadvantages including the presence of LH, contamination with 95% non FSH urinary proteins [5], high incidence of local allergic reactions [20] and batch to batch inconsistency. [21]

Daya et, al in a meta analysis demonstrated that the use of urinary FSH or rFSH was associated with a significantly higher clinical pregnancy rate than HMG. [22] Very low level or the absence of LH in the urinary FSH or rFSH preparation was considered as the main reason to explain >50% improvement in clinical pregnancy rates in women receiving FSH.

Our results are simultaneous with meta analysis of Cochrane that there is no difference in the quantity of follicles, the thickness of endometrium and the average of follicle's size between FSH and HMG, whereas the average of pregnancy in HMG is higher than rFSH. [16] The quantity of pregnancy on patients receiving Clomiphene Citrate + HMG is higher than that of patients receiving Clomiphene Citrate+ rFSH because the level of estradiol is higher after receiving HMG and it established a good circumstances of

endometrium, so that it influences implantation process. [23] Those are reasons why average of pregnancy in group B is higher than that of group A. Another recent study that compared HP-hMG and r-FSH for ovulation induction demonstrated that the LH activity in HP-hMG induces a more modulated folliculogenesis that is associated with a lower risk of excessive ovarian response and an ovulation rate similar to that obtained with r-FSH. [24] In other research concerning about efficacy of lyophilized urinary HMG and rFSH in 49 infertile women who are undergoing IUI is obtained that HP-HMG and rFSH have the same efficacy in stimulation of ovulation. [25] Turhan et al found that HP-HMG to be as effective as r FSH in terms of oocyte and embryo quality and clinical pregnancy outcomes. [26] From Ng, et al, their study comparing the effects of rFSH and HMG on the quality of oocytes and embryos. They found that HMG is as good as rFSH in terms of oocyte and embryo quality. [2]

5. Conclusions

The use of HMG and rFSH has the same effectiveness in stimulating ovulation in intrautein insemination. A larger population of study is necessary to know the significant effect from using two kinds of the medicines as well as more advanced research to understand the effects of both gonadotropins. Most studies investigated the pregnancy or the delivery rate, but those outcomes are affected with a lot of factors not only quality of embryo, but also number of embryo transferred, local hormone levels, uterine receptivity and other maternal complications. [27]

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