

Research Article

Recombinant FSH versus hMG in Controlled Ovarian Stimulation for IVF***Follicle Stimulating Hormone rekombinan dibandingkan hMG pada stimulasi ovarium terkontrol untuk Fertilisasi in Vitro*****Agus Supriyadi, Achmad K. Harzif, Wael O. Al Jaidy**

*Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Indonesia
Dr. Cipto Mangunkusumo General Hospital
Jakarta*

Abstract

Objective: To investigate the relationship between gonadotropins which are used in the process of controlled ovarian stimulation, rFSH and hMG, and the in vitro fertilization outcomes, which are oocyte number, embryo number, and fertilization rate during the period of 2013 to 2019.

Methods: This research was a cross sectional study. Data from medical record of patients who underwent the in vitro fertilization procedure at Melati Clinic, Harapan Kita Child and Mother Hospital were obtained. This research collected the oocyte number, embryo number, and fertilization rate of eligible patients who received rFSH or hMG stimulation.

Result: Four hundred and fifty four patients were eligible for the research, further divided into 309 patients who received rFSH and 145 patients who received hMG. Non-parametric test revealed that patients who belong to the rFSH group had a statistically significant higher oocyte number, embryo number, and fertilization rate compared to hMG group with $p < 0.05$.

Conclusions: Significant difference of oocyte number, embryo number, and fertilization rate exists between rFSH and hMG group ($p < 0.05$) with the mean oocyte number, embryo number, and fertilization rate are consistently observed higher in the rFSH group compared to hMG group.

Keywords: controlled ovarian stimulation, hMG, infertility, in vitro fertilization, rFSH.

Abstrak

Tujuan: Mengetahui hubungan stimulasi ovarium terkontrol yang mendapatkan sediaan gonadotropin berupa rFSH dan hMG dengan luaran FIV berupa jumlah oosit, jumlah embrio, dan tingkat pembuahan pada periode 2013– 2019.

Metode: Penelitian ini menggunakan desain potong lintang menggunakan data rekam medis yang menjalani program FIV di Klinik Melati Harapan Kita tahun 2013 – 2019. Data yang digunakan adalah data pasien yang menjalani program dengan protokol rFSH dan hMG dibandingkan dengan luaran jumlah oosit, tingkat pembuahan, dan jumlah embrio.

Hasil: Dari 454 pasien yang memenuhi kriteria, 309 pasien menggunakan rFSH sebagai obat stimulasi ovarium dan 145 pasien menggunakan hMG sebagai obat stimulasi ovarium. Hasil uji non parametrik lebih tinggi pada kelompok pengguna rFSH dengan ketiga variabel yang diteliti ditemukan bermakna secara signifikan dengan hasil $p < 0,05$.

Kesimpulan: Terdapat perbedaan yang signifikan antara jumlah oosit, fertilization rate, dan jumlah embrio pada kelompok rFSH dan hMG ($P < 0,05$) dengan rata-rata oosit, tingkat pembuahan, dan jumlah embrio kelompok rFSH lebih besar daripada kelompok hMG.

Kata kunci: hMG, infertilitas, fertilisasi in vitro, rFSH, stimulasi ovarium.

Correspondence author. Wael O. Al Jaidy. Department of Obstetrics and Gynecology.
Faculty of Medicine Universitas Indonesia. Jakarta. wael_oemar@yahoo.com

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INTRODUCTION

World Health Organization (WHO) defined infertility as a disease of the reproductive system characterized by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.¹ Regular sexual intercourse is defined as having sexual intercourse one or two times a week. In Indonesia, the most prevalent age group who is diagnosed with infertility is on the range of 20 until 24 years old, with a prevalence of 21.3%.²

Infertility is treated by using three main strategies, which are medical therapy, surgical therapy, and assisted reproductive technology.^{2,3} Assisted reproductive technology has become the leading choice of treatment due to its rapid development of knowledge and practice worldwide. One of the assisted reproductive technology is in vitro fertilization (IVF).⁴

IVF procedure consists of many steps, one of the most important among of them is controlled ovarian stimulation. The ovaries are stimulated using gonadotropins, such as recombinant Follicle Stimulating Hormone (rFSH) or human Menopausal Gonadotropin (hMG). As far as the knowledge advances, these groups of the drug are the most common drug used in the IVF procedure.⁴

Many studies have aimed to assess the efficacy of these two groups of drugs. A meta-analysis which was conducted in 2017, showed that there was no significant difference between the two, which were rFSH and hMG group, in terms of the IVF outcomes, which were clinical pregnancy and birth rate.⁵ However, there are three main reasons why research the same question still needs to be conducted. First, although there is evidence of the association between the drugs and IVF outcomes, which are clinical pregnancy and birth rate, evidence of other IVF outcomes such as the number of oocytes, number of embryos, and fertilization rate is yet to be studied. Second, there are only a few researches conducted which aimed to explore the association between the drugs and the IVF outcome in Indonesia. Third, there has never been any research to evaluate the IVF program in Melati Clinic of Harapan Kita Mother and Child Hospital.

Therefore, this research intends to explore the association between IVF outcomes, which are the number of oocyte, number of embryos, and pregnancy rates, and drugs used in IVF stimulation, which are rFSH and hMG, at Melati

Clinic, Harapan Kita Mother and Child Hospital.

METHODS

This study was a cross-sectional study conducted at Melati Clinic, Harapan Kita Mother and Child Hospital. The data was obtained from the medical record of patients who underwent the IVF procedure from January 2013 – July 2019. The inclusion rate of this study was any IVF patient who had either rFSH or hMG stimulation during the determined range of time. The exclusion criteria were patients who failed the stimulation process and patients who decided to freeze their eggs. The total sampling method was done during the process of data collection.

This study had obtained ethical clearance from the Committee of Medical Research Ethics FKUI Jakarta, and all subjects had given informed consent before joined this study. The patient's data was collected from the medical records, including the patient's identity, age, controlled ovarian stimulation protocol, type of gonadotropin stimulation, total dose of gonadotropin stimulation, the number of oocytes, the number of embryos, the number of fertilized embryo. A normality test was carried out to determine whether the data were normally distributed. The data were further analyzed by using univariate and bivariate analysis. Univariate analysis was done to provide the frequency distribution of each variable. On the other hand, bivariate analysis was done to find the association between the groups of drug and IVF outcomes. SPSS 22.0 was used during the process of data analysis.

RESULTS

This study initially obtained data from 557 patients who underwent IVF procedure in Melati Clinic, Harapan Kita Mother and Child Hospital from January 2013 to July 2019. However, only 454 patients who were eligible to be further analyzed. The other 103 patients were excluded from the study due to various reasons, such as incomplete data, cancellation of the procedure, failure of the procedure, and the decision to freeze the eggs.

From these 454 patients, the mean age was 35.2 years old. Most of the patients were more than 35 years old (52.5%), followed by patients ranging from 25 to 35 years old (46%), and the least common was patients with age less than

25 years old (15%). Based on the duration of infertility, the mean duration was 5.5 years. Patients who had been infertile for three until eight years of duration were the most common (36.1%), followed by those who had been infertile less than three years (35.9%), and more than eight years (28%). Based on the indication of IVF, the most common indication was male factor (49.8%), followed by unexplained infertility (24.9%), tubal factor (20.5%), endometrial factor (4.2%), and polycystic ovarian syndrome (0.7%). Patients who underwent the IVF protocol were assigned to different protocols of controlled ovarian stimulation. There were three different protocols, which were long protocol, short protocol, and antagonist protocol. The most common protocol used were the antagonist protocol (86.8%), followed by long protocol (10.1%), and short protocol (3.1%). The patient's characteristic and types of protocol are summarized in Table 1.

Table 1. Subject's Characteristics

Characteristic	Value, n=454 (100) %
Age (y.o)	35.2 ± 4.9
25	7 (1.5)
25-35	209 (46)
>35	238 (52.5)
Duration of Infertility	5.5 ± 3.8
3	163 (35.9)
3-8	164 (36.1)
>8	127 (28)
IVF Indication	
Male factor	226 (49.8)
Unexplained	113 (24.9)
Tubal factor	93 (20.5)
Endometrial factor	19 (4.2)
PCOS	3 (0.7)
Controlled Ovarian Stimulation Protocol	
Antagonist	394 (86.8)
Long	46 (10.1)
Short	14 (3.1)

Patients who underwent the process of controlled ovarian stimulation were stimulated using gonadotropins to stimulate the growth and release of oocytes from the ovaries. This study only included rFSH and hMG type of gonadotropins. Table 2 summarizes the distribution of patients who had either rFSH or hMG for the controlled ovarian stimulation and mean total dose value in each protocol. Most of the patients were stimulated using rFSH (68.1%). In contrast, only 31.9% of patients were stimulated using hMG. The mean total dose of rFSH was 2451.2 IU, whereas the mean total dose of hMG was 2494.7.

Table 2. Gonadotropin used in Controlled Ovarian Stimulation

Gonadotropin used in Controlled Ovarian Stimulation	Value n = (%)	Mean Total Dose Value (IU)
rFSH	309 (68.1)	2451.2
hMG	145 (31.9)	2494.7

This study analyzed the relationship between the type of gonadotropin used with the IVF outcomes, which were the number of oocyte, the number of embryo, and fertilization rate. The result of the analysis is presented on the Table 3.

Table 3. Relationship between Type of Gonadotropin Used with the IVF Outcomes

	rFSH (Mean ± SD; Median)	hMG (Mean ± SD; Median)	P-value ^a
Oocyte number	9.1 ± 6.9; 7	6.8 ± 5.1; 6	0.002
Fertilization rate	50% ± 23%; 50%	40% ± 27%; 40%	0.016
Embryo number	2.6 ± 1.6; 3	2.1 ± 1.4; 2	0.002

^aNon-parametric analysis, Mann-Whitney test, was used

DISCUSSION

In this study, most of the patients were given rFSH (68.1%) compared to hMG (31.9%) as the drug of choice in controlled ovarian stimulation.

Based on demographic data, this study showed that the average age of patients who underwent the IVF procedure was 35.2 years old. Further analysis compared the IVF outcomes of both intervention groups regarding the patient's age. The result reported that there was no significant association between IVF outcomes on both intervention groups in regard of the patient's age. However, the IVF outcomes on both intervention groups have a declining trend as the age increases, indicating a subtle effect of age on IVF outcomes. Many other studies have concluded that the risk of IVF failure increased as the age progressed. Starting from the age of 35 and beyond, the risk of IVF failure was increased progressively.^{6,7} The finding in this study indicates that the age of IVF patients at Melati Clinic reaches the upper limit before the risk of failure starting to increase gradually. Therefore, special concerns must be given to the patient's age to optimize the IVF outcome.

In this study, the mean duration of infertility was 5.5 years. Further analysis compared the IVF outcomes of both intervention groups regarding the patient's infertility duration. The result reported that there was a significant difference

in oocyte number and embryo number on the patients who had been infertile for less than three years and somewhere between three and eight years. These two findings were found higher on the rFSH group compared to the hMG group. Other findings noted that the fertilization rate was found to be significantly higher in the rFSH group on the duration of infertility between three and eight years. However, the IVF outcomes on both intervention groups have a declining trend as the duration of infertility increases, indicating a subtle effect on IVF outcomes. The length of infertility has been linked with IVF outcomes, one study reported.⁸ The duration of infertility of more than 13 years had a significant association with the risk of failure of pregnancy on IVF procedure.⁸ Less than 13 years, the research showed that the duration of infertility had no significant impact on IVF outcomes.

Most of the patients in this study were enrolled in the IVF procedure with an indication of the male factor, followed by unexplained infertility, tubal factor, endometrial factor, and polycystic ovarian syndrome subsequently. In general, further analysis showed that there was no significant association between IVF outcomes on both intervention groups regarding the IVF indication. The research which supported this finding was carried out, which found that there was no association between IVF indication with the IVF outcomes.⁸

In this study, three different protocols of ovarian stimulation were used. Many studies have explored the association between ovarian stimulation protocol with the IVF outcomes.^{9,10} Unfortunately, many of which were not the main interest of IVF outcomes studied on this research.^{9,10} Those studies found conflicting evidence of the association between protocols and IVF outcomes, such as clinical pregnancy and live birth rate.^{9,10} Nevertheless, there was only one study that examined the association between ovarian stimulation protocol with the number of the oocyte.¹¹ This study concluded that agonist protocol resulted in a significantly higher number of the oocyte compared to antagonist protocol.¹¹ In contrast, the result of this study showed that the most common protocol used at Melati Clinic was agonist protocol. This finding contradicted the previous study result. Therefore, further evaluation is needed to assess the efficacy of the ovarian stimulation protocol at Melati Clinic.

The mean total dose of the gonadotropin stimulation was also obtained in this study.

Based on the previous meta-analysis, there was no significant association between mean total dose with the IVF outcomes, such as clinical pregnancy or live birth.¹² Another retrospective study also reported that there was no significant association between clinical pregnancy with the differences among the mean total dose given to the patients.¹³ This study showed that rFSH had a higher mean doses, but had no significance to IVF outcomes.

The results of this study showed that there was a significant difference in the oocyte number, embryo number, and fertilization rate on both groups of intervention. All the findings reported that the rFSH group had a higher number of oocytes, a higher number of embryos, and a higher rate of fertilization compared to the hMG group.

Oocyte number was also observed significantly higher in the rFSH group compared to the hMG group on a meta-analysis conducted.⁵ Another study also showed the same result.¹⁴ These findings support the notion that oocyte development is directly under the influence of gonadotropin hormones, which are FSH and LH. Exogenous gonadotropin can stimulate multiple ovulation, thereby increasing the number of oocytes ovulated at the same time.⁵ The process of multi ovulation is crucial in IVF. Multiple oocytes will enhance the success rate of fertilization, therefore increasing the chance of implantation, pregnancy, and live birth.⁵ In this study, a significant difference between the oocyte number on rFSH and hMG group was observed.

This phenomenon can be explained from the physiological perspective of the hormones used, FSH and LH. rFSH contains only FSH, whereas hMG contains a combination of FSH and LH with a ratio of 1:1. In several studies, LH was found to induce apoptosis of follicular cells.⁵ Furthermore, it will decrease the number of oocytes.⁵ However, LH was also found to increase the quality of the ovum due to its role in inducing gene expression during the development process of follicle.⁵ This physiological basis will be useful for explaining the result found in the next section.

Conflicting evidence found on a meta-analysis of 11 studies.⁵ They discovered that there was no significant difference between fertilization rate in the rFSH group compared to the hMG group.¹⁴ This result can be attributed to the physiological basis of LH in hMG, which increased the quality of the ovum. As the quality of the ovum increased, the chance of the oocytes getting fertilized is also

increased. On another hand, in the rFSH group, they initially had a higher number of oocytes. Although FSH does not improve ovum quality, the higher ovum quantity can contribute to the higher likelihood of fertilization. Therefore, no significant difference is found on both groups. In this study, a significant difference was noted. The fertilization rate was higher on the rFSH group compared to the hMG group. The variance of the result that was found in this study can be attributed to the disparity of the sample size in both groups and the study design that allowed many factors can not be controlled.

Another conflicting evidence found on a meta-analysis of 16 studies.⁵ They found there was a significant difference between the amount of embryo in the rFSH compared to the hMG. However, the hMG group had a higher number of embryos compared to the rFSH group. On the other hand, this study found that the number of embryos was higher in the rFSH group compared to the hMG group. The result of the meta-analysis by Santi et al. was consistent with the physiological basis of LH. Because LH increase the quality of the ovum, the survival rate of the embryo will also be noted higher in the LH group compared to FSH group.⁵

This study had several limitations which significantly influenced the result of the research, including the study design, incomplete patient characteristics data, and disparity of the sample size in both groups. The best study design to assess the efficacy of an intervention is a randomized controlled trial. However, due to limited time and resources, we decided to perform a cross-sectional study. This study could not give us a clear causal relationship between variables that were being studied. Second, the patient's characteristics data was not comprehensive enough to provide us with a holistic condition of the patients. Data such as the duration of stimulation, initial FSH and LH level, size of the follicles, ovarium volume are also crucial for the research. Third, a disparity was noted in the sample size on the rFSH and hMG group. In the future, a proper ratio of both group is needed to draw an appropriate conclusion of the study.

CONCLUSION

The proportion of patients who had the rFSH was 68.1%, whereas the hMG was 31.9%. The patients had a mean age of 35.2, a mean duration of infertility of 5.5 years, and most of the patients

indicated of IVF due to male factor. A significant difference of oocyte number, embryo number, and fertilization rate existed between rFSH and hMG group ($p < 0.05$) with the mean oocyte number, embryo number, and fertilization rate are consistently observed higher in the rFSH group compared to hMG group.

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