

## Low Dose hMG As a First choice for Ovarian Stimulation in IUI cycles

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### Abstract

**Objective:** to compare pregnancy rates following low dose human menopausal gonadotrophin as a first choice in couples undergoing intrauterine insemination

**Study Design:** prospective controlled trial

**Patients & Methods:** This study conducted at the Kasr El-Aini Hospital in which the subfertile couples with unexplained infertility or mild male factor undergoing IUI were allocated either to Group (1): clomiphene citrate or Group (2): hMG one ampoule daily. Each couple had three cycles of IUI unless pregnancy occurs.

**Results:** There were 8 pregnancies in the 23 patients and 66 cycles in the clomide group and there were 14 pregnancies in the 22 patients and 59 cycles in the hMG group. There was no statistical significance in the pregnancy rates between the two groups Odds Ratio = 0.443 95% CI 0.171 - 1.149. P value = 0.071.

**Conclusion:** Induction of ovulation using low dose hMG was superior to using clomiphene citrate in the stimulated IUI cycles; but did not reach statistical significance

### Introduction

IUI could be carried out in natural cycles or in combination with controlled ovarian hyperstimulation (COH). The use of IUI in natural cycles has the advantage of lower cost and adds no risk from the drug treatment. Evidence clearly showed that IUI in cycles with COH generally improves the probability of conception compared with IUI in natural cycles [1].

The main two ovarian stimulation protocols for use with IUI are clomiphene citrate (CC), or clomiphene citrate followed by gonadotrophins [2]. There were no significant differences in conception rates when CC and IUI were compared to CC/ hMG and IUI in couples with unexplained infertility nor have there been any differences when letrozole and IUI were compared to CC or CC/hMG and IUI [3]. The advantages of CC over gonadotrophins for ovulation induction include low incidence of multiple pregnancies, low cost, ease of treatment, absence of need for daily cycle monitoring and low incidence of OHSS [4]. Recently, there have been a number of studies that showed that low dose gonadotrophins reduce the incidence of multiple birth rate without much influencing the clinical pregnancy rates [5]. The aim of the present study is to compare two different protocols of induction of ovulation, using clomiphene citrate or low dose human menopausal gonadotrophins.

### Participants & Methods:

Subfertile couples attending the infertility outpatient clinic in the Obstetrics and Gynecology Department Cairo University - Kasr Al-Aini Hospital were recruited for this study. The trial was conducted between January 2008 till July 2010. Women were included if they were less than or equal 37 years old, Body mass index (BMI) between 20-30 kg/m<sup>2</sup> and cause of infertility either mild male factor or unexplained infertility.

A mild male factor was defined with at least two of the following: Sperm analysis with 10 – 20 x10<sup>6</sup> sperm/ml. 15% - 25% progressive motility and/or <20 million progressively motile spermatozoa in the ejaculate. 30%–50% normal morphology. Unexplained infertility was defined based on the following criteria: Normal semen analysis by WHO (1992) standards showing a count more than 20x10<sup>6</sup> sperm/ml, motility > 50% (grade a or b, within 60 minutes of ejaculation), morphology > 50% normal forms. Bilateral patent tubes based on hysterosalpingography and/or laparoscopy. Normal ovulation as evidenced by regular menstrual cycles and midluteal serum progesterone levels > 10 ng/ml.

Patients having bilateral tubal block as seen in hysterosalpingography or previously done diagnostic laparoscopy report were excluded. We also excluded women with endocrinological disorders in the form of thyroid hypo/hyperfunction, hyperprolactinemia and Cushing syndrome as detected by history, examination and investigations were excluded. For all the patients, Pelvic ultrasound was performed using a 6.5 MHz transvaginal transducer (Model Sonoline Prima, Siemens Medical Systems, Japan, serial number BBE2461).

#### Controlled Ovarian Stimulation

Women were randomly assigned to receive two different induction protocols, Protocol (A): Ovarian stimulation was achieved using clomiphene citrate (Clomiphene tablets, Clomiphene citrate 50 mg, The Arab Drug Company, ADCO, Egypt), 100 mg/day from day 2 of the onset of menstruation for five days, that is, till day 6 of the cycle. Protocol (B): Ovarian stimulation was accomplished using highly purified urinary FSH ampoules (Fostimon 75IU, IBSA Institut Biochimique SA, Switzerland), starting with one ampoule on day 3 of the onset of menstruation for five days, that is, till day 7 of the cycle.

Patients were monitored by transvaginal ultrasound folliculometry every other day starting on cycle day 8. The patient was evaluated regarding the number and size of the follicles as well as endometrial thickness and pattern.

Ovulation triggering by highly purified hCG (Choriomon 5000 IU, IBSA Institut Biochimique SA, Switzerland) intramuscular injection (10,000 IU) was done when the leading follicle reached  $\geq 18$  mm.



#### Intrauterine insemination

For IUI at the preset timing for each patient, 0.3–0.5ml of sperm suspension was drawn into a Sperm Trans IUI catheter (Sperm Processor, Aurangabad, India) attached to a 1-ml tuberculin syringe. The suspension then was injected slowly into the uterine cavity after exposing and cleansing the cervix with a bivalve speculum, a single toothed tenaculum was used to stretch the cervix only in cases where the catheter passage proved to be difficult. Patients remained in the supine position for 30 minutes after insemination.

#### Outcomes:

Pregnancy rates were detected by serum  $\beta$ hCG test performed 16 days after IUI for patients who had no menstruation. Vaginal ultrasound was performed 2 weeks after the first positive  $\beta$ hCG to confirm the presence of an intrauterine gestational sac. Chemical pregnancy was defined as a positive serum  $\beta$ hCG  $> 10$  mIU/ml with no gestational sac detected on vaginal ultrasound. Clinical pregnancy was defined as the presence of gestational sac and later evidence of fetal heart activity on vaginal ultrasound or products of conception histologically if abortion occurred. Both chemical and clinical pregnancies were recorded.

#### Statistical analysis

Data were statistically represented in terms of range, mean, frequency tables and standard deviation (S.D.) where appropriate. For statistical analysis of categorical data, the Fisher exact test or the chi2 test was used where appropriate. Continuous data were analyzed with the unpaired (two sample) student's t test where appropriate. Test results were considered significant  $< 0.05$ . All statistical calculations were done using the computer programs Arcus Quickstat Biomedical version 1.0 & Microsoft Excel version 2000.

Figure 1: Transvaginal ultrasound showing a trilaminar endometrium measuring 9.2 mm.

Figure 2: Transvaginal ultrasound showing a dominant follicle measuring 22mm



### Results

The study included forty-five patients with unexplained infertility and mild male factor having 125 IUI cycles. (66 cycles in Clomid group and 59 cycles in low dose hMG group). The hMG group yielded higher number of follicles during the stimulation cycles with a mean of  $2.7 \pm 1$  follicles compared to the clomide group with a mean of  $2.1 \pm 1.3$  follicles. This was statistically significant (P value 0.009), giving a higher chance of improving the pregnancy rates.

Also, the mean endometrial thickness was higher in the hMG group reflecting the anti-estrogenic effect of CC on the endometrium. This was  $10.2 \pm 1.7$  mm in the hMG group and  $9.9 \pm 2.2$  mm in the clomide group, but this was not statistically significant. There were 8 pregnancies in the 23 patients and 66 cycles in the clomide group and there were 14 pregnancies in the 22 patients and 59 cycles in the hMG group. There was no statistical significance in the pregnancy rates between the two groups Odds Ratio = 0.443 95% CI 0.171 - 1.149. P value = 0.071.

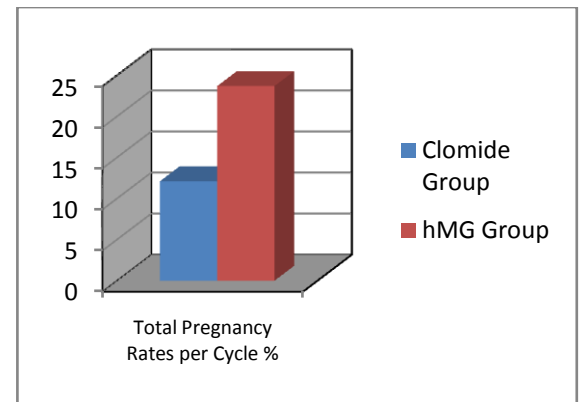


Table I: Comparison of pregnancy rates between the two groups.

	Clomide Group	hMG Group
Number of Patients	23	22
Number of Cycles	66	59
Clinical Pregnancy Rate per Cycle (%)	10.6	18.6
Chemical Pregnancy Rate per Cycle (%)	1.5	5.1
Total Pregnancy Rate per Cycle (%)	12.1	23.7

## Discussion

The rationale for the use of IUI in the management of infertility is to reduce the effect of factors that may impede the progress of spermatozoa, such as vaginal acidity and cervical mucus hostility, and to benefit from the deposition of a bolus of concentrated, motile, morphologically normal sperm as close as possible to the oocytes. While the rationale for the use of superovulation with IUI is to increase the number of oocytes available for insemination, and thus the chance of implantation occurring. [6]

Gonadotrophins have been long used for ovulation induction and recent evidence suggests that hMG could achieve better pregnancy rates over recombinant FSH [7]. Accordingly, we decided to use hMG for our participants especially that it is cheaper than recombinant FSH. In our study, patients were randomized to receive either clomiphene citrate, 100 mg per day from day 2 of the cycle for 5 days, or hMG 75IU per day from day 3 of the cycle for 5 days. The CC group included 23 patients who went through 66 cycles of IUI with 8 pregnancies (12.1%) and the hMG group included 22 patients performing 59 cycles of IUI with 14 pregnancies (23.7%). Although PR were higher in the hMG group no statistical significance was detected.

Our results are in line with a review of the efficacy of treatment for unexplained infertility, hyperstimulation with clomiphene citrate (CC) was shown to be a cost-effective treatment, although the use of gonadotrophin seemed to be a more efficacious option in IUI treatment [8]. Controlled ovarian hyperstimulation (COH) using gonadotrophins with IUI has been shown to be a most effective treatment of infertility compared with timed vaginal intercourse, intracervical insemination, or with IUI in natural cycles, presumably because it increases the number of available oocytes for fertilization and the number of spermatozoa that reach the oocyte [9].

Our results are also similar to studies published comparing the efficacy of CC with different types of gonadotrophins in IUI programs [10-12]. IUI cycles with hMG stimulation showed slightly higher but not significant pregnancy rates than cycles stimulated with CC [13]. A systematic review concluded that there is insufficient evidence to suggest that CC is inferior or superior to human menopausal gonadotrophin (hMG) or FSH in the treatment of unexplained infertility [14].

This review included trials comparing CC versus hMG or FSH in women with unexplained infertility, regardless of whether IUI or TI or direct intraperitoneal insemination was performed (i.e. all the insemination techniques were pooled together). The conclusion in this review was based on excluding two trials with hCG co-intervention in only the hMG or FSH treatment arm. However, when the two trials with co-intervention of hCG trigger injection were included, CC had a reduced odds of pregnancy compared to hMG or FSH.

In our study, low dose gonadotrophin induction was used which agrees with a Cochrane review involving forty three trials involving 3957 women. There were 11 comparisons in this review. Seven studies (n = 556) were pooled comparing gonadotrophins with anti-oestrogens showing significant higher pregnancy rates with gonadotrophins (OR 1.8, 95% CI 1.2 to 2.7).

Robust evidence is lacking but based on the available results gonadotrophins might be the most effective drugs when IUI is combined with ovarian hyperstimulation. When gonadotrophins are used for ovarian stimulation low dose protocols are advised since pregnancy rates do not differ from pregnancy rates which result from high dose regimen, whereas the chances to encounter negative effects from ovarian stimulation such as multiples and OHSS are limited with low dose gonadotrophins [15].

In conclusion, Induction of ovulation using low dose hMG was superior to using clomiphene citrate in the stimulated IUI cycles; with better pregnancy rates, follicular count and endometrial thickness.

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