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Bassem Sobhy
El-Galaa Maternity Teaching Hospital

M Yousef Elsemary
El-Galaa Maternity Teaching Hospital, myousef2@hotmail.com

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Original Article

The use of gonadotropin-releasing hormone antagonist in women undergoing intrauterine insemination

M. Yousef Elsemary, Bassem Sobhy
Obstetrics and Gynecology Department, El-Galaa Maternity Teaching Hospital, Cairo, Egypt

Abstract

Background
Intrauterine insemination (IUI) is considered to be a very popular treatment procedure that is used for many infertile women worldwide.

Aim
The aim was to evaluate whether the addition of gonadotropin-releasing hormone antagonist would improve the clinical pregnancy rate in women undergoing IUI.

Materials and methods
A prospective study was performed at El-Galaa Maternity Teaching Hospital where 124 women with primary or secondary infertility were subjected to controlled ovarian stimulation with human menopausal gonadotropin (74–150 IU/day) only (control group, *n*=62) or to human menopausal gonadotropin (75–150 IU/day) plus Cetrorelix (0.25 mg/day, starting when the leading follicle was ≥16 mm; *n*=62). A single insemination was performed 36 h after hCG was given (5,000 IU, intramuscularly) in both groups.

Main outcome measure(s)
Clinical pregnancy rate, premature luteinization (PL), and follicular development were measured.

Results
Clinical pregnancy rates (20 vs10.9%) and the number of mature follicles (2.2±1.1 vs 1.4±0.96) were statistically significantly higher in the antagonist group compared with the control group. The PL rate was significantly lower in the antagonist group (0.91 vs 4.61%).

Conclusion
The addition of a gonadotropin-releasing hormone antagonist to controlled ovarian stimulation and IUI was significantly associated with an increase in pregnancy rates in multifollicular cycles and a reduction in the incidence of PL.

Keywords: Gonadotropin-releasing hormone antagonist, intrauterine insemination, ovarian stimulation, pregnancy rates

Introduction

Intrauterine insemination (IUI) is probably one of the utmost applied assisted reproductive techniques worldwide. The use of IUI became very popular as a first-line treatment procedure in case of unexplained and mild male factor infertility. The success rates of this procedure are estimated to be between 10.5 and 17.9% per cycle [1].

The European Society of Human Reproduction and Embryology data reported that 162,843 IUI-H cycles were performed in 2009 compared with 135,621 cycles of classic in-vitro fertilization (IVF) during the same period [2]. Treatment with IUI-H is shorter, less invasive, and less expensive [3], with a lower multiple delivery rate (DR) (10.4 vs 20.2%) and lower morbidity than IVF [2]. The pregnancy rate per cycle (PR) with IUI-H is then comparable to that observed after IVF with mild ovarian stimulation [4].

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Correspondence to: M. Yousef Elsemary, MSc, FRCOG, El-Galaa Maternity Teaching Hospital, Cairo, Egypt, Tel: +20 100 848 5671. E-mail: myousef2@hotmail.com

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In France, the clinical pregnancy rate per IUI cycle is only 11.8%, and the rate of childbirth per cycle is below 9% [5]. Recently according to the French registry, the mean DR per insemination is 10.7%, with wide variations from one center to another (4.4–19%) [6].

Several factors could have an influence on the pregnancy rate after IUI such as women's age and indication for treatment, the obtained number of mature follicles, and the quality of the sperm[7] Cochrane meta-analysis[8] found significantly higher PR per IUI after the use of gonadotropins than CC (odds ratio: 1.8; 95% confidence interval: 1.2–2.7). Moreover, many reports showed that IUI combined with ovarian stimulation is associated with higher pregnancy rate compared with IUI alone [9,10].

One of the undesired mishaps during controlled ovarian stimulation (COS) is the occurrence of premature luteinization (PL), which could lead to cycle cancellation and cause severe patient distress. It has been estimated that PL can occur in up to 24% of COS [11].

Gonadotropin-releasing hormone antagonists (GnRH-a) have been introduced in clinical practice to prevent premature luteinizing hormone (LH) surge, and their suppressing effect on the pituitary is mediated immediately after their administration [12].

The use of the GnRH antagonist to control unexpected PL in COS–IUI cycles was first addressed by the work of Olivennes *et al.* [13].

The aim of this study was to assess whether the addition of gonadotropin-releasing hormone antagonist would improve the clinical pregnancy rate in women undergoing IUI.

Materials and methods

Ethics committee approval was taken. This was a prospective randomized study where 124 patients were recruited from El Galaa Maternity Teaching Hospital. All patients gave their informed consent for the participation in the study. The study included women with unexplained infertility and mild male factor infertility. Exclusion criteria were women with endometriosis or polycystic ovarian syndrome and if the follicle-stimulating hormone (FSH) was greater than 10 IU/ml. The cases were randomly divided into two groups. The first group is the GnRH antagonist only group (62 patients) and the second group is the GnRH antagonist plus Cetrorelix group (62 patients). The study was performed between March 2015 and October 2016. Inclusion criteria were women aged 20–38 years, with regular menstrual cycles, having primary or secondary infertility for more than 1 year, and with a BMI 24–32 kg/m^2. All patients underwent a hormonal profile; FSH, LH, estradiol (E2), and antimullerian hormone were measured at the second day of their menstrual cycle, and tubal patency test was performed (hysterosalpingography and/or diagnostic laparoscopy). Serum LH was also measured on the day of hCG administration, and an elevated LH greater than or equal to 10 IU/ml was used for a diagnosis of PL. On day 2 of the menstrual cycle and before the start of the treatment, transvaginal ultrasound was performed to ensure a normal uterine cavity and the absence of any ovarian cysts.

Semen was collected after 2–3 days of abstinence. It was either collected in the hospital or transferred to the laboratory within 0.5–1 h after collection. Male factor infertility diagnosis was based on the following WHO criteria: semen volume: 1.5 ml or more; sperm concentration: 15 million spermatozoa per ml or more; total sperm number: 39 million spermatozoa per ejaculate or more; total motility (percentage of progressive motility and nonprogressive motility): 40% or more motile or 32% or more with progressive motility; vitality: 58% or more live spermatozoa; and sperm morphology (percentage of normal forms): 4% or more. Mild male factor is a term that is used extensively in practice and in the literature. However, no formally recognized definition is currently available. In this study, we considered one or more variables below the WHO criteria as a case of male factor infertility.

Treatment was then started on the second day of the cycle in both groups with human menopausal gonadotropin (hMG) (Menogon-Ferring) dose of 75–150 IU/day. Transvaginal ultrasound was performed 6 days after COS to assess ovarian response and to adjust hMG dose. This was repeated every 2–3 days until the leading follicle had reached a mean diameter of 18–20 mm. Then 5,000 IU of hCG was given IM, and IUI was done after 36 h.

In the GnRH antagonist group, when the mean diameter of the leading follicle reached 16 mm, 0.25-mg Cetrotide was started daily up to the day of hCG administration. If more than three follicles were present at the time of hCG administration (>16–22 mm), then IUI was cancelled to avoid multiple pregnancy. Cancellation was also decided in case of unexpected premature ovulation diagnosed by LH greater than or equal to 10 IU/ml. In addition, if the semen total motile sperm count after preparation with the swim-up technique was less than 5 × 10 millions, then this couple was excluded from the study.

Semen for IUI was prepared using a standard swim-up technique. In both groups, a single insemination was performed 36 h after hCG using insemination catheter (Labotect Labor-Technik-Göttingen GmbH, 37087 Göttingen, Germany) inserted through the cervix. The inseminated volume was ~ 0.3 ml delivered into the uterine cavity, and bed rest was maintained for 10 min after IUI. Luteal support with progesterone was not used. Two weeks after the insemination procedure, an hCG assay was performed, and if positive, a transvaginal ultrasound was scheduled for 2 weeks later. Clinical pregnancy was defined as a positive hCG, together with a presence of a positive embryo heartbeat.

Results

Overall 124 patients were included in the study and were equally divided into two groups: one with antagonist and the

other is the control group. There were no statistically significant differences between the two groups regarding age, BMI, and the initial FSH, LH, and E2 (Table 1). There were also no statistically significant differences between the two groups in terms of duration of infertility and the total dose of hMG used (Table 1).

On the day of HCG, there was a statistically significant increase in the number of follicles with size greater than or equal to 16 mm in the antagonist group (2.2 ± 1.1 vs 1.4 ± 0.96; $P < 0.05$). In this respect, 44.8% of patients used hMG + Gn RH antagonist and 41.8% of patients used hMG alone, who recruited a single follicle. There was also a nonsignificant decrease in the level of E2 in the antagonist group (540 ± 168 vs. 660 ± 195 pg/ml) (Table 2).

Regarding the cancellation, of 126 cycles started, there was 11 (8.8%) cancellation (four patients in the antagonist group and seven in the control group). In six patients, the cancellation was due to PL (one patients in the antagonist group and five patients in the control group; $P < 0.05$), and in other five cases, it was done to avoid the risk of multiple pregnancy (three patients in the antagonist group vs two patients in the control group, a difference that was not statistically significant) (Table 2).

Regarding the pregnancy rates, there was a significant increase in pregnancy in the antagonist group compared with the control (20% 12/58 vs 10.9% 6/55; $P < 0.5$). It is to be mentioned that in patients who recruited only one follicle greater than 18 mm, there was no significant difference in pregnancy rates (15.3% 4/26 vs. 12.5% 4/32). However, if more than two follicles greater than 18 mm were recruited, the pregnancy rates was significantly increased in the antagonist group (25% 8/32 vs 8.6% 2/23) (Table 3).

There were no significant differences in the rates of single gestation or twins between the two groups, as shown in Table 3. There were no triplets in both groups.

Table 1: Comparison of baseline characteristics of patients (mean±SD); *P* values were not significant

Characteristics	GnRH anatgonist group (*n*=124)	Control group (*n*=124)	*P*
Age (years)	32.64±3.2	32.23±2.4	NS
BMI (kg/m^2)	24.6±4.5	24.2±3.9	NS
Basal FSH (mIU/l)	7.1±1.9	7.2±2.1	NS
Basal LH (mIU/l)	4.8±2.9	5.1±2.4	NS
Basal E2	42±18.2	38.2±30.2	NS

E2, estradiol; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

Table 2: Patient data during stimulation

Parameters	GnRH antagonist	Control	*P*
FSH total units	695.4±290	684.6±320	NS
Days of COS	8.2±2.4	7.8±2.8	NS
Number of follicles	2.5±1.2	1.4±1.1	<0.05 (S)
Monofollicular cycles	26/58 (44.8%)	23/55 (41.8%)	NS
Cancellation [*n* (%)]	4 (3.6%)	7 (6.4%)	NS
Cancellation due to risk of multiple pregnancy [*n* (%)]	3 (2.71%)	2 (1.81%)	NS
Cancellation due to PL [*n* (%)]	1 (0.91%)	5 (4.61%)	<0.05 (S)

COS, controlled ovarian stimulation; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; PL, premature luteinization; S, significance.

Table 3: Pregnancy rates

Parameters	GnRH antagonist [*n* (%)]	Control [*n* (%)]	*P*
Clinical pregnancy	12/58 (20)	6/55 (10.9)	<0.05
Pregnancies 1 follicle >18 mm	4/26 (15.3)	4/32 (12.5)	NS
Pregnancies >2 follicles >18 mm	8/32 (25)	2/23 (8.6)	<0.05
Singles	10/12 (84)	5/6 (83)	NS
Twins	2/12 (16)	1/6 (16.6)	NS
Triplets	0	0	

GnRH, gonadotropin-releasing hormone.

Discussion

IUI is one of the first lines of infertility treatment. Many efforts have been made to improve the results of this procedure. The meta-analysis by Luo *et al.*[14] drew a clear conclusion about the benefits of GnRH antagonists in COS for IUI.

In addition, a study by Monraisin *et al.* [15], where 707 patients entering the program to determine the best practice of IUI with partner's fresh sperm, showed that the use of GnRH antagonist has a positive effect on DR, particularly in the multifollicular stimulation.

This study showed that the use of GnRH antagonist was linked to an increase in pregnancy rates; however, this was only apparent in patients with multifollicular recruitment where more than one follicle greater than or equal to 18 mm was present on the day of hCG (2.5 ± 1.4 in the antagonist group compared with 1.4 ± 1.1 in the patients who did not used the GnRH antagonist).

The results of this study agreed with the results of the study by Gomez-Palomares *et al.*[16] who found that the clinical pregnancy rates were higher in the antagonist group only if more than one follicle greater than or equal to 18 mm was present on the day of hCG triggering. Bakas *et al.*[17] reported an improvement in pregnancy rate with a mean number of 2.1 ± 1.1 follicles.

On the contrary, Lambalk *et al.*[12] found no improvement with the use of GnRH antagonist; however, the number of mature follicles was only 1.3 ± 0.6.

We found that with the use of GnRH antagonist the recruited follicles can grow to the size of greater than or equal to 18 mm without the risk of premature ovulation and therefore the

pregnancy rates were increased owing to the presence of more than one follicles ready for fertilization.

On the contrary, when GnRH antagonist was not used, once the leading follicle reaches the size of 18 mm and irrespective of the number and the size of the other recruited follicles, hCG was given to avoid the risk of premature ovulation. In this case, the chances of pregnancy were considerably decreased because the pregnancy with IUI is related to the number of mature follicles that were present on the day of hCG [18,19].

Desynchronization between ovulation and insemination could contribute to the reduced chances of pregnancy where GnRH antagonist is not used because of a higher rate of premature LH surge when two or more follicles are recruited [20]. This finding was also confirmed by Luo *et al*.[14] who reported that the use of GnRH antagonist decreases the risk of PL by 78% (odds ratio: 0.22; 95% confidence interval: 0.16–0.30; $P = 0.00001$).

In our patients, there was no significant difference in the overall cancellation between the two groups. However, the cancellation from unexpected ovulation owing to PL was significantly higher in the group of patients not using the GnRH antagonist.

It is acknowledged that the risk of multiple pregnancy as well as ovarian hyperstimulation syndrome is associated with the number of follicles as well as the age of the woman [21,22]. We found in this study that there were no significant differences regarding multiple pregnancies between the two groups; 84% of the pregnancies in the antagonist group were single and 16% were twins. There were no triplets. None of the patients developed any symptoms of ovarian hyperstimulation syndrome.

In optimal IUI practice, bifollicular stimulation associated with the use of GnRH antagonists allows high DRs. However, the number of follicles recruited must be adjusted to the woman's age to limit the risk of multiple pregnancies, as in young age, the risk of multiple pregnancies is high even with bifollicular recruitment [15].

Considering the cost of adding GnRH in IUI cycles, although it might be seen an extra cost. we believe it could be of benefit to the patient, as it reduces the risk of cancellation owing to premature ovulation and improves the chances of pregnancy.

This study showed that the addition of GnRH antagonist to IUI cycles improved the pregnancy rates, and as IUI has the advantage of being shorter, less invasive, and less expensive[3] as well as lower morbidity than IVF [2], this makes it an attractive option in the treatment of unexplained subfertility. Recently, Nandi *et al.*[23] published a study evaluating the best first-line management option for the treatment of unexplained subfertility-controlled ovarian hyperstimulation with gonadotropins and IUI or IVF. The study shows that the singleton live birth rate with one IVF was not significantly different from three cycles of IUI + controlled ovarian hyperstimulation.

Conclusion

This study showed that the use of GnRH antagonist in patients undergoing IUI with COS with hMG can improve the pregnancy rate. This improvement in pregnancy rate is evident with the increased number of mature follicles. Multiple pregnancy is a real risk with IUI, and both clinicians and patients must be aware of that risk. Proper counselling is important, and bifollicular stimulation associated with the use of GnRH antagonists may be an ideal practice.

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Conflicts of interest

There are no conflicts of interest.

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