Research Article

iMedPub Journals
http://www.imedpub.com/

ARCHIVES OF MEDICINE
ISSN 1989-5216

2018
Vol.10 No.2:3

DOI: 10.21767/1989-5216.1000263

The Use of Gonadotropin Releasing Hormone Antagonist in Women Undergoing Intrauterine Insemination

Elsemary MY* **and Abdel Ghaffar BS**

El-Galaa Hospital, Al Qalayah, Boulaq, Cairo Governorate 11432, Egypt

***Corresponding author:** Elsemary MY, El-Galaa Hospital, Al Qalayah, Boulaq, Cairo Governorate 11432, Egypt, Tel: + 01270818583; E-mail: myousef2@hotmail.com

Received date: March 14, 2018; **Accepted date:** March 19, 2018; **Published date:** March 23, 2018

Citation: Elsemary MY, Abdel ghaffar BS (2018) The Use of Gonadotropin Releasing Hormone Antagonist in Women Undergoing Intrauterine Insemination. Arch Med Vol No:10 Iss No:2:3

Abstract

Background: Intrauterine insemination (IUI) is considered to be a very popular treatment procedure that is used for many infertile women worldwide. The aim of this study is to evaluate whether the addition of gonadotropin releasing hormone antagonist would improve the clinical pregnancy rate in women undergoing IUI.

Methods: A prospective study performed at El-Galaa Maternity Teaching Hospital where 124 women suffering from primary or secondary infertility were subjected to controlled ovarian stimulation (COS) with hMG (human menopausal gonadotropin) (74 to 150 IU/d) only (control group, n 62) or to hMG (75 to 150 IU/d) plus Cetrotide (0.25 mg/d, starting when the leading follicle was ≥ 16 mm; n 62). A single insemination was performed 36 hours after hCG was given (5,000 IU, IM) in both groups.

Main Outcome Measure: Clinical pregnancy rate, premature luteinization and follicular development.

Result: Clinical pregnancy rates (20% *vs.* 10.9%), 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 premature luteinization rate was significantly lower in the antagonist group (0.91% *vs.* 4.61%).

Conclusion: The addition of a GnRH 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 premature luteinization.

Keywords: GnRH antagonist; Pregnancy rates; IUI; Ovarian stimulation

Introduction

Intrauterine insemination 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 10.5-17.9% per cycle [1].

The European Society of Human Reproduction and Embryology (ESHRE) data report 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 (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].

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 delivery rate (DR) per insemination is 10.7%, with wide variations from one center to another (4.4% to 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 (OR 1.8; 95% CI, 1.2–2.7). Also, 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 causes severe patient distress. It has been estimated that PL can occur in up to 24% of COS. [11].

Gonadotropin-releasing hormone antagonists (GnRH-a) has been introduced in clinical practice to prevent premature 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 premature luteinization in controlled ovarian stimulation (COS)–intrauterine insemination (IUI) cycles was first addressed by, the work of Olivennes et al. [13].

This study's purpose is to assess whether the addition of gonadotropin releasing hormone antagonist would improve the clinical pregnancy rate in women undergoing IUI.

Material and Methods

This was a prospective randomized study where 124 patients were recruited from El Galaa Maternity Teaching Hospital. The study included women with unexplained infertility and mild male factor infertility. Exclusion criteria included women with endometriosis or polycystic ovarian syndrome and if the FSH was >10 IU/ml. The cases were divided into two groups. The first group is the GnRH antagonist group (62 patients) and the second group (62 patients). The study was performed between March 2015 and October 2016. Inclusion criteria included women aged 20-38, with regular menstrual cycles, primary or secondary infertility for more than one year, a body mass index 24 to 32 kg/m^2. All patients underwent a hormonal profile; FSH, LH, E2, AMH measured at the second day of their menstrual cycle, tubal patency test (hysterosalpingography and/or diagnostic laparoscopy). Serum LH was also measured on the day of hCG administration and an elevated LH ≥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 analysis was collected after 2-3 days of abstinence. It was either collected in the hospital or transferred to the laboratory within 1 to 2 hours after collection. Male factor infertility diagnosis was based on the World Health Organization 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 non-progressive motility): 40% or more motile or 32% or more with progressive motility, vitality: 58% or more live spermatozoa, 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 if one or more variables below the WHO criteria we considered this as a male factor infertility. Treatment was then started in both groups with hMG (Menogon Ferring) dose of 75 to 150 IU/day. Transvaginal ultrasound was performed 7 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 to 20 mm. Then 5,000 IU of hCG was given IM, and IUI was done after 36 hours.

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 to 22 mm), then IUI was cancelled to avoid multiple pregnancy. Cancellation was also decided in case of unexpected premature ovulation diagnosed by LH ≥ 10 IU/ml. Also, If the semen total motile sperm count after preparation with the swim-up technique was <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 hours after hCG using insemination catheter (Labotect, Germany) inserted through the cervix. The inseminated volume was approximately 0.3 mL delivered into the uterine cavity, and bed rest was maintained for 10 minutes after IUI. 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

An overall of 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, body mass index and the initial FSH, LH, 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).

Table 1: Comparison of baseline characteristics of patients, mean ± SD P values were not significant.

Characteristic	GnRH antagonist group (n =124)	Control group (n= 124)	P value
Age (Y)	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

On the day of HCG there was a statistically significant increase in the number of follicles with size ≥ 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 recruited one single follicle.

There was also a non-significant decrease in the level of E2 in the antagonist group (540 ± 168 *vs.* 660 ± 195 pg/ml) (Table 2).

As regard the cancellation; out of 126 cycles started there was 11 (8.8) cancellation (4 patients in the antagonist group and 7 in the control group).

In 6 patients, the cancellation was due to premature lutenization (1 patients in the antagonist group and 5 patients in the control group; P<0.05), and in 5, it was done to avoid the risk of multiple pregnancy (3 patients in the antagonist group vs. 2

patients in the control group, a difference that was not statistically significant) (Table 2).

Table 2: Patient data during stimulation.

Parameter	GnRH antagonist	Control	P value
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 ≥ 18 mm	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	3 (2.71%)	2 (1.81%)	NS
Cancellation due to PL	1 (0.91%)	5 (4.61%)	<0.05 (S)

As regard the pregnancy rates; there was a significant increase in pregnancy in the antagonist group compared to 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 >18 mm there was no significant difference in pregnancy rates (15.3% 4/26 *vs.* 12.5% 4/32). However if more than 2 follicles >18 mm recruited the pregnancy rates is significantly increased in the antagonist group (25% 8/32 *vs.* 8.6% 2/23) (Table 3).

Table 3: Pregnancy rates.

Parameter	GnRH antagonist	Control	P value
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	

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.

Discussion

Intrauterine insemination 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 controlled ovarian stimulation for IUI.

Also, in a study by Oriana 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 delivery rate, 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 appeared in patients with multifollicular recruitment where more than one follicle ≥ 18 mm was present on the day of hCG 2.5 ± 1.4 in the antagonist group compared to 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 ≥ 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 other hand, 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 ≥ 18 mm without the risk of premature ovulation and therefore the pregnancy rates were increased due to the presence of more than one follicles ready for fertilization.

On the other hand, 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 are considerably decreased because the pregnancy with IUI is related to the number of mature follicles that are present on the day of hCG [18,19].

Desynchronization between ovulation and insemination could also 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 premature luteinization by 78% (odds ratio 0.22; 95% confidence interzal, 0.16 to 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 duo to premature luteinization 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 about 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 delivery rates. 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 due to premature ovulation and improves the chances of pregnancy.

This study showed that the addition of GnRH antagonist to IUI cycles improves 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 Anupa et al. [23] published a study evaluating the best first line management option for the treatment of unexplained subfertility-controlled ovarian hyperstimulation(COH) with gonadotropins and IUI or IVF. The study shows that the singleton live birth rate with one IVF was not significantly different than three cycles of IUI + COH.

Conclusions

This study showed that the use of GnRH antagonist in patients undergoing IUI with COS 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.

References

1. Kaplan IF, Austin DJ, Freund R (2000) Subcutaneous human menopausal gonadotropin administration for controlled ovarian hyperctimulation with intrauterine inseniinatioii cycles. Am J Obssrrr Gynrrnl 182: 1421-1426.
2. Ferraretti AP, Goossens V, Kupka M, Bhattacharya S, de Mouzon J, et al. (2013) Assisted reproductive technology in Europe, 2009: Results generated from European registers by ESHRE. Hum Reprod 28: 2318-2331.
3. Abdelkader AM, Yeh J (2014) The potential use of intrauterine insemination as a basic option for infertility: A review for technology-limited medical settings. Obstet Gynecol Int.
4. Fauser BCJM, Nargund G, Andersen AN, Norman R, Tarlatzis B, et al. (2010) Mild ovarian stimulation for IVF: 10 years later. Hum Reprod 25: 2678-2684.
5. Annual report of the French Biomedicine Agency (2005).
6. Biomedicine Agency (2016) Evaluation of the results of laboratories providing medical assistance to procreation practicing intrauterine artificial insemination in vitro in France: National results report 2012. Saint-Denis la Plaine, France: Biomedecine Agency.
7. Merviel P, Heraud MH, Grenier N, Lourdel E, Sanguinet P, et al. (2010) Predictive factors for pregnancy after intrauterine insemination (IUI): An analysis of 1038 cycles and a review of the literature. Fertil Steril 93: 79-88.
8. Cantineau AEP, Cohlen BJ, Heineman MJ (2007) Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. Cochrane Database Syst Rev 2: CD005356.
9. Houmard BS, Juang MP, Soules MR, Fujimoto VY (2002) Factors influencing pregnancy rates with a combined clomiphene citrate-gonadotropin protocol for non-assisted reproductive technology fertility treatment. Fertil Steril 77: 384-386.
10. Steures P, Van Der Steeg JW, Verhoeve HR, van Dop PA, Hompes PG, et al. (2004) Does ovarian hyperstimulation in intrauterine insemination for cervical factor subfertility improves pregnancy rates?. Hum Reprod 16: 644-651.
11. Ragni G, Somigliana E, Vegetti W (2004) Timing of intrauterine insemination: Where are we?. Fertil Steril 82: 25-26.
12. Lambalk CB, Leader A, Olivennes F, Fluker MR, Andersen AN, et al. (2006) Treatment with the GnRH antagonist ganirelix prevents premature LH rises and luteinization in stimulated intrauterine insemination: Results of a double-blind, placebo-controlled, multicenter trial. Hum Reprod 21: 632-639.
13. Olivennes F, Fanchin R, Bouchard P, Taieb J, Frydman R (1996) Triggering of ovulation by a gonadotropin-releasing hormone (GnRH) agonist in patients pretreated with a GnRH antagonist. Fertil Steril 66: 151-153.
14. Luo S, Li S, Jin S, Li Y, Zhang Y (2014) Effectiveness of GnRH antagonist in the management of subfertile couples undergoing controlled ovarian stimulation and intrauterine insemination: A meta-analysis. PLoS One 9: e109133.
15. Monraisin O, Chansel-Debordeaux L, Chiron A, Floret S, Cens S, et al. (2016) Evaluation of intrauterine insemination practices: A 1-year prospective study in seven French assisted reproduction technology centers. Fertil Steril 105: 1589-1593.
16. Gomez-Palomares JL, Acevedo-Martin B, Chavez M, Manzanares M, Ricciarelli E, et al. (2008) Multifollicular recruitment in combination with gonadotropin-releasing hormone antagonist increased pregnancy rates in intrauterine insemination cycles. Fertil Steril 89: 620-624.
17. Bakas P, Konidaris S, Liapis A, Gregoriou O, Tzanakaki D, et al. (2011) Role of gonadotropin- releasing hormone antagonist in the management of subfertile couples with intrauterine insemination and controlled ovarian stimulation. Fertil Steril 95: 2024-2028.
18. Gomez-Palomares JL, Julia B, Acevedo-Martin B, Martinez-Burgos M, Hernandez ER, et al. (2005) Timing ovulation for intrauterine insemination with a GnRH antagonist. Hum Reprod 20: 368-372.

19. Kaplan PF, Katz SL, Thompson AK, Freund RD (2002) Cycle fecundity in controlled ovarian hyperstimulation and intrauterine insemination. Influence of the number of mature follicles at hCG administration. J Reprod Med 47: 35-39.

20. Dinelli L, Courbiere B, Achard V, Jouve E, Deveze C, et al. (2014) Prognosis factors of pregnancy after intrauterine insemination with the husband's sperm: Conclusions of an analysis of 2,019 cycles. Fertil Steril 101: 994-1000.

21. RagniG, Caliari I, Nicolosi AE, Arnoldi M, Somigliana E, et al. (2006) Preventing high-order multiple pregnancies during controlled ovarian hyperstimulation and intrauterine insemination: 3 years' experience using low-dose recombinant follicle-stimulating hormone and gonadotropinreleasing hormone antagonists. Fertil Steril 85: 619-624.

22. Dickey RP, Taylor SN, Lu PY, Sartor BM, Rye PH, et al. (2005) Risk factors for high-order multiple pregnancy and multiple birth after controlled ovarian hyperstimulation: Results of 4,062 intrauterine insemination cycles. Fertil Steril 83: 671-683.

23. Nandi A, Bhide P, Hooper R, Gudi A, Shahet A, et al. (2017) Intrauterine insemination with gonadotropin stimulation or in vitro fertilization for the treatment of unexplained subfertility: A randomized controlled trial. Fertil Steril 107: 1329-1335.