Evaluation of Role of GnRH Antagonist in Intrauterine Insemination (IUI) Cycles with Mild Ovarian Hyperstimulation (MOH): A Prospective Randomised Study

Leena Wadhwa^{1,4} · Rupali Khanna¹ · Taru Gupta¹ · Sangeeta Gupta¹ · Sarika Arora² · Sumi Nandwani³

Received: 18 May 2015 / Accepted: 11 December 2015 / Published online: 26 February 2016
© Federation of Obstetric & Gynecological Societies of India 2016

About the Author

Dr. Leena Wadhwa MD, DNB, MNAMS, FICOG, is working as Associate Professor, Obst & Gynae, at ESI-PGIMSR, Basaidarapur, New Delhi. She has received FOGSI Ethicon travelling fellowship in the field of endoscopy and FOGSI-Dr. Vasantben Shah overseas scholarship in Reproductive Medicine and Endoscopy. She has received training in embryology in Chennai, India. She has delivered Dr. Kamini Rao FOGSI Oration on Maternal Mortality at AICOG 2012 and edited the book on 'Current Concepts in Contraception & Women's Health'. She has 40 paper publications in International and National journals. Her field of interest is infertility and fertility-enhancing endoscopic surgery. She is an Executive member of Indian Fertility Society and endometriosis committee of AOGD.

Abstract

Aims and Objective To evaluate the role of GnRH antagonist in prevention of premature LH surge and

Presentation at a meeting: Presented paper on Evaluation of role of GnRH antagonist in Intrauterine insemination (IUI) cycles with mild ovarian hyperstimulation (MOH) at IFFS/ASRM, Boston, USA 12–17 October 2013.

Leena Wadhwa, M.D., DNB, is Associate Professor in Department of Obstetrics and Gynecology at ESI-Post Graduate Institute of Medical Science and Research; Rupali Khanna is ex post graduate student and senior resident of Department of Obstetrics and Gynecology at ESI-Post Graduate Institute of Medical Science and Research; Taru Gupta, M.D., is Associate Professor in Department of Obstetrics and Gynecology at ESI-Post Graduate Institute of Medical Science and Research; Sangeeta Gupta, M.D., is Assistant Professor in Department of Obstetrics and Gynecology at ESI-Post Graduate Institute of Medical Science and Research; Sarika Arora, M.D., is Associate Professor in Department of Biochemistry at ESI-Post Graduate Institute of Medical Science and Research; Sumi Nandwani, M.D., is Associate Professor in Department of Microbiology at ESI-Post Graduate Institute of Medical Science and Research.

increasing pregnancy rates in IUI cycle with mild ovarian hyperstimulation (MOH).

Study Design Prospective parallel, randomised controlled study.

Material and Methods Couples diagnosed with unexplained, male factor subfertility and with one or both tubes patent were randomised to receive either a GnRH antagonist (study group) or no intervention (control group). All

✉ Leena Wadhwa
drleena_123@yahoo.co.in

¹ Department of Obstetrics and Gynecology, ESI-Post Graduate Institute of Medical Science and Research, Basaidarapur, New Delhi 110015, India

² Department of Biochemistry, ESI-Post Graduate Institute of Medical Science and Research, Basaidarapur, New Delhi 110015, India

women were treated with clomiphene citrate (D3–D7) followed by HMG. A GnRH antagonist was added when one or more follicles of 16 mm diameter or more were visualised in the study group. When at least one follicle reached a size of ≥ 18 mm, ovulation was induced by hCG injection. A single IUI was performed 36 h later. The primary outcome was premature LH surge and pregnancy rate. The secondary outcomes were the amount of gonadotropins used, duration of use of GnRH antagonist and incidence and severity of OHSS.

Results A total of seventy patients attending the infertility clinic in the outpatient department of Obstetrics and Gynecology, of a tertiary care centre, were recruited in the study which was carried out from August 2011 to March 2013. The study group included 34 women and 36 in the control arm. The incidence of premature LH surge was significantly lower in the antagonist group as compared to the control group 2.9 vs. 13.9 %, with a *p* value of <0.001 . The clinical pregnancy rates were similar in both the groups 8.8 vs. 11.1 %, *p* value being 1.000. The amount of gonadotropins used in GnRH antagonist group was lower than in control group but not statistically significant. Duration of GnRH antagonist was 1.85 ± 0.61 days in the study group.

Conclusion The delayed administration of GnRH antagonists in MOH with IUI cycles when follicle size is ≥ 16 mm is beneficial in terms of preventing the occurrence of premature LH surge but with no improvement in pregnancy rates.

Keywords Mild ovarian hyperstimulation · Antagonist · IUI

Introduction

The special programme of research development and training in human reproduction of the WHO has estimated 60–80 million infertile couples worldwide. It has been estimated that in India between 10 and 15 % of the couples are infertile. As a result there is ever increasing demand for diagnostic and therapeutic interventions for the management of infertile couples. One in six couples requires referral to a fertility clinic.

Worldwide, intrauterine insemination is still one of the most applied treatment options for couples with long-standing subfertility caused by either hostile cervix, a male factor, or by unexplained infertility.

IUI when used in combination with mild ovarian hyperstimulation (MOH) improves the outcome. Several drugs are available to achieve MOH. Oral clomiphene citrate (CC) is first choice as it is inexpensive, does not require regular ultrasound monitoring and is thought to correct subtle ovulatory dysfunction. Besides CC, gonadotropins (HMG-LH + FSH, urinary and recombinant FSH) are used frequently for ovarian stimulation in IUI cycles [1, 2].

However, the application of MOH for IUI is associated with an increased risk of premature ovulation, a common cause of cancellation of assisted reproductive technology (ART) cycles [3]. Strategies to inhibit premature LH surges have primarily entailed the use of agents that modify the action of GnRH. Early attempts to prevent LH surges used GnRH agonists (e.g. leuprolide acetate). Daily administration of the agonist, after a transient initial stimulatory effect, results in downregulation of the pituitary GnRH receptors and suppression of pituitary gonadotropin release. The use of GnRH agonists leads to more aggressive stimulation with increased risk of ovarian hyperstimulation and rates of multiple pregnancies [4]. The need to control LH surge as well as to avoid expensive regimens involving prolonged agonist treatment led to the development of newer GnRH antagonists such as cetrorelix and ganirelix. GnRH antagonists suppress ovulation by competitively blocking GnRH receptors of the pituitary. The advantage with it is that it induces a rapid suppression of gonadotropin secretion without flare-up effect.

The majority of studies using MOH with antagonist have been carried out in ART cycles with variable effects on pregnancy rates. India being a developing country with increasing infertility rate requires a cheaper alternative to IVF and such studies carried out in the subcontinent are few.

This study was carried out to see whether the similar concept can be applied in IUI cycles with MOH with delayed administration of antagonist when follicle size reaches ≥ 16 mm, might prove beneficial to patients in terms of cost, prevention of premature LH surge and improvement in pregnancy rates.

Aims and Objectives

The aim of this study was to evaluate the role of GnRH antagonist in prevention of premature LH surge and its effect on increasing pregnancy rates in IUI cycle with mild ovarian hyperstimulation (MOH).

³ Department of Microbiology, ESI-Post Graduate Institute of Medical Science and Research, Basaidarapur, New Delhi 110015, India

⁴ Flat No 225, Sector-9, Pocket-1, DDA/SFS, Dwarka, New-Delhi 110075, India

Materials and Methods

This is a prospective parallel, randomised controlled study conducted in the Department of Obstetrics and Gynecology in a tertiary centre from August 2011 to March 2013. The study was approved by the institutional ethical committee. Couples attending the infertility clinic and planned for MOH with IUI were recruited for the study for first treatment cycle.

The inclusion criteria were women in the age 21–35 years with either primary or secondary infertility, BMI 18–30 kg/m², regular menstrual cycles (25–35 days), normal basal FSH (<10 m IU/l), women with unexplained infertility, mild male factor (minimum of 10 million sperms/ml), with patency of both or either one of the tubes (HSG/laprophysteroscopy). The women with age >35 years, antral follicle count <4, those with uterine anomalies, PCOS and endometriosis were excluded from the study.

The study was carried out as part of thesis work and was limited by time. All the patients fulfilling the inclusion criteria who presented in our OPD during the mentioned time period were included in the study.

Out of 110 patients assessed for eligibility, 76 patients fulfilling the inclusion criteria were enrolled in the study (consort flow diagram).

At recruitment informed consent was taken from each woman.

Patients were randomly allocated into two groups using randomisation table:

Group A (study group)—GnRH antagonist administered ($n = 37$)

Group B (control group)—GnRH antagonist not administered ($n = 39$)

All patients underwent baseline hormonal profile (S-FSH, S-LH, S-estradiol, S-prolactin, S-TSH), baseline USG on day 2/day 3 for antral follicle count and endometrial thickness.

Patients in both groups A and B, with normal hormonal profile and endometrial thickness <5 mm, underwent ovarian stimulation with clomiphene citrate (CC) 100 mg (days 3–7) followed by injection HMG 75 IU/150 IU daily depending on follicular response.

Follicle growth monitoring was carried out from day 8 of cycle in both the groups by the same resident doctor. Urinary LH was measured daily from day 10 of cycle/earlier if follicle size was ≥ 16 mm before day 10, using urinary LH kit. The urinary LH surge was measured using cassette test which is a qualitative immunoassay for detection of human luteinising hormone in urine sample. The test is considered positive if both the lines on the strip appear red.

Serum LH, progesterone and estradiol levels were measured on the day when follicle was ≥ 16 mm and again on the day of hCG trigger. The serum LH, FSH, prolactin,

estradiol and progesterone were measured with electrochemiluminescent analyser ROCHE e411 with a variation of <3 % for LH and <5 % for FSH, estradiol and progesterone, using kits, calibrators and controls from ROCHE.

Group A patients with negative LH surge received 0.25 mg of cetrorelix acetate subcutaneously when at least one follicle reached 16 mm and continued till it attained a diameter of 18–20 mm; 10,000 IU hCG was administered intramuscularly to patients in both the groups when follicle was ≥ 18 mm on USG and within 24–30 h of last dose of antagonist in group A. A single IUI was performed 36–40 h after hCG administration. Single IUI was carried out after 24–30 h in patients with positive LH surge after 10,000 IU hCG trigger. All patients received luteal phase support daily with micronised progesterone 200 mg BD vaginally. Pregnancy was checked by detection of beta-hCG in serum/urine 2 weeks after IUI.

The cut-off value of serum LH for premature LH surge was taken as 20 mIU/ml and that for premature progesterone rise as 1 ng/ml. The combination of the two (LH > 20 mIU/ml plus progesterone >1 ng/ml) was taken as premature luteinisation [5].

The trial could not be blinded as planned initially due to technical problems.

Consort flow diagram

Results

Statistical analysis was performed using statistical software (prism/SPSS).

The basic demographic profile was comparable in both the groups with similar age groups, rate of primary and secondary infertility. On analysing the type of infertility, it was found that 64.7 % ($n = 22$) couples in study group had primary infertility and 35.3 % ($n = 12$) had secondary infertility. In the control group, 72.2 % ($n = 26$) of couples had primary infertility and 27.8 % ($n = 10$) had secondary infertility. The majority of cases in our study had unexplained infertility (Table 1). The duration of infertility was in the range of 5–8 years in 41.2 % women in group A and 44.4 % in group B.

The total dose of gonadotropins (HMG used along with clomiphene citrate) used was similar in the group receiving GnRH antagonist ($313.24 + 127.21$) and the control group ($337.50 + 95.71$) with p value of 0.369. The duration of use of gonadotropins in both the groups was not significantly different with a p value of 0.968 (Table 2). The total duration of therapy (12.45 ± 1.91 days in the study group and 12.42 ± 1.75 days in the control group) in our study was similar in the two groups.

GnRH antagonist was administered in group A when at least one of the follicles was ≥ 16 mm and was continued till the follicle reached 18 mm diameter on USG. The mean duration of administration of GnRH antagonist was $1.85 + .61$ in the study group.

The mean serum LH and progesterone levels when follicle size was ≥ 16 mm and before starting antagonist

were similar in both the groups. In our study there was no case of premature LH surge in either of the groups till the day when follicle attained the size of 16 mm.

On the day of hCG trigger, serum LH values in GnRH antagonist group were significantly lower as compared to the control group with a p value of <0.001 . The progesterone values were lower in the GnRH antagonist group than in the control group with a p value of <0.001 . Estradiol levels were similar in the control group as compared to the study group with a p value of 0.989 (Table 3). In group A only one patient had premature LH surge and no patient with premature luteinisation, whereas in group B five patients had premature LH surge and one patient had premature luteinisation. Although the difference was statistically insignificant, apparently the number of premature LH surge was higher in the control group. The pregnancy rates were similar in both the groups. Three patients in group A and four patients in group B had positive urine pregnancy test, p value being 1.000 (Table 4).

The number of mature follicles ≥ 18 mm was similar in the two groups on the day of hCG trigger with p value of 0.854. The minimum number of follicles ≥ 18 mm on the day of trigger in group A was 1 and maximum number was 5. In group B the minimum number of follicle ≥ 18 mm was 1 and maximum was 6. The IUI cycles were cancelled if the maximum follicles were more than four on day of hCG trigger or serum E2 > 1500 pg/ml. The endometrial thickness on the day of hCG was higher in the control group (8.61 ± 1.17 mm) as compared to the study group (7.75 ± 1.24 mm). The difference is significant with a p value of 0.004.

One of the complications of ovulation induction is ovarian hyperstimulation syndrome. One patient in group A (2.9 %) and two patients (5.6 %) in group B had mild OHSS and were excluded from the study. This difference is statistically insignificant with p value of 1.000.

Table 1 Demographic profile and causative factors

	Group A ($n = 34$) (study group)	Group B ($n = 36$) (control group)
Age	27.88 ± 2.88 years	28.22 ± 3.14 years
BMI	21.47 ± 2.32	21.91 ± 2.09
Primary infertility	64.7 % ($n = 22$)	72.2 % ($n = 26$)
Secondary infertility	35.3 % ($n = 12$)	27.8 % ($n = 10$)
Tubal factor	11.8 % ($n = 2$)	5.6 % ($n = 3$)
Male factor	5.9 % ($n = 4$)	8.3 % ($n = 1$)
Unexplained infertility	82.4 % ($n = 28$)	86.1 % ($n = 31$)

Table 2 Total dose and duration of gonadotropins

Gonadotropins	Group A ($n = 34$)		Group B ($n = 36$)		p value
	Mean $\pm$ SD	Min–max	Mean $\pm$ SD	Min–max	
Total dose	313.24 ± 127.21	150–675	337.50 ± 95.71	150–525	0.369
Total duration	3.76 ± 1.54	2–8	3.75 ± 1.56	2–8	0.968

Discussion

Mild ovarian hyperstimulation (MOH) is defined as the administration of low doses (fewer days) of exogenous gonadotropins in GnRH antagonist co-treated cycles and/or

Table 3 Hormonal levels on day (D) follicle ≥ 16 mm and on day of hCG trigger

	Group A (<i>n</i> = 34) Mean	Group B (<i>n</i> = 36) Mean	<i>p</i> value
LH on D follicle ≥ 16 mm	7.71 $\pm$ 1.73	7.97 $\pm$ 2.42	0.606
Progesterone on D follicle > 16 mm	0.60 $\pm$ 0.20	0.57 $\pm$ 0.21	0.508
E2 on D hCG	502.4 $\pm$ 130.94	509.12 $\pm$ 180.75	0.989
LH on D hCG	4.9 $\pm$ 4.4	12.6 $\pm$ 8.5	<0.001
Progesterone on D hCG	0.35 $\pm$.15	0.8 $\pm$ 0.8	<0.001

oral compounds (like anti-estrogens or aromatase inhibitors) along with gonadotropins for ovarian stimulation, aiming to limit the number of oocytes obtained less than eight [6, 7]. MOH when used in combination with IUI improves the pregnancy outcome. Various studies have been carried out using low doses of exogenous gonadotropins with antagonist in IUI cycles and one study by Lee et al. [8] used letrozole with gonadotropins in IUI cycles. There is no study in literature using CC with gonadotropins with antagonist in IUI cycles. CC is cheap and simple to administer and has been in use since decades and is still the first-line therapy in normogonadotropic anovulatory women. The combination of CC plus gonadotropins has been a standard therapy. Due to the synergistic effect of these two, the amount of gonadotropins required is lower and so is the cost. But due to high rate of premature LH surges this stimulation protocol was not successful. Soft protocols such as CC + HMG seem to offer promising results when GnRH antagonist is administered over short period in midcycle, thus avoiding any premature LH surge. The majority of the studies of MOH with antagonist have been carried out in ART cycles.

The total dose of gonadotropins (HMG) used in our study was less as compared to other studies as it was used in combination with CC and antagonist was started when follicle ≥ 16 mm. The gonadotropin dose required in other studies was higher which can be attributed to the fact that other studies used only low dose gonadotropins with antagonist for stimulation.

The mean duration of administration of GnRH antagonist in our study was 1.85 ± 0.61 which was less as compared to

other studies. In the study conducted by Allegra et al. [9], the mean duration of GnRH antagonist was 3.5 ± 0.8 , and in study conducted by Cantineau et al., it was 2.2 days. This could be due to the fact that these studies started using GnRH antagonist when the follicle reached 14 mm, whereas in our study it was started when the follicle reached 16 mm. Study by Kamath et al. [10], Bakas et al. [11] and Gomez-Palomares et al. [12] used antagonist at follicle size of 16 mm. In our study no premature LH surge had occurred in either group when the follicle was ≥ 16 mm concluding that it is safe to administer GnRH antagonist with IUI on day till follicle reaches 16 mm. Lambalk et al. [13] have reported no case of premature LH surge before start of antagonist at follicle size of ≥ 14 mm.

Research has shown that in stimulated IUI cycles spontaneous LH surges occur frequently in upto one-third of all cycles resulting in higher cycle cancellation rates and lower pregnancy rates [6]. Our study demonstrates that treatment with GnRH antagonist (cetorelix) significantly reduces premature LH surge, progesterone rises and premature luteinisation. The serial LH surge detection in our study was carried out by urinary LH surge which demonstrated positive result with serum LH levels > 20 mIU/ml. The cut-off value of premature LH surge was slightly higher in our study as compared to other similar studies to keep false-positive results and thus cycle cancellations to a minimum. The cut-off of serum progesterone level was taken as 1 ng/ml as per different studies which show decrease in pregnancy rates at levels above 1 ng/ml.

The incidence of premature LH surge in study group was 2.9 %, whereas it was 13.9 % in the control group. With LH > 10 mIU/ml as cut-off the incidence of premature LH surge would have been 14.7 % in the study group and 38.8 % in the control group. The pregnancy rate in our study was comparable in the two groups (8.8 % in study group and 11.1 % in the control group). GnRH antagonist use did not show increased conception rate in our study. This may be related to long duration of infertility, unknown detrimental effects of antagonist on endometrium and small sample size.

According to a study conducted by Kamath et al. [10], the incidence of premature LH surge and premature luteinisation was lower in the antagonist group as compared to the control group not receiving GnRH antagonist

Table 4 Comparison of premature LH surge and pregnancy rates

	Group A (<i>n</i> = 34)		Group B (<i>n</i> = 36)		<i>p</i> value
	Frequency	%	Frequency	%	
Premature LH surge	1	2.9	6	16.7	0.192
Premature luteinisation	0	0.0	1	2.8	1.000
Pregnancy rate	3	8.8	4	11.1	1.000

(5 vs. 10.3 %, $p = 0.45$ and 5 % vs. 13.8, $p = 0.31$) but not statistically significant. The clinical pregnancy rates were lower in the antagonist group (2.8 vs. 10 %, $p = 0.12$), which was also not statistically significant. Study by Cantineau has reported no increase in live birth rates by adding a GnRH antagonist in cycles with MOH in an IUI program.

In a study conducted in 2006, Lambalk et al. [13] evaluated the role of the GnRH antagonist (ganirelix) in the treatment of subfertile couples. This study revealed that the incidence of LH surge (>10 mIU/ml) was lower in the group receiving GnRH antagonist (ganirelix) compared with the control group receiving only rFSH. It did not document any difference in pregnancy rates between the two groups.

Study conducted by Steward et al. [14], 2011, demonstrated decreased incidence of premature luteinisation 20 % ($n = 8$) with no effect on the pregnancy rates with the use of GnRH antagonist as compared to the patients not receiving GnRH antagonist 46.2 % ($n = 18$). Still other studies conducted by Williams et al. [15] and Ragni et al. [6] did not find any significant differences in regard to pregnancy rates between patients treated with rFSH + GnRH antagonist or rFSH alone.

In our study the number of mature follicles (≥ 18 mm) on the day of trigger is similar between the two groups. The mean value obtained in the study group was 1.65 ± 0.95 , and in the control group the mean was 1.94 ± 0.98 , with no statistical difference between the two ($p = 0.203$). In study conducted by Allegra et al. [9], the number of mature follicles on the day of trigger was similar in the two groups. In another study conducted by Lambalk et al. [13], there was no statistically significant difference in the number of mature follicles in the two groups. It was $1.3 + 0.6$ in the study group and $1.2 + 1.0$ in the control group.

In the study performed by Bakas et al. [11], the number of mature follicles was higher in the GnRH antagonist group ($2.1 + 1.08$ in the study group and $1.4 + .95$ in the control group) and the increasing pregnancy rate in antagonist group was related to the number of mature follicles. Study by Graziano et al. (European review MPS 2013) [16] found significant increase in number of mature follicles in antagonist group with a trend towards higher pregnancy rate.

The endometrial thickness in our study was more in the control group (8.61 ± 1.17 mm) as compared to the patients using GnRH antagonist (7.75 ± 1.24 mm). This could also be an incidental finding related to difference in patient profiles. Study conducted by Checa et al. [17] showed increased endometrial thickness in GnRH antagonist group as compared to the control group. Studies conducted by Lee et al. [8], Graziano et al. [16], Allegra et al. [9] and Steward et al. [14] did not show significant

difference between endometrial thicknesses in the two groups. Kolibianakis et al. [18] reported dysfunctional endometrium in IVF antagonist cycles.

Ovarian hyperstimulation syndrome is an iatrogenic complication of ovulation induction with exogenous gonadotropins. With regard to the stimulation protocol, no significant difference was found between the incidences of ovarian hyperstimulation syndrome in the two groups.

Study conducted by Allegra et al. [9] did not show any difference in the incidence of OHSS in patients using cetorelix and those who did not. There was no case of OHSS in either group. Study by Cantineau et al. [19, 20] and Kamath et al. [10] also did not show any significant difference with or without GnRH antagonist use. There were three cases in the control group and one case in the antagonist group of mild OHSS, and all were in cycles that resulted in pregnancy. Overall, the incidence of even mild OHSS was minimal.

Conclusion

Overall the regimen of using CC with HMG along with delayed administration of antagonist for 1–2 days when follicle is ≥ 16 mm is more cost-effective in terms of prevention of premature LH surge as it prevents cancellation of the cycle. Although the premature LH surges were prevented, no improvement in pregnancy rates was observed. The papers published in the past with improved pregnancy rates using antagonist have been carried out in IUI superovulated cycles using gonadotropins [21, 22]. A larger study is required to find out whether adding GnRH antagonist to mild ovarian stimulation protocol using CC with HMG improves the pregnancy rate. These results cannot be generalised and need to be validated with larger multicentric trials.

Compliance with Ethical Standards

Conflict of interest Leena Wadhwa, Rupali Khanna, Taru Gupta, Sangeeta Gupta, Sarika Arora, Sumi Nandwani declare that they have no conflict of interest.

Ethical Statement The study was approved by the Institute Ethics committee and is registered with Clinical Trial Registry India CTRI/2012/05/002682.

Informed consent Informed consent was obtained from all patients for being included in the study.

References

1. Cantineau AE, Janssen MJ, Cohlen BJ. Synchronised approach for intrauterine insemination in subfertile couples. *Cochrane Database Syst Rev.* 2010;14(4):006942. doi:[10.1002/14651858](https://doi.org/10.1002/14651858).

2. Mahani IM, Afnan M. The pregnancy rates with intrauterine insemination (IUI) in superovulated cycles employing different protocols (clomiphene citrate (CC), human menopausal gonadotropin (HMG) and HMG + CC) and in natural ovulatory cycle. *J Pak Med Assoc.* 2004;54(10):503–5.
3. Cantineau AE, Cohlen BJ, Dutch IUI study group. The prevalence and influence of LH surges in stimulated cycles combined with IUI during a prospective cohort study. *Fertil Steril.* 2007;88:107–12. doi:[10.1016/j.fertnstert.2006.11.136](https://doi.org/10.1016/j.fertnstert.2006.11.136).
4. Bellver J, Labarta E, Bosch E, et al. GnRH agonist administration at the time of implantation does not improve pregnancy outcome in intrauterine insemination cycles: a randomized controlled trial. *Fertil Steril.* 2010;94(3):1065–71. doi:[10.1016/j.fertnstert.2009.04.044](https://doi.org/10.1016/j.fertnstert.2009.04.044).
5. Speroff L, Fritz MA. Clinical gynaecologic endocrinology and infertility. 8th ed. Philadelphia: Lippincott Williams and Wilkins; 2011. p. 1304. Chapter 31, Induction of ovulation.
6. Ragni G, Alagna F, Brigante C, et al. GnRH antagonists and mild ovarian stimulation for intrauterine insemination: a randomized study comparing different gonadotrophin dosages. *Hum Reprod.* 2004;19(1):54–8. doi:[10.1093/humrep/deh023](https://doi.org/10.1093/humrep/deh023).
7. Al-Inany H, Azab H, El-Khayat W, et al. The effectiveness of clomiphene citrate in LH surge suppression in women undergoing IUI: a randomized controlled trial. *Fertil Steril.* 2010;94(6):2167–71. doi:[10.1016/j.fertnstert.2010.01.069](https://doi.org/10.1016/j.fertnstert.2010.01.069).
8. Lee TH, Lin YH, Seow KM, et al. Effectiveness of cetrorelix for the prevention of premature luteinizing hormone surge during controlled ovarian stimulation using letrozole and gonadotropins: randomized trial. *Fertil Steril.* 2008;90(1):113–20. doi:[10.1016/j.fertnstert.2007.06.029](https://doi.org/10.1016/j.fertnstert.2007.06.029).
9. Allegra A, Marino A, Coffaro F, et al. GnRH antagonist induced inhibition of the premature LH surge increases pregnancy rates in IUI-stimulated cycles. A prospective randomized trial. *Hum Reprod.* 2007;22:101–8. doi:[10.1093/humrep/del337](https://doi.org/10.1093/humrep/del337).
10. Kamath MS, Ramya R, Bhav P, et al. Effectiveness of GnRH antagonist in intrauterine insemination cycles. *Eur J Obstet Gynecol Reprod Biol.* 2013;166(2):168–72. doi:[10.1016/j.ejogrb.2012.09.023](https://doi.org/10.1016/j.ejogrb.2012.09.023).
11. Bakas P, Konidaris S, Liapis A, et al. Role of gonadotropin-releasing hormone antagonist in the management of subfertile couples with intrauterine insemination and controlled ovarian stimulation. *Fertil Steril.* 2011;95(6):2024–8. doi:[10.1016/j.fertnstert.2011.01.167](https://doi.org/10.1016/j.fertnstert.2011.01.167).
12. Gomez-Palomares JL, Acevedo-Martin B, Chavez M, et al. Multifollicular recruitment in combination with Gonadotropin-releasing hormone antagonist increased pregnancy rates in intrauterine insemination cycles. *Fertil Steril.* 2008;89(3):620–4.
13. Lambalk CB, Leader A, Olivennes F, et al. Treatment with the GnRH antagonist ganirelix prevents premature LH rises and luteinization in stimulated intrauterine insemination: results of a double-blind, placebo-controlled, multicentre trial. *Hum Reprod.* 2006;21(3):632–9. doi:[10.1093/humrep/dei386](https://doi.org/10.1093/humrep/dei386).
14. Steward RG, Gill I, Williams DB, et al. Cetrorelix lowers premature luteinization rate in gonadotropin ovulation induction–intrauterine insemination cycles: a randomized-controlled clinical trial. *Fertil Steril.* 2011;95(1):434–6. doi:[10.1016/j.fertnstert.2010.07.1076](https://doi.org/10.1016/j.fertnstert.2010.07.1076).
15. Williams RS, Hillard JB, De Vane G, et al. A randomized, multicenter study comparing the efficacy of recombinant FSH vs recombinant FSH with Ganirelix during superovulation/IUI therapy. *Am J Obstet Gynecol.* 2004;2:648–51. doi:[10.1016/j.ajog.2004.06.072](https://doi.org/10.1016/j.ajog.2004.06.072).
16. Graziano A, Caserta D, Piva I, et al. The addition of GnRH antagonists in intrauterine insemination cycles: a pilot study. *Eur Rev Med Pharmacol Sci.* 2013;17(12):1604–10.
17. Checa MA, Prat M, Robles A, et al. Use of gonadotropin-releasing hormone antagonists to overcome the drawbacks of intrauterine insemination on weekends. *Fertil Steril.* 2006;3:573–7. doi:[10.1016/j.fertnstert.2005.08.040](https://doi.org/10.1016/j.fertnstert.2005.08.040).
18. Kolibianakis E, Bourgain C, Albano C, et al. Effect of ovarian stimulation with recombinant follicle-stimulating hormone, gonadotropin releasing hormone antagonists, and human chorionic gonadotropin on endometrial maturation on the day of oocyte pick-up. *Fertil Steril.* 2002;78:1025–9.
19. Cantineau AE, Cohlen BJ, Klip H, et al. The addition of GnRH antagonists in intrauterine insemination cycles with mild ovarian hyperstimulation does not increase live birth rates—a randomized, double-blinded, placebo-controlled trial. *Hum Reprod.* 2011;26(5):1104–11. doi:[10.1093/humrep/der033](https://doi.org/10.1093/humrep/der033).
20. Cantineau AE, Cohlen BJ, Heineman MJ. Ovarian stimulation protocols (anti-oestrogens, gonadotropins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. *Cochrane Database Syst Rev.* 2007;2:CD005356. doi:[10.1002/14651858.CD005356.pub2](https://doi.org/10.1002/14651858.CD005356.pub2).
21. Kosmas IP, Tatsioni A, Kolibianakis EM, et al. Effects and clinical significance of GnRH antagonist administration for IUI timing in FSH superovulated cycles: a metaanalysis. *Fertil Steril.* 2008;90(2):367–72. doi:[10.1016/j.fertnstert.2007.06.064](https://doi.org/10.1016/j.fertnstert.2007.06.064).
22. Luo S, Li S, Jin S, et al. Effectiveness of GnRH antagonist in the management of subfertile couples undergoing controlled ovarian stimulation and intrauterine insemination: a meta-analysis. *PLoS One.* 2014;9(10):e109133. doi:[10.1371/journal.pone.0109133](https://doi.org/10.1371/journal.pone.0109133).