IN THE NAME OF GOD

ISFAHAN UNIVERSITY OF MEDICAL SCIENCE
GYNECOLOGY DEPARTMENT

Thesis for obtaining the speciality degree in Gynecology

Title :

Investigation of outcome of assessment reproduction treatment and prevention of ovarian hyper stimulation syndrome in GnRH agonist protocol compared to GnRH antagonist protocol

NUMBER:390428

Author :
Dr.Setareh Nasiri Zeidi

Supervisor's :
Dr.Behnaz Khani (Associate Professor of Gynecology)

Summer 2012

دانشکده پزشکی

بسمه تعالی

پس از حمد خدا و درود وصلوات بر محمد و آل محمد(ص)

جلسه دفاع از پایان نامه تحقیقاتی آقای / خانم

دکتر.....سیمین نصیری.....

تحت عنوان:.....Investigation of outcome of assessment reproduction treatment and prevention of ovarian hyperstimulation in CinRH agonist protocol compared to CinRH antagonist protocol.....

برای دریافت درجه دکترای تخصصی رشته .....زنان..... در تاریخ .....۹۱/۳/۲۵..... با حضور امضاء کنندگان زیر تشکیل و پس از ارائه پلیان نامه و بحث و بررسی با درجه .....عالی.....

عالی

مورد تصویب قرار گرفت.

اساتید راهنما: دکتر.....بهناز خانی.....

دیگر اعضای هیات داوران:

۱- دکتر مرادیان

۲- دکتر خانی

۳- دکتر شهریان

۴- دکتر مردانیان

۵- دکتر دانش

دکتر نقشینه

دکتر روح الامین

دکتر [illegible]

دکتر مستاجران

دکتر طهرانی

دکتر تهیری

مدیر گروه:.....دکتر بهناز خانی.....

معاون پژوهشی دانشکده پزشکی : دکتر طالب آزرم

معاون آموزشی / تخصصی دانشکده پزشکی : دکترسید مجتبی ابطحی

YAHOO! MAIL Classic

Thursday, August 23, 2012 1:49 AM

[JRMS]:Article provisionally accepted.

From: "Journal of Research in Medical Sciences" <jrms@mui.ac.ir>

To: setare_n99@yahoo.com

If you cannot see this page properly, please **click here.**

Dear Dr. Nasiri zeidi,

We are pleased to inform that your manuscript "Investigation of outcome of assessment reproduction treatment and prevention of ovarian hyper stimulation syndrome in GnRH agonist protocol compared to GnRH antagonist protocol." is provisionally accepted. You would receive an edited version of article in about 2-3 weeks from now for a final check and correction.

The journal does not charge for submission, processing or publication of manuscripts and except for color reproduction of photographs.
We thank you for submitting your valuable research work to Journal of Research in Medical Sciences.
With warm personal regards,

Yours sincerely,
Nastaran Eizadi-Mood
Journal of Research in Medical Sciences

Message sent on Thursday, August 23, 2012
Please add **jrms@mui.ac.ir** as a contact in your E-mail client to ensure that this mail is not considered as a junk mail.

--- END OF MESSAGE ---

مجله پژوهش در علوم پزشکی
Journal of Research in Medical Sciences

مجله پژوهش در علوم پزشکی

Investigation of pregnancy outcome and ovarian hyper stimulation syndrome prevention in agonist and antagonist gonadotropin-releasing hormone protocol

Abstract:

Background:

Given the controversies regarding the effectiveness of gonadotropin-releasing hormone (GnRH) antagonists in ovarian stimulation, this study was designed to compare GnRH agonist protocol with GnRH antagonist protocol in ovarian stimulation of patients who were candidate for assisted reproductive techniques (ARTs).

Methods:

This investigation was performed on 136 patients who were randomly allocated to two groups of GnRH agonist and GnRH antagonist. In the first group stimulation was performed by administration of Buserelin, and in the second group, it was performed by giving Cetrorelix. Then patients were compared regarding results of ovarian stimulation, pregnancy outcomes and rate of ovarian hyperstimulation syndrome (OHSS).

Results:

There were not significant differences between 2 groups regarding the ovarian stimulation, pregnancy outcomes and rate of OHSS (P value > 0.05).

Conclusion:

Administration of GnRH antagonists in ovarian stimulation will be a reasonable option to GnRH agonists **in assessment reproduction treatment** ; however, further studies are suggested.

Keywords:

Assisted reproductive techniques, GnRH antagonist, GnRH agonist, pregnancy rate, ovarian hyperstimulation syndrome, ovarian stimulation

Introduction:

In vitro fertilization (IVF) has been widely used to treat most causes of subfertility; however, pregnancy rate following IVF remains around 20-30% per started cycle. Therefore, some adjuvant therapies are used to achieve better outcomes (1). Administration of high doses of exogenous gonadotropins stimulates ovaries, and improves IVF success rate (1-2). In order to prevent the premature surge of luteinizing hormone (LH), Gonadotropin-releasing hormone (GnRH) agonists were introduced in ovarian stimulation for IVF(3). Despite several benefits, use of GnRH agonists is associated with some adverse effects including initial flare up with possible ovarian cyst formation and gonadotrophin release down-regulation which may cause spotting, hot flushes tiredness, sleep disturbance, headaches and dizziness. In addition, along with the increased rate of pregnancy, long GnRH agonist protocols are associated with increased incidence of ovarian hyperstimulation syndrome (OHSS) (3-4).

Given the potentially fatal outcomes related to OHSS, many studies are performed to find out safer methods of ovarian stimulation therapy to minimize this risk. Treatment with GnRH antagonists is considered as an alternative for prevention of premature LH surge during ovarian stimulation. In contrast with GnRH agonists which downregulate pituitary GnRH receptors, and desensitize gonadotropic cells, GnRH antagonists bind pituitary GnRH receptors competitively, and inhibit gonadotropin release directly (3, 5). Lower incidence of OHSS has been reported in recent studies after using GnRH antagonists (6); however, some other studies doubted these results(7).

Given the controversies regarding the effectiveness of gonadotropin-releasing hormone (GnRH) antagonists in ovarian stimulation, this study was designed to compare GnRH agonist protocol with GnRH antagonist protocol in ovarian stimulation of patients who were candidate for assisted reproductive techniques (ARTs).

Materials and methods:

Study design and patients:

This randomized clinical trial (RCT) was performed on women who were referred to the infertility center of Beheshti hospital, Isfahan, Iran, for IVF or intra cytoplasmic sperm injection (ICSI).from2009-2011

-According to the study criteria, 136 patients were randomly allocated to 2 groups: 67 patients were treated with GnRH agonist, and 69 patients were treated with GnRH antagonist.Paitients selected by simple randomaized Inclusion criteria were undergoing assisted reproduction techniques (ARTs) for the first time, age ≤35years and serum FSH level ≤10 IU/literin3th *days of menstrual cycle* and male or female factor

In addition to women with the previous history of IVF or ICSI, patients who had hyperprolactinemia, thyroid dysfunction, uterine abnormality, severe endometriosis(diagnose d by laparoscopy) and secondary infertility were excluded from the study(8).

Intervention:

According to the previous studies, treatment protocols were defined for patients in each group (8-11).

In the first group, a daily dose of Buserelin 500 µg (Suprefact, Aventis, Germany) was given to the patients subcutaneously. Treatment was commenced on the 21st day of pervious menstrual cycle, and vaginal ultrasonography was done and Buserelin continued onward until the baseline evaluation of serum level of estradiol (E2) on the second day of the menstruation.

If the serum level of E2 is less than 50 pg/ml, the dose of Buserline would be reduced to 250 µg per day, and ovarian stimulation would be commenced with subcutaneous injection of recombinant FSH (Gonal F, Serono, Switzerland), 75 IU daily.

In the second group, GnRH antagonist (Cetrorelix , Serono, Switzerland) was administered. Ovarian stimulation was started on the second day of the cycle by subcutaneous injection of 75 IU of recombinant FSH daily.

On the sixth day of stimulation, 0.25 mg Cetrorelix was initiated when the follicle reaches to14 mmdiameter. Based on the ovarian response detected by ultrasonography every 2-3 days, gonadotropin dose was adjusted in both groups. Administration of Buserelin and Cetrorelix was continued until the time of human chorionic gonadotropin (HCG) injection.

When at least 3 follicles with a mean diameter of 18 mm were developed, HCG 10,000 IU (Profasi, Serono, Switzerland) was injected intramuscularly.

At this stage, endometrial thickness was studied Trans vaginal ultrasonographically, and after 36 hours, oocyte retrieval was performed.

After IVF or ICSI, Cyclogest suppository 800 mg (Abureihan, Iran) was prescribed daily to provide luteal phase support. Cyclogest was continued till the activity of fetal heart was confirmed Trans vaginal ultrasonographically.

Sixteen days after the oocyte retrieval, serum HCG level was checked to determine chemical pregnancy (8). TVS was carried out for clinical determination of pregnancy.

Patients with ovarian enlargement up to 12 by 12 cm, accompanied by abdominal discomfort and gastrointestinal symptoms, or a sudden weight increase more than 3 kg were considered as moderate OHSS (8-11).

Severe OHSS was described as presence of enlarged ovarian cysts more than more than 12 by 12 cm, ascites, pleural and/or pericardial effusion, electrolyte imbalance (hyponatremia, hyperkalemia), hypovolemia, and hypovolemic shock (12-14).

Statistical analysis:

Data were analyzed by SPSS 16 software chicago, IL, USA). Chi-square and independent T-test were used for the analysis. P-values less than 0.05 were considered statistically significant.

Ethical issues:

This study was approved by the ethic committee of Isfahan University of Medical Sciences(IRCT201205309910N1). The study was completely explained to the patients, and informed consent was obtained before starting the intervention.

Results:

There was no statistically significant difference in the baseline characteristics between 2 groups (table-1).

Table-1 baseline characteristics of patients

	Agonist group (N=67)	Antagonist group (N=69)	p-value
Age(year)	28.65±3.94	28.36±3.40	0.64

BMI (kg/m2)	24.94±2.53	24.91±2.57	0.95
Basal FSH (IU/L)	5.98±1.73	5.94±1.62	0.90

Data are presented as mean±SD

BMI: body mass index

FSH: follicle-stimulating hormone

No significant difference was found between 2 groups regarding the duration of the treatment, the number of retrieved oocytes, number of transferred embryo and serum E2 level on the day of HCG administration; however, in the antagonist group, the total number of gonadotropin ampoules was significantly lower than the agonist group (Table-2).

Table-2 comparison of results of the ovarian stimulation between 2 groups

	Agonist group (N=67)	Antagonist group (N=69)	p-value
Treatment duration (day)	12.11±2.63	12.25±2.82	0.78
Retrieved oocytes (number)	9.76±5.22	9.29±4.80	0.59
Serum E2 level (pg/ml) in day of HCG adminastration	1,144.04±490.10	1,227.48±435.71	0.29
Gonadotropin ampoules (number)	20.14±9.51	17.04±6.04	0.02

Transferred embryo (number)	2.71±0.86	2.66±0.90	0.74

Data are presented as mean±SD

Serum E2 level: serum estradiol level on day of administration of HCG

Despite higher relative frequency of chemical pregnancy and ongoing pregnancy and lower rate of OHSS (moderate and severe) in the antagonist group, no significant difference was observed between 2 groups (Table-3).

Table-3 comparison of outcomes between 2 groups

		Agonist group (N=67)	Antagonist group (N=69)	p-value
Chemical pregnancy	Positive	23(34%)	24(35%)	0.55
	negative	44(66%)	45(65%)	
Clinical pregnancy	Positive	21(31%)	20(29%)	0.45
	negative	46(69%)	49(71%)	

effective and safe as GnRH agonists. Moreover, less need for gonadotropin consumption decreases the procedure cost and adverse effects. However, in order to overcome the controversies, further studies with larger sample size are needed to investigate and compare different treatment protocols.

References:

1. Macklon NS, Stouffer RL, Giudice LC, Fauser BCJM. The science behind 25 years of ovarian stimulation for in vitro fertilization. Endocr Rev. 2006;27(16434510):170-207.
2. Santos MA, Kuijk EW, Macklon NS. The impact of ovarian stimulation for IVF on the developing embryo. Reproduction. 2010 Jan;139(1):23-34.
3. Al-Inany H, Wahba A, Peitsidis P. Changing attitudes in ovarian stimulation. Womens Health (Lond Engl). 2011 Sep;7(5):505-7.
4. Comparable clinical outcome using the GnRH antagonist ganirelix or a long protocol of the GnRH agonist triptorelin for the prevention of premature LH surges in women undergoing ovarian stimulation. Hum Reprod. 2001 Apr;16(4):644-51.
5. Felberbaum RE RT, Kuper W et al. Preserved pituitary response under ovarian stimulation with hMG and GnRHantagonists (Cetrorelix) in women with tubal infertility. Eur J Obstet Gynecol Reprod Biol. 1995;61(2):151-5.
6. Ludwig M, Katalinic A, Banz C, Schroder AK, Loning M, Weiss JM, et al. Tailoring the GnRH antagonist cetrorelix acetate to individual patients' needs in ovarian stimulation for IVF: results of a prospective, randomized study. Hum Reprod. 2002 Nov;17(11):2842-5.
7. Al-Inany H, Aboulghar M. GnRH antagonist in assisted reproduction: a Cochrane review. Hum Reprod. 2002 Apr;17(4):874-85.
8. Firouzabadi RD, Ahmadi S, Oskouian H, Davar R. Comparing GnRH agonist long protocol and GnRH antagonist protocol in outcome the first cycle of ART. Arch Gynecol Obstet. 2010 Jan;281(1):81-5.
9. Cedrin-Durnerin I G-DD, LaVy A et al. Recombinant human LH supplementation during GnRH antagonist administration in IVF/ICSI cycles: A prospective randomized study. Hum Reprod. 2004;19:1979-84.
10. Berin I, Stein DE, Keltz MD. A comparison of gonadotropin-releasing hormone (GnRH) antagonist and GnRH agonist flare protocols for poor responders undergoing in vitro fertilization. Fertil Steril. 2010 Feb;93(2):360-3.
11. Aboulghar MA MR, Serour GI et al. Increasing the dose of human menopausal gonadotropins on the day of GnRH antagonist administration: randomized controlled trial. Reprod Biomed Online. 2004;8:524–7.
12. Elchalal U, Schenker JG. The pathophysiology of ovarian hyperstimulation syndrome--views and ideas. Hum Reprod. 1997;12(9221989):1129-37.
13. Knox CL, Allan JA, Allan JM, Edirisinghe WR, Stenzel D, Lawrence FA, et al. Ureaplasma parvum and Ureaplasma urealyticum are detected in semen after washing before assisted reproductive technology procedures. Fertil Steril. 2003;80(14556813):921-9.

14. Whelan JG, Vlahos NF. The ovarian hyperstimulation syndrome. Fertil Steril. 2000;73(10785212):883-96.
15. The European and Middle East Orgalutran Study Group. Comparable clinical outcomes using the GnRH agonist Triptorelin for the prevention of premature LH surges in women undergoing ovarian stimulation. Hum Reprod. 2001;16:644-51.
16. The North American Ganirelix study Group. Efficacy and safety of ganirelix acetate versus leuprolide acetate in women undergoing controlled ovarian hyperstimulation. Fertil Steril. 2001;75:38-45.
17. Tarlatzis BC, Fauser BC, Kolibianakis EM, Diedrich K, Rombauts L, Devroey P. GnRH antagonists in ovarian stimulation for IVF. Hum Reprod Update. 2006 Jul-Aug;12(4):333-40.
18. Nikolettos N A-HS, Felberbaum R, Demirel LC, Kupker W, Montzka P, et al. Gonadotropin-releasing hormone antagonist protocol: a novel method of ovarian stimulation in poor responders. Eur J Obstet Gynecol Reprod Biol. 2001;97:202-7.
19. Varney NR, Syrop C, Kubu CS, Struchen M, Hahn S, Franzen K. Neuropsychologic dysfunction in women following leuprolide acetate induction of hypoestrogenism. J Assist Reprod Genet. 1993 Jan;10(1):53-7.
20. Tazequl A GH, Ozdemir S et al. Comparison of multiple dose GnRH antagonist and minidose long agonist protocol in poor responders undergoing invitro fertilization: a randomized controlled trial. Arch Gynecol Obstet. 2008;278:467-72.
21. Xavier P CC, Calejo L et al. A randomized s tudy of GnRH antagonist versus agonist for ovarian stimulation. Eur J Obstet Gynecol Reprod Biol 2005;120:185-9.
22. Sirayapiwat P SS, Triratanachat S et al. The effect of GnRH antagonist on the endometrium of normally menstruating women. J Assist Reprod Genet. 2007;24:579-86.
23. Orvieto R RJ, Meltzer S et al. GnRH agonist versus GnRH antagonist in ovarian stimulation: is the improper naker? Clin Exp Obstet Gynechol. 2006;33:197-9.