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Original Article

Efficacy of daily GnRH agonist for luteal phase support following GnRH agonist triggered ICSI cycles versus conventional strategy: A Randomized controlled trial

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ABSTRACT

Objective: The use of gonadotropin-releasing hormone agonist (GnRHa) as an alternative for human chronic gonadotropin (hCG) trigger has potential benefits, but the optimal luteal phase support (LPS) following GnRHa trigger remains to be elucidated. We aimed to investigate a new strategy (daily GnRH agonist for LPS following GnRH agonist trigger) as an alternative for the conventional approach to the patients undergoing intracytoplasmic sperm injection (ICSI).

Methods: In this randomized controlled trial study, 44 ICSI patients were randomly assigned into two groups: group 1, patients received standard strategy (hCG trigger [10000 IU] and progesterone bid [400 mg/BD] for LPS); group 2, patients received a dose of GnRHa (0.2 mg) for ovulation trigger and subcutaneous injection of GnRHa bid (0.2 mg) for LPS.

Results: The pregnancy, miscarriage, and live birth rates for the patients undergoing LPS following the GnRHa trigger were similar to those of patients undergoing the standard strategy.

Conclusions: We showed that a daily subcutaneous injection of GnRHa for LPS following the GnRHa trigger can be successfully performed as an alternative to the standard strategy, with comparable pregnancy and live birth rates in ICSI patients.

Keywords: GnRH agonist, intracytoplasmic sperm injection, luteal phase, pregnancy rate, live birth

INTRODUCTION

Controlled ovarian hyperstimulation (COH), because of the supra-physiologic hormonal levels, leads to the suppression of hypophysial luteinizing hormone (LH) production and defects ovulation in assisted reproductive technology (ART) cycles (Fauser & Devroey, 2003). COH also results in premature luteolysis, which reduces ovarian steroid production and causes luteal phase failure (Fauser & Devroey, 2003). Hence, nowadays, ovulation triggers and luteal phase support (LPS) for proper implantation of the transferred embryos and pregnancy maintenance are the essential parts of the ART cycles.

Administration of exogenous human chorionic gonadotropin (hCG), as a long-acting analogue of LH, is the standard approach for ovulation trigger in ART cycles for induction of the final oocyte maturation and formation of corpus luteum. The main serious complication of hCG administration is ovarian hyperstimulation syndrome (OHSS), which is related to the prolonged circulating half-life of hCG (Damewood *et al*., 1989). Severe OHSS in women undergoing ART may result in morbidity and mortality (Schenker & Weinstein, 1978). The use of gonadotropin-releasing hormone agonist (GnRHa) has been introduced as an alternative for ovulation trigger in GnRH antagonist–stimulated cycles to avoid OHSS. Administration of GnRHa, with a shorter half-life than hCG, for ovulation trigger induces LH surge by the pituitary, approximately in the levels of the natural menstrual cycles, which thought to be able to restrict the risk of OHSS and other COH complications (Schenker & Weinstein, 1978; Garcia-Velasco *et al*., 2010). The induced LH surge by GnRHa is adequate for final oocyte maturation, meiosis resumption, and ovulation, but the surge is short and causes premature luteolysis and luteal phase insufficiency. The efficiency of the progesterone administration, as the standard strategy for LPS, following GnRHa trigger is still under question because it has been reported that this strategy may result in decreased pregnancy and live birth rates in ART (Youssef *et al*., 2011).

Recently, GnRHa administration has also been proposed for supporting the luteal phase in women undergoing ART to induce the LH production by the pituitary and sustain corpus luteum activity (Pirard *et al*., 2005). Besides, GnRHa may directly act on the transferred embryo or the endometrial cells through GnRH receptors (Pirard *et al*., 2005; Tesarik *et al*., 2004). The use of GnRHa for LPS was investigated via different routes and administration dosages. A single dose injection of GnRHa for LPS following hCG triggering in patients who underwent intracytoplasmic sperm injection (ICSI) cycles has been reported to increase implantation and pregnancy rates (Tesarik *et al*., 2004). Intranasal administration of GnRHa has also been suggested for LPS in GnRH antagonist–stimulated ICSI cycles (Pirard *et al*., 2015; Bar Hava *et al*., 2017; Bar-Hava *et al*., 2016).

Despite the potential benefits of GnRHa as an alternative for the hCG trigger, there is still no consensus on the optimal LPS strategy when the ovulation trigger is carried out by GnRHa administration. Accordingly, in this study, we aimed to investigate the usefulness and effectiveness of subcutaneous GnRHa administration for LPS after GnRHa triggering, among normal responder patients undergoing GnRH antagonist–stimulated ICSI cycles, compared to the standard LPS using progesterone following hCG trigger.

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MATERIALS AND METHODS

Study design

This prospective, comparative, randomized controlled study was designed at the *in vitro* fertilization (IVF) center of Taleghani Hospital in Tehran, from April 2018 to September 2018. The study project was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.REC.1397.029), and the trial was registered as IRCT20160722029027N7. All the included patients gave written informed consent before entering the study.

We included 44 infertile women scheduled to receive intracytoplasmic sperm injection (ICSI) with fresh embryo transfer that met the following criteria: age 20-40 year and body mass index 20-30 kg/m^2. The exclusion criteria were: recurrent implantation failure, severe male factor, endometriosis, polycystic ovarian syndrome, cycles with frozen spermatozoa or oocytes, oocyte donation, poor responders to ovulation stimulation, and uterine anomalies.

Ovarian stimulation

Ovarian stimulation was carried out with standard gonadotropin-releasing hormone (GnRH) antagonist protocol. Initiation of stimulation was started on day 3 of the menstrual cycle with a daily dose of 150-300 IU exogenous gonadotropin (Gonal-F, Merck Serono Europe Ltd, UK). Follicular monitoring was performed using serial ultrasonography. When the diameter of follicles reached approximately 14 mm, the GnRH antagonist was started with a daily dose of 0.25 mg cetrorelix acetate (Cetrotide, Serono, UK). When at least three follicles > 17 mm diameter were visualized in the ovaries, the patients were randomly assigned to two groups of the study using a permuted block randomization method. In group one; the ovulation trigger was carried out using 10000 IU of human chorionic gonadotropin (hCG) (Pregnyl; MSD, Brussels, Belgium). In group 2, the ovulation trigger was performed using Triptorelin (Variopeptyl 0.1 mg, Varian Darou Pajooh, Iran) at a bolus dose of 0.2 mg. The oocytes were aspirated from the ovaries 36 hours later.

ICSI and luteal phase support

All mature oocytes were inseminated by ICSI. Fertilization was evaluated approximately 20 hours after ICSI, and the embryos were transferred to the uterine cavity 3 days later. Supporting the luteal phase in all patients was started on the day of oocyte retrieval and continued until 10 weeks of gestation in case of positive pregnancy. For LPS of the patients in group 1, vaginal progesterone (Cyclogest; Cox Pharmaceuticals, Barnstaple, UK) at a daily dose of 400 mg twice a day was administrated. In group 2, the luteal phase was supported with a subcutaneous injection of Triptorelin (Variopeptyl 0.1 mg, Varian Darou Pajooh, Iran) at a daily dose of 0.2 mg twice a day. Serum luteinizing hormone (LH) and progesterone levels were measured after ovulation triggering. Pregnancy was characterized by the presence of an embryonic sac at 6 weeks of gestation. Miscarriage was determined as loss of pregnancy before 20 weeks of gestation.

Statistical analysis

Differences between characteristics and outcomes of the two studied groups were assessed by independent t-test, Mann Whitney test, and Chi-squared test. The data was presented as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables and frequency (percentage) for categorical variables. The covariance analysis (ANCOVA) and logistic regression were performed to adjust the outcome measures of the study for confounding variables. All the analyses were performed using the SPSS version 21 (Armonk, NY: IBM Corp), and the p-value < 0.05 was considered as statistically significant.

RESULTS

The baseline characteristics of the patients in two studied groups are presented in Table 1. Female age (p=0.202), body mass index (p=0.653),infertility duration (p=0.859),and serum levels of anti-mullerian hormone (AMH) (p=0.557), baseline follicle-stimulating hormone (FSH) (p=0.332), luteinizing hormone (LH) (p=0.083), Estrogen (p=0.733), and progesterone (p=0.062) did not significantly differ between the studied groups (Table 1).

No significant difference was noticed in the total dose of gonadotrophins used for ovarian stimulation between studied groups (p=0.312) (Table 2). The number of follicles (p=0.019) in the ovaries on the day of ovulation trigger was higher in group 2 (Table 2). The total number of oocytes aspirated (p=0.069), metaphase II oocytes (p=0.050), fertilization rate (p=0.241) did not show any significant differences among the studied groups (Table 2). While we did not notice a significant difference in serum LH levels after ovulation trigger between two groups of patients (p = 0.190); progesterone level after ovulation trigger was higher in group 2 (p=0.005) (Table 2). Pregnancy (p=0.448), miscarriage (p=0.447), and live birth (p=0.693) rates were not significantly different between the studied groups (Table 2). Moreover, we did not have any case of OHSS among the included patients.

The multivariable analysis for the confounding variables (the number of follicles on the day of ovulation trigger) was demonstrated that there were no significant differences between the groups regarding pregnancy (p=0.364) and live birth rates (p=0.673) (Table 3).

DISCUSSION

The use of GnRHa for ovulation trigger in GnRH antagonist-stimulated ART cycles is nowadays considered as an alternative for hCG to reduce the potential risk of OHSS (Engmann *et al*., 2016). However, the optimal LPS strategy after GnRHa trigger is still a matter of choice. In the current study, we evaluated the effectiveness of subcutaneous GnRHa administration for LPS after the GnRHa trigger compared to the standard strategy for ovulation trigger and LPS (hCG trigger followed by progesterone for LPS). For the first time, to the best of our knowledge, we demonstrated that daily subcutaneous GnRHa administration for LPS following the GnRHa trigger could be applied instead of standard strategy, which achieved comparable pregnancy and live birth outcomes in normal responder patients.

Similar to our finding, it has been previously reported that the pregnancy and implantation rates after the intranasal administration of GnRHa for ovulation trigger and LPS were comparable to the standard strategy in GnRH antagonist-stimulated ART cycles (Pirard *et al*., 2015). Moreover, the efficacy of intranasal GnRHa administration for ovulation trigger and LPS in high responder ART patients was demonstrated in another previously reported study (Bar-Hava *et al.*, 2016). Although the live birth rate was not reported in these latter studies, it seems that the intranasal and subcutaneous GnRHa administration had the same efficacy for pregnancy achievement. Therefore, we suggest the new method, subcutaneous route of GnRH administration, which provides more options for the women undergoing ICSI, so the patients can choose their friendlier route of GnRHa administration.

Several strategies for the counterbalance of luteal phase insufficiency following the GnRHa trigger have been investigated (Haahr *et al*., 2017; Humaidan, 2009; Kol, 2019). LH activity for LPS following the GnRHa trigger was

Table 1. Baseline characteristics for patients			
Parameter	**Group 1 (Cyclogest) n = 23**	**Group 2 (Variopeptyl) n = 21**	***p*-value**
Female age (Y), mean (SD)	31.78±5.3	29.85±4.34	0.20
BMI (kg/m2), mean (SD)	24.22±2.29	23.9±2.27	0.65
AMH (ng/ml), median (IQR)	2.4 (1.4-4.5)	3.3 (1.6-4.7)	0.55
Baseline FSH (IU/L), mean (SD)	3.07±1.03	3.34±0.77	0.33
Baseline LH (IU/L), mean (SD)	4.77±1.89	3.68±2.14	0.08
Baseline Estrogen (pg/mL), median (IQR)	43 (35-54.9)	44 (36-55)	0.73
Baseline Progesterone (ng/mL), median (IQR)	0.6 (0.49-0.7)	0.78 (0.57-0.9)	0.06
Infertility duration (Y), median (IQR)	3 (2-4)	3 (2-4)	0.85
Male factor infertility, n (%)	7 (30.4)	4 (19.0)	0.38

Table 2. Characteristics of ICSI cycles			
Parameters	**Group 1 (Cyclogest) N = 23**	**Group 2 (Variopeptyl) N = 21**	***p*-value**
Total dose of gonadotrophins (IU), mean (SD)	1676.09±662.23	1492.86±507.51	0.31
Follicles on the day of ovulation trigger (n), median (IQR)	8(7-9)	10(8-11)	0.01
LH after ovulation trigger, mean (SD)	31.44±18.86	41.37±29.82	0.19
Progesterone after ovulation trigger, mean (SD)	4.97±1.77	7.86±4.21	0.005*
Total oocytes aspirated (n), median (IQR)	5(5-8)	8(5-11)	0.06
Metaphase II oocytes (n), median (IQR)	5(3-6)	5(5-11)	0.05
Ratio of metaphase II oocytes/total oocytes, median (IQR)	0.75(0.6-1)	0.86(0.75-1)	0.13
Fertilization rate (%),mean (SD)	68.68±22.48	59.83±26.36	0.24
Embryos transferred, n (%) 1 2 3	 2 (8.7) 18(78.3) 3 (13)	 5 (23.8) 12 (57.1) 4 (19)	0.59
Pregnancy rate, n (%)	3 (13)	5 (23.8)	0.44
Miscarriage rate, n (%)	0 (0)	1 (4.8)	0.44
Live birth rate, n (%)	3 (13)	4 (19)	0.69

*ANCOVA adjusted for Baseline Progesterone level as a covariate

Table 3. Multivariable analysis of potential factors associated with outcome measures								
	Crude OR	***p*-value**	**95% C.I. for OR**		**Adjusted OR***	***p*-value**	**95% C.I. for OR**	
			Lower	**Upper**			**Lower**	**Upper**
Pregnancy rate	2.08	0.36	0.43	10.06	2.19	0.36	0.40	11.92
Live birth rate	1.57	0.58	0.30	8.01	1.47	0.67	0.24	8.69

* Multivariable model adjusted for the follicles on the day of ovulation trigger.

shown to be able to achieve live birth rates comparable to that presented by standard hCG trigger, followed by progesterone for LPS (Haahr *et al*., 2017). Besides, a single hCG bolus after oocyte retrieval has been suggested for LPS following GnRHa trigger in GnRH antagonist-stimulated ART cycles (Humaidan, 2009; Kol, 2019). However, there is still the risk of OHSS occurrence in some patients undergoing these strategies, which may be a cause for concern (Seyhan *et al*., 2013). Currently, the progesterone administration is the safe and standard LPS for hCG triggered ART cycles, but the use of progesterone following the GnRHa trigger leads to poor reproductive outcomes in ART cycles (Leth-Moller *et al*., 2014).

The beneficial effects of GnRHa on the pregnancy and live birth outcomes could be explained by some hypothesized mechanisms. The presence of the GnRH receptor in the human embryo, endometrial cells, decidua, and placenta may imply that the GnRHa not only acts on the pituitary gonadotrophic cells but also has direct effects on the embryonic development, endometrial receptivity, and implantation (Reshef *et al*., 1990). Moreover, it has been proposed that the induced LH secretion by

GnRHa administration in the luteal phase may stimulate the secretion of relaxin by the corpus luteum, and also angiogenesis growth factors and cytokines from the endometrium, which facilitate implantation (Loumaye *et al*., 1984; Stewart, 2001; Rao & Lei, 2002). The use of GnRHa for LPS was not associated with any reported complications regarding the pregnancy outcomes and congenital malformations (Marcus & Ledger, 2001; Martins *et al*., 2016). Besides, we did not find a significant difference regarding the miscarriage rate between the two studied groups.

The limitation of the present study was a relatively small number of the patients included. We did not have any case of OHSS in the studied patients who received GnRHa; therefore, we suggest that GnRHa may be a safe and useful strategy for both ovulation trigger and LPS. However, there is still a need for further randomized controlled trials with a larger sample size to confirm the safety, efficacy, and possible complications of this strategy.

CONCLUSION

Daily subcutaneous injection of GnRHa for LPS following GnRHa trigger in women undergoing GnRH antagonist-stimulated ICSI cycles was a safe strategy that resulted in pregnancy and live birth outcomes comparable to the standard strategy, hCG trigger followed by progesterone for LPS.

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Disclosure statement:

The authors declare that they have no conflicts of interest.

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REFERENCES

Bar-Hava I, Mizrachi Y, Karfunkel-Doron D, Omer Y, Sheena L, Carmon N, Ben-David G. Intranasal gonadotropin-releasing hormone agonist (GnRHa) for luteal-phase support following GnRHa triggering, a novel approach to avoid ovarian hyperstimulation syndrome in high responders. Fertil Steril. 2016;106:330-3. PMID: 27114332 DOI: 10.1016/j.fertnstert.2016.04.004

Bar-Hava I, Blueshtein M, Herman HG, Omer Y, David GB. Gonadotropin-releasing hormone analogue as sole luteal support in antagonist-based assisted reproductive technology cycles. Fertil Steril. 2017;107:130-135.e1. PMID: 28228316 DOI: 10.1016/j.fertnstert.2016.10.011

Damewood MD, Shen W, Zacur HA, Schlaff WD, Rock JA, Wallach EE. Disappearance of exogenously administered human chorionic gonadotropin. Fertil Steril. 1989;52:398-400. PMID: 2776893 DOI: 10.1016/S0015-0282(16)60906-8

Engmann L, Benadiva C, Humaidan P. GnRH agonist trigger for the induction of oocyte maturation in GnRH antagonist IVF cycles: a SWOT analysis. Reprod Biomed Online. 2016;32:274-85. PMID: 26803205 DOI: 10.1016/j.rbmo.2015.12.007

Fauser BC, Devroey P. Reproductive biology and IVF: ovarian stimulation and luteal phase consequences. Trends Endocrinol Metab. 2003;14:236-42. PMID: 12826330 DOI: 10.1016/S1043-2760(03)00075-4

Garcia-Velasco JA, Motta L, López A, Mayoral M, Cerrillo M, Pacheco A. Low-dose human chorionic gonadotropin versus estradiol/progesterone luteal phase support in gonadotropin-releasing hormone agonist-triggered assisted reproductive technique cycles: understanding a new approach. Fertil Steril. 2010;94:2820-3. PMID: 20673892 DOI: 10.1016/j.fertnstert.2010.06.035

Haahr T, Roque M, Esteves SC, Humaidan P. GnRH agonist trigger and LH activity luteal phase support versus hCG trigger and conventional luteal phase support in fresh embryo transfer IVF/ICSI cycles-a systematic PRISMA review and meta-analysis. Front Endocrinol. 2017;8:116 PMID: 28638367 DOI: 10.3389/fendo.2017.00116

Humaidan P. Luteal phase rescue in high-risk OHSS patients by GnRHa triggering in combination with low-dose HCG: a pilot study. Reprod Biomed Online. 2009;18:630-4. PMID: 19549440 DOI: 10.1016/S1472-6483(10)60006-5

Kol S. A rationale for timing of luteal support post gonadotropin-releasing hormone agonist trigger. Gynecol Obstet Invest. 2019;84:1-5. PMID: 30007966 DOI: 10.1159/000491088

Leth-Moller K, Jagd SH, Humaidan P. The luteal phase after GnRHa trigger-understanding an enigma. Int J Fertil Steril. 2014;8:227-34. PMID: 25379149

Loumaye E, Depreester S, Donnez J, Thomas K. Immunoreactive relaxin surge in the peritoneal fluid of women during the midluteal phase. Fertil Steril. 1984;42:856-60. PMID: 6500078 DOI: 10.1016/S0015-0282(16)48256-7

Marcus SF, Ledger WL. Efficacy and safety of long-acting GnRH agonists in in vitro fertilization and embryo transfer. Hum Fertil. 2001;4:85-93. PMID: 11591262 DOI: 10.1080/1464727012000199351

Martins WP, Ferriani RA, Navarro PA, Nastri CO. GnRH agonist during luteal phase in women undergoing assisted reproductive techniques: systematic review and meta-analysis of randomized controlled trials. Ultrasound Obstet Gynecol. 2016;47:144-51. PMID: 25854891 DOI: 10.1002/uog.14874

Pirard C, Donnez J, Loumaye E. GnRH agonist as novel luteal support: results of a randomized, parallel group, feasibility study using intranasal administration of buserelin. Hum Reprod. 2005;20:1798-804. PMID: 15890740 DOI: 10.1093/humrep/deh830

Pirard C, Loumaye E, Laurent P, Wyns C. Contribution to more patient-friendly ART treatment: efficacy of continuous low-dose GnRH agonist as the only luteal support-results of a prospective, randomized, comparative study. Int J Endocrinol. 2015;2015:727569. PMID: 25945092 DOI: 10.1155/2015/727569

Rao CV, Lei ZM. Consequences of targeted inactivation of LH receptors. Mol Cell Endocrinol. 2002;187:57-67. PMID: 11988312 DOI: 10.1016/S0303-7207(01)00694-3

Reshef E, Lei ZM, Rao CV, Pridham DD, Chegini N, Luborsky JL. The presence of gonadotropin receptors in nonpregnant human uterus, human placenta, fetal membranes, and decidua. J Clin Endocrinol Metab. 1990;70:421-30. PMID: 1688865 DOI: 10.1210/jcem-70-2-421

Schenker JG, Weinstein D. Ovarian hyperstimulation syndrome: a current survey. Fertil Steril. 1978;30:255-68. PMID: 361440 DOI: 10.1016/S0015-0282(16)43508-9

Seyhan A, Ata B, Polat M, Son WY, Yarali H, Dahan MH. Severe early ovarian hyperstimulation syndrome following GnRH agonist trigger with the addition of 1500 IU hCG. Hum Reprod. 2013;28:2522-8. PMID: 23633553 DOI: 10.1093/humrep/det124

Stewart EA. Gonadotropins and the uterus: is there a gonad-independent pathway? J Soc Gynecol Investig. 2001;8:319-26. PMID: 11750866 DOI: 10.1016/S1071-5576(01)00136-8

Tesarik J, Hazout A, Mendoza C. Enhancement of embryo developmental potential by a single administration of GnRH agonist at the time of implantation. Hum Reprod. 2004;19:1176-80. PMID: 15070873 DOI: 10.1093/humrep/deh235

Youssef MA, Van Der Veen F, Al-Inany HG, Griesinger G, Mochtar MH, Aboulfoutouh I, Khattab SM, Van Wely M. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles. Cochrane Database Syst Rev. 2011;1:CD008046. PMID: 21249699 DOI: 10.1002/14651858.CD008046.pub3