Original Article

Freeze all Strategy in Polycystic Ovarian Syndrome Patients After Triggering with Different Doses of Gonadotropin Agonist

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ABSTRACT

Objectives: The main aim of this study was to compare the optimal dose of GnRH agonist for triggering ovulation in PCOS cases to obtain the best outcome. Therefore, we studied the difference between 0.1 ml and 0.2 ml Decapeptyl and the pregnancy rate in each group as a primary outcome.

Study Design: A retrospective non-randomized study.

Materials and Methods: The study was approved by the medical ethical committee of the Faculty of Medicine, Alexandria University. It was conducted on 227 patients who were diagnosed with PCOS and indicated for ICSI. All cases were stimulated by GnRH antagonist protocol and triggered by GnRH agonist triptorelin for final ovarian maturation. They were allocated into two groups. The first group (n=163) was triggered by triptorelin 0.1mg (Decapeptyl 0.1 mg, Ferring®), and the second group (n=64) was triggered by triptorelin 0.2mg (Decapeptyl 0.2 mg, Ferring®). The two groups underwent ICSI and frozen all embryos followed by thawed embryo transfer in an artificial endometrial priming cycle from April 2018 to December 2020.

Results: The difference in the pregnancy rate of Day 3 thawed embryos was not statistically significant (77.8% and 62.8% respectively, p=0.127), while the rate in Day 5 thawed embryos was higher in group A (82.2% and 61.9% respectively, p=0.040).

Conclusion: The chance of pregnancy in the first group is approximately 2.5 times more than the chance of pregnancy in the second Group regarding Day 5 embryos.

Key Words: freeze all, GnRH agonist triggering, ICSI, PCOS.

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INTRODUCTION

PCOS is the most common endocrinal disorder in females of reproductive age with a prevalence of 4 to 15%.[1] The AES has proposed a new set of diagnostic criteria as the patient demonstrates both hirsutism and/or hyperandrogenemia, and oligo-anovulation and/or polycystic ovaries after exclusion of other etiologies of androgen excess and anovulatory infertility.[2]

AMH is a useful test in the evaluation of infertility, its levels remain consistent during the menstrual cycle.[3] Women with PCOS present AMH levels 2 to 3 folds higher than non-PCOS females because of increased preantral and small antral follicles. The increased level seems correlated with the severity of PCOS.[4]

Gonadotropin therapy is used clinically in anovulatory PCOS cases who failed to ovulate with other first-line ovulation induction agents such as letrozole and metformin. To prevent overstimulation and multiple pregnancies, the traditional standard step-up regimens were replaced by either low-dose step-up regimens or step-down regimens.[5]

In the absence of an absolute indication for IVF ± ICSI, women with PCOS could be offered IVF as a third line where other ovulation induction therapies have failed. GnRH antagonist protocol is preferred over a GnRH agonist long protocol, to reduce the duration of stimulation, total gonadotrophin dose, and incidence of OHSS. HCG should be used at the lowest doses to trigger final oocyte maturation to reduce the incidence of OHSS. Triggering final oocyte maturation with a GnRH agonist and freezing all embryos could be considered in women with a GnRH antagonist protocol and at an increased risk of developing OHSS or where fresh embryo transfer is not planned.[5] Prevention of premature LH surge can be achieved with GnRH antagonists as it is associated with a shorter duration of stimulation, lower estradiol levels, and a smaller number of follicles.[6] The incidence of severe OHSS was significantly lower in GnRH antagonist cycles[7]

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The choice to trigger final oocyte maturation with GnRH-agonist instead of hCG is important in the prevention of OHSS. GnRH agonist triggers are associated with lower pregnancy rates, primarily in fresh embryo transfers, which can be overcome in the freeze-all strategy.[5] For many years hCG has been the choice of final follicular maturation. Alternatively, final follicular maturation and ovulation triggering using GnRH agonist to stimulate the endogenous LH surge in patients at risk of OHSS is now performed. While patients are receiving GnRH antagonist, the pituitary response to GnRH remains intact and the administration of GnRH agonist can trigger an endogenous LH surge replicating the flare effect, this surge may be sufficient for final follicular maturation and lowers the risk of OHSS compared with an injection of hCG.[7] The incidence of OHSS was 3% with the hCG trigger while a GnRH agonist trigger varied between 0 to 2.6%.[8]

According to previous publications, the outcome of different doses of GnRH agonist is controversial and still different ART centres are adopting different strategies.

AIM OF THE WORK

This study aims to assess the outcome of the freeze-all strategy in PCO patients who underwent ICSI and were triggered with different doses of GnRH agonist regarding the Pregnancy rate as a primary outcome and the fertilization rate the number of oocytes, the number of mature oocytes, class A embryos, vitrified embryos and as secondary outcomes.

PATIENTS AND METHODS

Setting

A retrospective study of the clinical outcomes of PCOS patients who were scheduled for ICSI in a private center in Alexandria between April 2018 to December 2020

Patients

This study included 227 women who were diagnosed with PCOS with primary or secondary infertility and scheduled for ICSI from April 2018 to December 2020. The inclusion criteria were primary or secondary infertility, their age was less than 38 years, BMI < 35, AMH level > 5.5 and ovarian stimulation was done by antagonist protocol. The exclusion criteria were recurrent failed ICSI, severe male factor and uterine abnormalities.

METHODS

All patients were examined by transvaginal ultrasound to assess the ovarian volume and AFC. The AMH level and BMI were measured. In the previous cycle, the patients received combined oral contraceptive pills (Gestodene 0.075 mg + Ethinyl estradiol 0.03 mg) (Gynera, Bayer ®) to induce menstruation. The Ovarian stimulation was initiated on the second day of the pill-free interval by administering a starting dose of recombinant FSH (Gonal-F, Merck Serono ®). The dose adjustment during stimulation was based on the ovarian response which was assessed by follicular development using the ultrasound examination and hormonal monitoring, to avoid hypo or hyper-ovarian responses. The doses of FSH can be adjusted at the start or during the stimulation phase. A starting dose of 150 to 225 IU per day was indicated, with adjustment after 5 days but the dose should not exceed 300 IU/day. On the 6th day of the stimulation, daily subcutaneous administration of GnRH antagonist cetrorelix acetate 0.25mg (Cetrotide, Merck Serono ®) with the daily rFSH dose, and this dose was adjusted according to the follicular response until the day of final oocyte maturation. The Estradiol level was measured on day five and day eight of stimulation.

When the follicles reached 17 mm in diameter, the cases were divided into two groups, the first group cases (n=163) were triggered for final follicular maturation by GnRH agonist triptorelin 0.1 mg (Decapeptyl, Ferring ®) and the second group cases (n=64) were triggered for final follicular maturation by GnRH agonist triptorelin 0.2 mg (Decapeptyl, Ferring ®).

After 35 hours following triggering, Transvaginal oocyte retrieval under sedation was performed. The follicular fluid was taken into the laboratory to identify the oocytes and complete the ICSI procedure. The successful fertilization of the oocytes was defined as the presence of two pronuclei 17 to 19 hours after the procedure.

All the class A embryos (Day 3 embryos and Day 5 embryos after oocyte retrieval) were vitrified (freeze-all strategy). The selected number of embryos after counsel with each case were thawed and transferred per cycle in an artificial menstrual cycle.

The endometrium was primed by daily oral estradiol valerate from 6 to 8 mg per day for at least 10 days, then adding progesterone in vaginal suppository form (Prontogest 200 mg, Marcyrl co ®) when endometrial thickness reached 7mm. After 4 days for Day 3 embryos and 6 days for Day 5 embryos of progesterone supplementation, the embryo transfer was planned.

Biochemical pregnancy was detected by measuring β-hCG levels (>10 IU/L) on Day 12 after embryo transfer. Clinical pregnancy was defined as the presence of a gestational sac with a fetal heart rate present on ultrasound after 7 weeks of gestation.

Data collection and statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY:

IBM Corp) The Kolmogorov-Smirnov test was used to verify the normality of distribution. Comparisons between groups for categorical variables were assessed using the Chi-square test (Fisher or Monte Carlo). Mann-Whitney test was used to compare two groups for abnormally distributed quantitative variables. Student t-test was used to compare two groups for normally distributed quantitative variables. Kruskal Wallis test was used to compare different groups for abnormally distributed quantitative variables. Spearman coefficient was used to correlate between quantitative variables. Regression was used to detect the most independent/ affecting factor for the parameters that affect pregnancy. The significance of the obtained results was judged at the 5% level.

RESULTS

The overall pregnancy rate of the studied cases in the first group was 81.0 % and in the second group was 62.5 % and this difference is statistically significant (p=0.004). The chance of pregnancy in the first group is approximately 2.5 times more than the chance of pregnancy in the second Group. The pregnancy rate of thawed Day 3 embryos in the studied cases in the first group (n=45) was 77.8 % and in the second group (n=43) was 62.8 % and this difference is not statistically significant (p=0.127). The pregnancy rate of thawed Day 5 embryos in the studied cases in the first group (n=118) was 82.2 % and in the second group (n=21) was 61.9 % and this difference is statistically significant (p=0.040) (Figure 1).

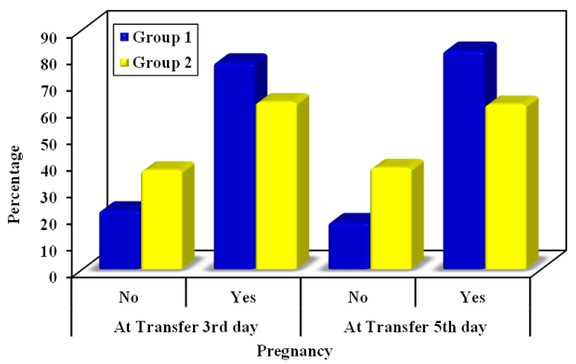

Fig. 1: The pregnancy rate in Day 3 and Day 5 embryos

The secondary outcomes are shown in (Table 1). According to our results, the number of oocytes retrieved and the MII oocytes were higher in group B. while the fertilization rate is higher in group A. the number of Day 3 class A embryos was higher in group B while the difference in Day 5 embryos was not statistically significant between the two groups. However, the number of Day 3 vitrified embryos in group B was better, and the difference in Day 5 embryos was not statistically significant. The difference in the pregnancy rate of Day 3 thawed embryos was not statistically significant, while the rate in Day 5 thawed embryos was higher in group A.

Table 1: The differences in the secondary outcomes between the two group

Outcome (Mean ±SD)	First group (n=163)	Second group (n=64)	*P value*
Oocytes retrieved	24.39 ± 6.86	28.31 ± 8.39	0.003
MII oocytes	17.68 ± 6.29	20.98 ± 7.81	0.003
Fertilization rate	75.65 ± 16.79	65.09 ± 21.52	0.001
Class A embryos			
Day 3	6.53 ± 3.29	11.60 ± 5.01	<0.001
Day 5	11.56 ± 4.62	11.43 ± 4.22	0.911
Vitrified embryos			
Day 3	7.04 ± 2.77	9.19 ± 4.10	0.012
Day 5	7.56 ± 3.28	7.62 ± 3.54	0.946

SD: stander deviation *p*; significant < 0.05

DISCUSSION

The optimal dose of the GnRH agonist is controversial, so the main aim of this study is to compare the different doses of GnRH agonist for triggering ovulation in PCOS cases to obtain the best outcome. Therefore, we studied the difference between triptorelin 0.1 ml and 0.2 ml (Decapeptyl, Ferring ®) and the pregnancy rate in each group as a primary outcome.

This study's results showed a significant difference in the age of the studied patients, the number of oocytes retrieved, MII oocytes rate and Class A embryos, Fertilization rate, number of vitrified embryos and pregnancy rate between the two groups. Whereas group B had a better result than group A in the number of oocytes retrieved and MII oocytes, the number of Class A embryos and the number of vitrified embryos. However, group A had better results in fertilization rate and pregnancy rate as a primary outcome.

In comparison between our group A finding with Hwang *et al*. (2018) who studied 40 PCOS patients. All cases were planned for ICSI with GnRH antagonist protocol and final maturation by triptorelin 0.1 mg (Decapeptyl, Ferring ®) between January 2014 and December 2014 in Memorial Hospital, Taiwan. All embryos were frozen on Day 3. The median age of their patients was higher than patients in our group A (32 vs 30 years). They had the same results as regards the number of oocytes, number of MII oocytes, fertilization rate and pregnancy rate. While this study patients had better results in the number of vitrified embryos (11.7 vs 7.04 embryos).[9]

While comparing our group B result with Vlaisavljevic *et al*. (2017) conducted a retrospective study of 123 PCOS

patients who underwent ICSI and triggered by triptorelin 0.2 mg (Decapeptyl, Ferring ®) and they planned for elective cryopreservation of all embryos on Day 5 from January 2012 to December 2014. The median age of their patients was higher than patients in our group B (32 against 27 years). They had the same results approximately in the number of oocytes and embryos. Against the results of our study, they had a lower number of MII oocytes and pregnancy rate while they had better result as regards vitrified embryos (8.8 against 7 embryos). Our group B had better results in class A embryos.[10]

Pabuccu *et al*. (2015) conducted a retrospective study in Ankara, Turkey to compare the impact of different GnRH-a doses (leuprolide not triptorelin) for the final oocyte maturation on cycle outcomes and OHSS rates in high-responder patients undergoing ovarian stimulation. They examined 77 cases that were detected receiving GnRHa. Group I consisted of 38 patients who received 1 mg and Group II consisted of 39 patients who received 2 mg. There was no significant difference between the two groups in studying the number of oocytes retrieved and pregnancy rate. So, they suggest that a volume of 1 or 2 mg leuprolide acetate yields similar outcomes when used for the final oocyte maturation in high-responder patients.[11]

Gülekli *et al*. (2015) examined 23 women to investigate the efficacy of low-dose GnRH agonist for final oocyte maturation in females undergoing ART cycles in the Department of Obstetrics and Gynecology, İzmir, Turkey. This retrospective study was all cases had GnRH antagonist protocol for ovarian stimulation cycles between March 2012 and May 2013. The cases were divided into two groups, Group I (n=9) had 0.1 mg and Group II had 0.2 mg (Decapeptyl, Ferring ®) for ovulation triggering. There was no significant difference between the two groups in the number of oocytes retrieved, MII oocytes and embryos, fertilization rate and pregnancy rate. This study's results suggest that 0.1 mg triptorelin acetate effectively induces final oocyte maturation in IVF cycles. However, as this was a small case series, larger randomized controlled studies are needed to determine the optimal dose for GnRH agonist triggering.[12]

The limitation of this study is that it was not a randomized trial, our study did not report long-term outcomes of cases like the occurrence of OHSS and live birth rate.

The strategy for future studies is to do prospective randomized studies with a relatively higher number of cases recited in this literature to support our findings.

CONCLUSION

We can conclude that low dose triptorelin (0.1 mg) can be as effective as the traditional dose (0.2 mg) and even it may give a better pregnancy rate.

RECOMMENDATION

we recommend further studies using larger sample sizes and randomization to confirm our conclusion of triptorelin 0.1 mg for triggering final oocyte maturation to improve pregnancy rate and cost saving.

CONFLICT OF INTERESTS

There are no conflicts of interest.

REFERENCES

1. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril 2016; 106(1):6-15.

2. Lujan ME, Chizen DR, Pierson RA. Diagnostic criteria for polycystic ovary syndrome: pitfalls and controversies. J Obstet Gynaecol Can 2008; 30(8):671-9.

3. Dewailly D, Lujan ME, Carmina E, Cedars MI, Laven J, Norman RJ, *et al*. Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update 2014; 20(3):334-52.

4. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril 2013; 99(1):63.

5. Norman RJ, Teede HJ. A new evidence-based guideline for assessment and management of polycystic ovary syndrome. Med J Aust 2018; 209(7):299-300.

6. Humaidan P, Papanikolaou EG, Kyrou D, Alsbjerg B, Polyzos NP, Devroey P, *et al*. The luteal phase after GnRH-agonist triggering of ovulation: present and future perspectives. Reprod Biomed Online 2012; 24(2):134-41.

7. Youssef MA, Van der Veen F, Al-Inany HG, Griesinger G, Mochtar MH, Aboulfoutouh I, *et al*. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology cycles. Cochrane Database Syst Rev 2011; (1): Cd008046.

8. Marci R, Senn A, Dessole S, Chanson A, Loumaye E, De Grandi P, *et al*. A low-dose stimulation protocol using highly purified follicle-stimulating hormone can lead to high pregnancy rates in in *vitro* fertilization patients with polycystic ovaries who are at risk of a high ovarian response to gonadotropins. Fertil Steril 2001; 75(6):1131-5.

9. Hwang JL, Chen SU, Chen HJ, Chen HF, Yang YS, Chang CH, *et al*. Feasibility of corifollitropin alfa/GnRH antagonist protocol combined with GnRH agonist triggering and freeze-all strategy in polycystic ovary syndrome patients. J Formos Med Assoc 2018; 117(6):535-40.

10. Vlaisavljević V, Kovačič B, Knez J. Cumulative live birth rate after GnRH agonist trigger and elective cryopreservation of all embryos in high responders. Reprod Biomed Online 2017; 35(1):42-8.

11. Vlaisavljević V, Kovačič B, Knez J. Cumulative live birth rate after GnRH agonist trigger and elective cryopreservation of all embryos in high responders. Reprod Biomed Online 2017; 35(1):42-8.

12. Gülekli B, Göde F, Sertkaya Z, Işık AZ. Gonadotropin-releasing hormone agonist triggering is effective, even at a low dose, for final oocyte maturation in ART cycles: Case series. J Turk Ger Gynecol Assoc 2015; 16(1):35-40.