Original Article

Prevention Of Ovarian Hyperstimulation Syndrome By Using The Alternative Drug To Induce Final Ovulation Trigger In Invitro Fertilization Cycles

Safia Sultana Munir[1], Misbah Sultana[2], Shazia Ashraf[3], Muhammad Khan[4]

[1] Professor Department of Obstetrics & Gynecology, Shalamar Institute of Health Sciences Lahore & Australian Concept Infertility, and Medical Centre Lahore
[2] Associate Professor, Pharmacy Department Punjab University Lahore.
[3] Associate Professor, Department of Obstetrics & Gynecology, Allama Iqbal Medical College Lahore & Australian Concept Infertility and Medical Centre Lahore.
[4] House Officer, Lahore Medical and Dental College.

Author's Contribution
[1,6] Conception of study
[1] Experimentation/Study conduction
[4] Analysis/Interpretation/Discussion
[1,5] Manuscript Writing
[3] Critical Review
[2] Facilitation and Material analysis

Corresponding Author
Dr Safia Sultana Munir
Professor Department of Obstetrics & Gynecology
Shalamar Institute of Health Sciences Lahore & Australian Concept Infertility and Medical Centre
Lahore
Email: drsafiamunir@yahoo.com

Article Processing
Received: 13/06/2022
Accepted: 14/12/2022

Cite this Article: *Sultana, S., Sultana, M., Ashraf, S., & Khan, M. (2023). Prevention Of Ovarian Hyper Stimulation Syndrome By Using Gonadotrophic Releasing Hormone Analogue To Induce Final Ovulation Trigger In Invitro Fertilization Cycles. Journal of Rawalpindi Medical College, 27(1).*
DOI: https://doi.org/10.37939/jrmc.v27i1.1970

Conflict of Interest: *Nil*
Funding Source: *Nil*

Abstract

OBJECTIVES: To find out the occurrence of ovarian hyperstimulation in patients who were hyper responders in vitro fertilization cycles. The secondary outcome was to assess the number of metaphase II oocytes and fertilization rate, cleavage rate, and pregnancy outcome when GnRHa is used for final maturation and triggering ovulation.

STUDY DESIGN, SIZE, and DURATION: This is a retrospective descriptive analysis of cases managed at a single center from June 2017 till May 2018.

PATIENTS & METHODS: Twenty patients were identified as hyper responders based on the baseline, ovarian reserve characteristics, that is antral follicle count, (AFC) > 25, AMH > 4ng/ml and on the day of trigger, follicles >-25 on a number of ≥ 11mm were administered GnRHa trigger and 1500IU hCG on oocyte retrieval day while luteal phase was supported with daily vaginal progesterone and twice daily estradiol valerate. Sixteen patients underwent fresh transfer while four patients had their embryos frozen.

MAIN RESULTS: Twenty patients were identified as high risk and their baseline charmeansristics were, a mean age of 31.7 ± 4.50, mean antral follicle count of 25.7 ± 5.01, Anti Mullerian hormone level mean of 4.64 ± 2.52 and PCOS present in 35% cases. Peak estradiol level means 13455-± 6632pmol/l and mean follicles count of 25.45 ± 8.78 confirmed a high response. The oocyte yield was 11.45+ Metaphase oocyte retrieved was 85.5% and the cleavage rate of 93%. No case of early-onset OHSS was identified. Only one patient developed moderate OHSS. The pregnancy rate was 31.25%. The miscarriage rate was 6.3% and ongoing pregnancy was 25%.

CONCLUSION: This small retrospective descriptive analysis supports the view of current literature that GnRH trigger not only prevents early onset OHSS but also achieves an increase of M11 oocytes. In addition, pregnancy outcome is not statistically different to those cycles where hCG is used as a trigger.

KEYWORDS: GnRH trigger, PCOS, IVF outcome, OHSS

Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious consequence after ovulation induction by gonadotrophins in assisted reproductive technology (ART). Multiple follicles start growing in response to ovarian stimulation, and granulosa cells from these follicles secrete estrogen. In response to rising estrogen levels, a positive feedback effect on the pituitary results in a high Luteinizing Hormone (LH) level. To complete the cycle of ovarian stimulation and get the optimum number of oocytes for in vitro fertilization, the LH level should be suppressed to avoid premature ovulation. For that purpose, a gonadotrophin-releasing hormone antagonist (cetrotide) is given during the ovarian stimulation cycle. When follicles have achieved the desired size, that is ≥ 17mm, for further maturation and induction of ovulation, conventionally humane chronic gonadotrophin (hCG) 10,000iu is given as a trigger. It acts as a surrogate for the luteinizing hormone (LH).[1] Thirty-five hours after hCG administration, transvaginal ovum pickup is carried out, But hCG has a prolonged half-life of >24 hours and this sustained LH receptor activity, results in multiple corpora Lutea development. As a result, the steroids such as (estrogen & progesterone) from these corpora will lead to the development of ovarian hyperstimulation syndrome (OHSS), especially in those patients who are at risk. [2]

Risk factors for developing OHSS are present in those patients, who are young, < 20 years of age, whose BMI is < 16kg/m2, and who are diagnosed as suffering from polycystic ovarian syndrome as defined by Rotterdam Criteria 2003.

The risk of OHSS also increases in those patients in whom after ovarian stimulation in the IVF cycle with gonadotrophins, a large number of follicles >25 and ≥ 11 mm develop. It is more common when higher doses of gonadotrophins are given for ovarian stimulation and in those patients whose estrogen level after stimulation reaches > 10,000pmol/L.

To overcome this increased risk of OHSS with the use of hCG for induction of ovulation, an alternative to hCG, gonadotrophin-releasing hormone analog (GnRHa) was first time introduced in 1990 and it has emerged as a novel alternative. [3]

GnRHa has a short half-life of only 60 minutes; it leads to the acute release of FSH and LH from the pituitary which results in final oocyte nuclear maturation. [4]

As GnRHa has a short half-life and there is the absence of continuous support of corpus luteum by low LH from the pituitary. Luteal phase rescue is achieved by delivering 1500 iu at oocyte retrieval. This protocol was suggested by various authors to improve the pregnancy rate. [5-6]

Materials and Methods

This is a single-center retrospective descriptive analysis of patients who were considered hyper-responders, and the primary aim was to illustrate the outcome of those patients where oocyte maturation was carried out by GnRHa in GnRH antagonist ovarian stimulation cycles. These patients were treated and managed by primary authors at Australian Concept Infertility and Medical Centre Lahore from June 2017 till May 2018.

PATIENTS:

Twenty consecutive patients were identified as high risk, dependent on their demographic features, ovarian reserve parameters, and response to ovarian stimulation. Inclusion criteria were PCOS status, Antral follicle count (AFC) >15 in number and those in whom controlled ovarian stimulation (COH) resulted in >25 follicles of ≥ 11 mm diameter on the day of trigger for final oocyte maturation. Patients between ages of 20-40 years with and BMI range of 18-30 kg/m^2 were selected. These were all ICSI cycles where the antagonist was used as a co-treatment of ovarian stimulation. Exclusion criteria were those patients who had undergone GnRH agonist as a pituitary suppressant, (long protocol) or used alternative methods for prevention of OHSS, such as coasting.

HORMONAL TREATMENT:

Controlled ovarian hyperstimulation started from cycle day 2 or 3. The dose of gonadotrophins was adjusted according to age, BMI, Antral Follicle Count (AFC), and Antmullerian Hormone (AMH) level. Antagonist (Cetrorelix) was started when the largest follicle size reached 13-14 mm combined with ovarian stimulation.

Final oocyte maturation was achieved by administration of 0.2mg of Triptorelin (Decapeptyl; Ferring Pharmaceuticals) as soon as ≥ 3 follicles of ≥ 17mm were observed on transvaginal ultrasound. Approximately 34-36 hours after the GnRH analog trigger, the oocytes were retrieved. This was followed by the administration of 1500 IU hCG (pregnyl: Organon), within an hour. Further luteal support was provided by Intravaginal micronized progesterone

400mg twice a day and estradiol valerate 2mg (progynova;Bayer) orally twice daily[7]. These medications were continued till menstruation or 7-8 weeks of gestation (according to NICE guidelines 2013) [8].

OUTCOMES AND STATISTICAL ANALYSIS:

The main outcome measure was the incidence of early and late-onset Ovarian Hyperstimulation Parameters used as defined by Golan et al 1989 [9] were used to assess the presence of OHSS once at 3 days after egg retrieval and again at 14 days post embryo transfer. The secondary aim was to see the effect of GnRH analog on oocyte yield, maturity of oocyte, fertilization, and cleavage rate, as well as on clinical pregnancy rate. Pregnancy was considered positive when serum β hCG was more than 5 IU on 19 post-oocyte retrieval days and clinical pregnancy as the presence of fetal pole and cardiac activity on ultrasound. When at 8 weeks of gestation no viable fetus was seen on USG it was considered as a miscarriage.

SPSS-20 was employed for statistical analysis and values were presented as mean and ± SD (Standard Deviation).

ETHICAL APPROVAL:

Full ethics committee approval was not required because of the retrospective nature of the study.

Results

The study population included 20 consecutive women who had received analog trigger and 1500 IU of hCG as luteal phase rescue. Among them, 16 patients had embryo transfer in a fresh cycle, while 4 had their embryos cryopreserved as a number of follicles ≥ 11mm on the day of the trigger were more than 25 in number. These four patients are not included in the final analysis of pregnancy outcomes. Out of 16 patients, 5(31.25%) patients were pregnant. There was one pregnancy loss and ongoing pregnancies were 4(25%).

OHSS:

In this analysis, none of the patients had symptoms of early-onset OHSS. One patient complained of mild nausea. She was managed conservatively, on an outdoor basis by monitoring her daily for worsening of symptoms and signs. She remained stable without progression of symptoms beyond two days. One patient developed moderate late-onset OHSS. This patient was younger 28 years old, diagnosed as PCOS, and was a hyper responder. Her follicular count was 22 on the day of the trigger and E2 was 28, 300pmol/l. 5 Blastocysts developed and 2 were transferred in the same cycle. The patient got pregnant. She developed nausea, vomiting lower abdomen discomfort, and ultrasound evidence of ascites at 6 weeks of pregnancy.

She was managed on an outdoor basis with intravenous hydration and advised to increase her oral intake of proteins in the form of egg whites. She was monitored daily for changes in weight and an increase in abdominal girth and inquired about urine output. Her hematocrit, WBC count, and serum creatinine remained within normal limits.

Table I shows the baseline characteristics of patients who received agonist triggers. The mean ± SD female age was 31.75 ±4.50 years. The mean AFC was 25.7 ±5.01 and the mean AMH level was 4.64-±2.52 ng/ml. The most common indication of treatment was PCOS which was present in 7 (35%) of participants. Clearly, the women treated with agonist trigger and hCG rescue were at high risk for OHSS.

Table II summarizes the stimulation days, the total amount of exogenous FSH required, fertilization and cleavage rate, and the number of embryos transferred. The mean days of stimulation were 8.6 ±0.88 days. The total FSH administered was 1998.5 ±2704IU, the mean number of follicles developed was 25.45 ±8.78, and estradiol on the day of ovulation induction was 13455-±66 pmol/l. The mean oocyte yield was 11.45 ±4.2. The mean metaphase II (MII) oocytes obtained were 85.5% and the fertilization rate was 73.33%. Whereas the cleavage rate was 93%, and while the mean number of embryo transfers was 2.1 (2-3). Four (21%) of participants had their embryos cryopreserved.

Table III depicts the pregnancy outcome of these patients. Out of 20 patients included in the study, 6 patients underwent fresh transfer of a mean of 2.1 embryos on day 3 while 5 patients (31.25%) had positive pregnancy tests. One patient (6.3%) miscarried at 6 weeks of pregnancy. The ongoing clinical pregnancy rate was (25%).

Table-1 Demographic Data of Women Receiving GnRH trigger for oocyte maturation.

Age (Years)	*31.75 ± 4.50*
Body mass Index (Kg/m^2)	26.50 ± 4.12
Baseline FSH Level (IU/L)	5.76 ± 1.76
AMH Level (ng/ml)	4.64 ± 2.52
AFC (n)	25.7 ± 5.01
P. Infertility n (%)	11 (55)
Sec. Infertility n (%)	9 (45)
Infertility Causes	
Idiopathic n (%)	2 (10)
Tubal n (%)	3 (15)
Male n (%)	6 (30)
PCOS n (%)	7 (35)
PCOM n (%)	2 (10)

All continuous variables are expressed as mean ± SD

Table-2 IVF Cycle characteristics

Stimulation (Days)	*8.6 ± 0.88*
Total FSH (IU)	1998.55 ± 705
Number of follicles on the day of trigger	25.45 ± 8078
Serum Estradiol Day of ovulation Induction Pmol/l	13455.00 ± 6632.09
Number of oocytes retrieved n	11.45 ± 4.2
Number of MII oocytes retrieved, mean ± SD n (%)	9.35 ± 3.8 195/229 (85.15)
Fertilization rate, n (%)	143/195 (73.33)
Cleavage rate, n (%)	133/143 (93)
Number of Embryones transferred n (range)	2.1 (2-3)
Number of cycles with all embryos cryopreserved n (%)	4/16 (21)

All continuous variables are expressed as mean ± SD

Table-3 Pregnancy Outcome

Positive hCG test/Cycle n (%)	*5/16 (31.25)*
Early pregnancy loss n (%)	1/16 (6.3)
Clinical ongoing pregnancy n (%)	4/16 (25)

Discussion

In this retrospective descriptive analysis of patients who were considered to be hyper responders and were administered GnRH agonist for final oocyte maturation with 1500IU of hCG as luteal phase rescue on the day of oocyte retrieval were studied, to find out the incidence of OHSS. There was no case of early onset OHSS. Only one patient developed late-onset moderate OHSS. This patient had embryo transfer in a fresh cycle and got pregnant, but later on missed miscarriage.

The reported incidence of OHSS in these high-risk groups is 32%. [(10)]

Another study by Radiesic and Tremelien reported their experience of 71 women who received GnRH trigger + hCG support protocol. All women underwent fresh embryo transfer and there was not a single case of early OHSS. [(6)]

Our study corroborates these large studies. Current literature concludes that GnRH agonist trigger not only prevents severe early onset OHSS but also reduces the occurrence of late-onset cases.

In our analysis, the number of oocytes retrieved was 11.45±4.2, and out of these MII oocytes retrieved were (85.15%). This may be another possible benefit of the use of GnRHa for final oocyte maturation in terms of induction of a surge of FSH as well as a surge of LH and possible retrieval of more (MII) oocytes as reported in previous studies. [(11-12)]

The Fertilization rate (73.33%) and cleavage rate 93% were comparable to cycles using conventional 10,000IU of hCG as a final trigger. [(13)]

Another study observed a rapid cleavage rate in those cycles employing GnRH antagonist + GnRH agonist. [(14)]

Previous studies have reported lower pregnancy rates and higher pregnancy loss rates of 80% in GnRHa group, when it was used as a trigger for final oocyte maturation in normal responder patients, despite intensive luteal support. [(12, 15, 16))] (Kolibianakis et al., 2005, [(14)] Itrkovitz-Eldor et al.,2000) [(15)] The lower

pregnancy rates after GnRH trigger have been attributed to a defective luteal phase and decreased endometrial receptivity.

In view of the low luteal phase serum LH levels and the absence of continuous hCG stimulation of the corpus luteum after the GnRHa trigger, multiple strategies have been proposed to optimize the luteal phase function and improve the pregnancy rate. [17]

Therefore, it has been suggested to deliver a 1500 IU hCG at induction combined with GnRh agonist. [4,5,7] This low dose does not lead to the induction of OHSS. The reproductive outcomes are clinical pregnancy rate of 33% and 37% between GnRHa and hCG triggers respectively were not different statistically although the difference was in favour of 10,000 IU of hCG, future studies with minor modification in a dose of hCG as luteal rescue might help to overcome this result.

In our study pregnancy rate was (31.25%) and clinical pregnancy rate was a low 25%, while miscarriage 1/10 (6.3%). Although it is a small retrospective analysis of cases, our results as regards pregnancy rates are comparable to a study [7] but clinical pregnancy rates are low.

To improve our results, we are performing a larger study in our two ACIMC centres in hyper responders with further addition of small doses of hCG as a luteal rescue for a reduction in late-onset OHSS as well as to improve the clinical pregnancy rates.

Taken together, a small bolus of 1500IU hCG administered at the time of oocyte retrieval seems to secure the luteal function and achieves statistically comparable pregnancy outcome without increasing early onset OHSS rate when GnRHa is used to induce final oocyte maturation [7].

In our study, 4 patients had their embryos frozen and did not undergo fresh transfer, as the number of follicles developed on the day of the trigger was between 33 and 45. This is another way to overcome the problem of adequate luteal phase support, early pregnancy loss, and risk of OHSS.[18] In this large RCT the authors recommended fresh transfer when up to 25 follicles are obtained, there was no case of OHSS seen in cycles where GnRHa trigger and 1500IU hCG as luteal phase support compared to (3.4%) cases of hCG trigger. When follicles retrieved are above 25 freezes all policy should be adopted to avoid any risk of OHSS. In such patients no luteal rescue in the form of hCG should be given. [19]

Conclusion

In conclusion, this retrospective small study supports the previous larger RCT that in hyper responders the final oocyte maturation by GnRHa trigger and luteal phase rescue by 1500IU of hCG not only prevents early onset OHSS as well as achieving an increase in M11 oocytes and secures clinical pregnancy outcome. In the future, larger studies are needed to find out the minimum effective dose of hCG as luteal phase rescue after GnRHa trigger cycles to achieve high pregnancy and delivery rates without developing OHSS.

References

1. Schwartz M, Jewelewicz R. .The use of gonadotrophins for induction of ovulation. Fertil Steril.1981;5:3-12
2. Yen S.S.C, Lenera G, et al Disappearance rate of endogenous luteinizing hormone and chorionic gonadotropin in max. J.Clin. Endocrinol. Metab 1968;28:1763---1767
3. Kumer Ne, Feinn Rs, Griffen DW et al. Predicting successful induction of oocyte maturation after gonadotrophin releasing hormone agonist GnRH trigger. Hum Reprod 2013;28:152-9
4. Gonan Y, Balakier H, Powell W, Casper RF Use of gonadotrophin- releasing hormone agonist to trigger follicular maturation for in vitro fertilization Clin Endocrinol Metab. 2002;5:232-9
5. 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: 630-634
6. Radesic B, Tremellen k. Oocyte maturation employing a GnRH agonist in combination with low-dose hCG luteal rescue minimizes the severity of ovarian hyperstimulation syndrome while maintaining excellent pregnancy rates. Human Reproduction 2011; 26: 3437-42
7. Humaidan P, Ejdrup BH, Westergoard LG, Y ding AC. 1500 IU of human chorionic gonadotrophin administered at oocyte retrieval rescues the luteal phase when gonadotropin releasing hormone agonist is used for ovulation induction: a prospective, randomized controlled study. Fertil Steril 2010; 93: 847-854
8. NICE. Fertility; Assessment and treatment for people with fertility problems. London: National Institute for Health and Care Excellence, 2013
9. Golan A, Ron El, Herman A, et al.. Ovarian hyper stimulation syndrome: an update review obstet. Gynaecol. Surv.1989; 44: 43-440.
10. Wada I, Matson Pl, Troup SA et al., Does elective cryopreservation of all embryo from women at risk of ovarian hyper stimulation syndrome reduce the incidence of condition? Br. J. obstet. Gynaecol 1993; 100: 265-269
11. Imoedemhe DA, Sigue AB, Pacpaco EL. Stimulation of endogenous surge of luteinizing hormone with gonadotrophin releasing hormone analog after ovarian stimulation for in vitro fertilization. Fertil Steril 1991; 55: 328-32
12. Humaidan P, Bredkjaer HE, Bungum L.2005 GnRH agonist or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles. A prospective randomized study. Hum Repord 2005; 20:1213-1220

13. Saijiao Li, Danni Zhou, Tailang Yin, Wangming Xu, Qingzhen Xie, Dancheng. Dual trigger of triptorelin and hCG optimizes clinical outcome for high responders in GnRH antagonist protocol. Impact journal 2018.
14. Munoz M, Cruz M, Humaidan P, et al., The type of GnRH analogue used during controlled ovarian stimulation influences early embryo development kinetics: a time – lapse study. Eur J obstet Gynaecol Reprod Biol 2013; 168: 167-172
15. Kolibianakis EM, Schultz – Mosgan A, Schroer A, Vansteirteghem A. A lower ongoing pregnancy rate can be expected when GnRH agonist is used for triggering final oocyte maturation instead of hCG in patients undergoing IVF with GnRH antagonist. Hum Reprod 2005; 20: 2887-2892
16. Itskovitz – Eldor J, Kol S, Mannaerts B. Use of single bolus of GnRH agonist triptorelin – Human Reproduction. 2000; 15: 1965-8
17. Engmann L, Benadiva C. Ovarian hyper stimulation syndrome prevention strategies: Luteal phase strategies to optimize pregnancy success in cycles with gonadotrophin releasing hormone agonist ovulatory trigger. Semin Reprod Med 2012; 28: 506-12
18. Griesinger G, Von Ott S, Schroer A et al. Elective cryopreservation of all pronuclear oocytes after GnRH agonist triggering of final oocyte maturation in patients at risk of developing OHSS: a prospective observational proof-of-concept study. Human Reproduction 2007; 22: 1348-1352
19. Seyhan A, Ata B, Polat M, Son WY. Yarali H. Dahan MH. Severe early ovarian hyper stimulation syndrome following GnRH antagonist trigger with the addition of 1500IU of hCG. Hum Reprod 2013; 28: 2522