Research Article

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Ovarian Hyperstimulation Syndrome Ratio And In Vitro Fertilization Success With Gonadotrphine Releasing Hormone Trigger And 1500 IU Human Chorionic Gonadotrophine For Luteal Support

Ayca Nazli BULUT[1]*, Semih Zeki ULUDAG[2], Mustafa Ercan AYGEN[2] and Yilmaz SAHIN[2]

[1]*Kayseri Education and Research Hospital, Department of Obstetrics and Gynecology, Kayseri, Turkey*

[2]*Kayseri Erciyes University, Department of Obstetrics and Gynecology, Kayseri, Turkey*

***Corresponding author**
Ayca Nazli Bulut, Kayseri Training and Research Hospital, Department of Obstetrics and Gynecology, 38030 Kocasinan, Kayseri, TURKEY; Phone: +90 505 625 14 33; Fax: +90 352 305 2315; E-mail: dr.nazlibulut@gmail.com

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Abstract

Intraduction: *Ovarian hyperstimulation syndrome (OHSS) is very serius complication of in vitro fertilisation (IVF) treatments. Human chorionic gonadotrophine (hCG) is the trigger factor of the syndrome. Gonadotrophine releasing hormone agonist (GnRHa) can use instead of hCG for triggering the ovulation.*

Matherial and Methods: *This study aims to evaluate the effects of ovulation triggering with Gonadotrophine Releasing Hormone Agonists (GnRHa) on ovarian hyperstimulation syndrome (OHSS) rates and pregnancy success in patients at risk of OHSS. 51 cycles were evaluated in 50 women. Gonadotrophine (Gn) was applied to all patients with a flexible GnRHa protocol. To trigger ovulation, 0.2 mg triptorelin was applied when the estradiol level was 3500-7000 pg/mL and/or when at least 18 follicles were determined at ≥10mm. Oocyte Pick-Up (OPU) was performed 35 hours after the triptorelin injection. Within 1 hour of OPU, luteal support with 1500 IU hCG was administered to the patients and on the night of OPU, vaginal progesterone and oral estrogen were started.*

Results: *OHSS was determined in 5 cycles (9.8%), and 4 of them (7.8%) were early OHSS. Embryo transfer was applied in 49 cycles. The pregnancy rate was determined as 44.9%, clinical pregnancy rate as 26.5%, continuing pregnancy rate as 24.4% and the abortus rate as 2%.*

Conclusion: *GnRHa triggering applied before treatment to patients at risk of early OHSS does not completely eliminate the risk of OHSS. Nevertheless, this protocol improved treatment results without increasing the rates of severe OHSS.*

Keywords: Ovarian Hyperstimulation Syndrome, Gonadotrophine-Releasing Hormone, analog, Chorionic Gonadotrophine, Fertilization in Vitro

Abbrevations

OHSS: Ovarian Hyperstimulation Syndrome
hCG: human Chorionic Gonadotrophine
GnRHa: Gonadotrophine Releasing Hormone agonist
Gn: Gonadotrphine
COH: Controlled Ovarian Hyperstimulation
TV-USG: Transvaginal Ultrasonography
VEGF: Vasculer Endotelial Growth Factor
OPU: Oosite Pick Up; E2: Estradiol
AFC: Antral Follicule Count
PCOS: Policyctic Ovarian Syndrome

Intraduction

In controlled ovarian hyperstimulation (COH) it is aimed to provide a suitable balance between two conflicting outcomes. Thus, the aim is to obtain the highest number of mature oocytes and embryos without exposing the patient to the risk of severe OHSS. The difficulty in COH is the correct identification of patients who will give an hyper, normal or poor response to stimulation [1].

The group at highest risk of OHSS are those who give an hyper response. This group is defined as young, thin, with polycystic ovary syndrome or only polycystic component in the ovaries seen on ultrasonography (USG) without a clinical or biochemical pattern of the syndrome, and a history of hyper response to previous applications of Gn. The risk is known to increase with an increasing number of developing follicles [1,2].

Although there is often no negative effect on the patient, all ovarian stimulation protocols can result in hyperstimulation of varying degrees. OHSS is an iatrogenic complication characterised by cystic expansion of the ovaries and rapid fluid leakage from the intravascular compartment to the 3rd cavities on USG. The severe form is a potentially life-threatening situation, resulting in hospitalisation of 1.9% of cases and is a triggering factor of endogenous or exogenous human chorionic gonadotropin (hCG) syndrome [3]. The relationship between hCG and OHSS is thought to be mediated by vascular endothelial growth factor (VEGF), which is an angiogenic molecule [2,3].

Traditionally, to start final oocyte maturation in ovarian stimulation cycles, hCG has been applied to replace the natural increase in luteinising hormone (LH) [4]. In comparison with LH, the long half-life of hCG has given rise to the opinion that hCG has a significant role in granulosing cells, in extending the luteinising effect and in the development of OHSS [4,5]. The application of the luteinising stimulus with exogenous hCG forms a major compelling power for the development of early OHSS within 8 days of OPU, and late OHSS starts with endogenous hCG of pregnancy 8 days after OPU [4]. In studies related to this subject, the use of bolus Gonadotropin Releasing Hormon analog (GnRHa) has been investigated to find a more physiological trigger and to reduce the incidence of OHSS [5]. GnRHa can be applied in COH cycles which use GnRH antagonist for hypophysis supression [4].

Studies related to GnRHa have revealed that despite the potential for normal implantation of collected mature oocytes, there have been unacceptably high rates of early pregnancy losses resulting from severe luteal phase failure and a reduction in continuing pregnancy rates [5,6]. The important point is that luteal phase deficiency cannot be eliminated with a standard luteal support protocol. Therefore, to protect the luteal function, it is recommended that 1500 IU hCG is applied 35 hours after the GnRHa trigger [7,8]. While GnRHa provides the facility for endogenous LH and FSH fluctuations, low-dose bolus hCG after OPU will maintain implantation and luteal ovarian steroidoenesis [9]. It is thought that the low dose of hCG for the triggering of OHSS is a very low dose [7,8].

The aim of this study was to evaluate the effects of ovulation triggered with GnRHa on OHSS rates and pregnancy outcomes in patients at risk of OHSS.

Matherial and Method

This prospective study included patients at high risk of OHSS who were applied with COH with IVF or ICSI-ET protocol. We received all of the paticipants confirmation before the study. All of the participants were informed abaut the study, it's complications and results. Ethics approval wasn't necessary because the method which used in the study is used routine practise and many centers apply this method routinly. So we didn't think essential to receive an ethic approval.

Criteria for inclusion in the study were defined as age between 19 and 38 years, body mass index (BMI) between 18-39 kg/m2, observation of at least 18 follicles of ≥10mm and estradiol (E2) value of 3500-7000 pg/mL on ovulation trigger day.

Exclusion criteria were defined as irregular continuation of treatment, >50 follicles on ovulation trigger day and E2 > 7000 pg/mL. Accordingly, 51 cycles of 50 patients were included in the study. Two cycles were applied to only 1 patient and a single cycle was applied to all the others. Embryo transfer could not be performed in 2 patients, as sperm for 1 patient and the embryo for 1 patient could not be obtained. Thus, embryo transfer was performed in 49 cycles. The criteria defined as high risk for OHSS were a history of OHSS, a history of PCOS, ovaries with a polycystic appearance on TV-USG and a requirement for high-dose gonadotropin in previous COH.

COH with Gn and a GnRH antagonist flexible protocol were applied to all patients. According to this protocol, recombinant FSH was started on the 3rd day of the menstrual cycle. The Gn dose was defined according to age, BMI, antral follicle count (AFC) and previous treatment received and with consideration of the need for Gn in the previous cycle and wheher or not there was a history of OHSS. The AFC was determined on TV-USG and the Gn dose was adjusted by observing the ovarian response with E2 measurements. All the TV-USG imaging and determinations of AFC were performed by a single researcher.

When the E2 value was >400 pg/mL and the leader follicle ≥14mm, 0.25mg cetrorelix acetate was applied. Gonadotropin antagonist application was continued until the ovulation trigger day. On the ovulation trigger day, 0.2mg triptorelin was applied to those with at least 18 follicles of ≥10mm and/or E2 value of 3500-7000 pg/mL for ovulation triggering. OPU was performed 35 hours after triggering, after which all the patients were questioned in respect of OHSS symptoms, including nausea, vomiting, abdominal distention and gastrointestinal symptoms.

Patients evaluated as OHSS were separated into 3 groups according to the severity of the findings. Patients with no ascites or minimal fluid observed on USG were evaluated as mild OHSS, those with evident fluid as moderate and those with abdominal distention, dyspnea and massive ascites as severe OHSS. Patients who developed OHSS in the first 9 days were accepted as early OHSS and those with later development as late OHSS.

For the purpose of luteal support, all patients were applied with 1500 IU hCG within 1 hour of OPU, and from the evening of OPU, progesterone vaginal gel /one a day and oral estrofem of 2mg/ 3 times per day were started. Following fertilisation in the laboratory, embryo transfer was performed on the 2nd, 3rd or 5th day depending on the quality of the embryo. On the 12th day after transfer, pregnancy was assessed with β-hCG measurement. In cases determined with a positive β-hCG value, at the 48th hour, at least 66% of β-hCG was evaluated in the surrounding folding. In cases clinically determined with pregnancy, the fetal heartbeat was evaluated with transabdominal USG in the 7th gestational week. Luteal support was continued in these cases. Treatment was terminated in cases not determined as pregnant.

Accordingly, the cases included in the study group were evaluated in respect of the total number of oocytes obtained, the number of mature oocytes obtained, pregnancy, live births and the presence of OHSS.

Results

The study included a total of 51 cycles in 50 patients. All the patients received GnRHa trigger and a luteal support protocol in the Kayseri Erciyes University Medical Faculty Reproductive Center. The mean

age of the female patients was 28.0 ± 4.3 years. PCOS diagnosis was made according to the Rotterdam criteria. A diagnosis of PCOS was made in 22 (44.0%) patients and PCOS was the most common reason for treatment. AFC was mean 25.2 ± 9.4 and was accepted as a marker of increased ovarian response. A total of 33 (64.7%) patients were in the first cycle of IVF. The patient characteristics are shown in Table 1.

Table 1: Patient Characteristic

			Ort.±s.s./n-%
Age (year)			28,0 ± 4,3
Height (cm)			160,6 ± 7,5
Weight (kg)			64,4 ± 12,6
BMI (kg/m²)			25,2 ± 4,6
Cyclus Count			1,5 ± 0,8
		1.Cyclus	64,7%
		2.Cyclus	14 27,5%
		≥ 3.Cyclus	4 7,8%
İnfertility Cause		Anexplained	13 25,5%
		Male factor	14 27,5%
		PCOS	13 25,5%
		PCOS+Male factor	9 17,6%
		Tubal Factor	1 2,0%
İnfertility Duration (year)			5,1 ± 2,7
İnfertility Type	Primer		46 90,2%
	Seconder		5 9,8%
PCOS	Absent		28 56,0%
	Present		22 44,0%
BMI: Bady mass index, PCOS: Policystic Ovarian Syndrome			

The IVF cycle characteristics and results are shown in Table II. The study included a total of 51 cycles. Due to unexplained infertility in 1 case and azoospermia in 1 case, no embryo could be obtained from 2 patients and therefore transfer could not be applied (2/51, 3.9%). Data related to the oocytes and embryos are presented in Table III.

Table 2: IVF cycle characteristics and results

	25-75 percentil	Median
Cyclus informations		
Cyclus duration (day)	9 - 11	10
FSH Inıtial dose (IU)	150 - 225	150
Total FSH (IU)	1163 - 2025	1575
Trigger Day		
E_2 (pg/mL)	2453 - 3962	3364
Endometrium Thickness (mm)	9,0 - 12,3	10,0
Trigger Day Follicule Count		
Follicule Count 10-12 mm	3,0 - 8,0	5,0
Follicule Count ≥ 13 mm	13,0 - 26,0	17,0
Follicule Count ≥10 mm total	19,0 - 31,0	24,0
FSH: Follicule stimülation hormone, E2: Estraiol		

Table 3: Data related to the oocytes and embryos

	25-75 percentil	Median
OOCYTEInformations		
GV	0,0-5,0	3,0
MI	0,0-1,0	0,0
MII	5,0-15,0	11,0
2PN oocyte	2,0-11,0	9,0
Total Oocyte Count	11,0-20,0	16,0

GV: Germinal vesicule, MI: Metafase I oocyte, MII Metafase II oocyte, 2 PN Oocyte: 2 pronucleer oocyte

	number	n-%
EMBRIO Informations		
Clivaj	16	32,7%
Blastocyst	33	67,3%
Total	49	100,0%

OHSS

Moderate level OHSS developed in 5 (9.8%) of the patients included in the study, of which 4 were early OHSS and 1 was late OHSS. In respect of the clinical characteristics of the patients who develped OHSS, 1 patient presented the day after OPU with complaints of nausea and abdominal discomfort. On TV-USG, the ovaries were of normal size and 3-4cm of fluid was observed in the Douglas pouch. The β-hCG value was positive and later decreased and the patient was evaluated as biochemical pregnancy. On the 2nd day after OPU, a patient presented with complaints of groin pain, nausea, gas and constipation. There was no defence and rebound in the physical examination. On USG, the right ovary was 54 x 44 mm in size and the left ovary was 70 x 41 mm. There was 3-4cm of fluid in the Douglas pouch and no fluid between the upper abdomen and the intestinal loops. Pregnancy could not be achieved in this patient. The 3rd patient presented 2 days after OPU with complaints of moderate nausea accompanied by vomiting and abdominal discomfort. On TV-USG, the ovaries were of normal size and 3-4cm of fluid was observed in the Douglas pouch. Pregnancy could not be achieved in this patient. The 4th patient presented 2 days after OPU with abdominal discomfort and nausea. On TV-USG, the right ovary was 60 x 80 mm in size and the left ovary was 100 x 80 mm and there was 3cm of fluid in the Douglas pouch. Biochemical pregnancy was observed in this patient. These 4 patients were followed up as out-patients and the symptoms recovered spontaneously within 1 week.

The single patient who developed late OHSS presented in the 4th gestational week with complaints of nausea, vomiting and abdominal pain. In the physical examintion, there was widespread sensitivity in the abdomen and defence and rebound. On USG, the right ovary was 90 x 60 mm in size and the left ovary was 100 x 100 mm and diffuse oedema and increased echo were observed. Fluid was observed in the para-ovarian area, on the anterior surface of the uterus and in the Douglas pouch. The patient was hospitalised for follow-up. On admittance to hospital, Hb was 9.5 g/dL, WBC 13,200 $10^3/\mu L$, Htc 33.3% and thrombocytes 354,000 $10^3/\mu L$. On Doppler USG, vascularisation was observed in both ovaries. Diagnostic laparoscopy was applied to discount ovarian torsion. As appendicitis was determined in the laparoscopic follow-up, appendectomy was performed. No intra-operative complications developed. In the postoperative period, the pain recovered. When the USG findings and general status improved and vital findings were stable, the patient was discharged. This pregnancy resulted in a single, live birth at term.

No cases of severe OHSS were observed in the study. The OHSS rates are shown in Table IV.

Table 4: OHSS Ratio

	OHSS-Absent (n=46)	OHSS-Present (n=5)	p
	Median.±s.d./n-%	Median.±s.d./n-%	
Age (year)	28,1±4,4	27,6±2,6	0,505
BMI (kg/m²)	25,3±4,7	24,4±3,8	0,284
AFC	25,7±9,5	21,2±8,1	0,290
PCOS			
Absent	26 56,5%	2 40,0%	0,481
Present	20 43,5%	3 60,0%	
Total FSH dose (IU)	1679 ± 638	1535 ± 459	0,796
Cyclus duration (day)	10,3 ± 1,9	9,8 ± 1,6	0,409
Follicule Count			

10-12 mm	5,9 ± 4,5	6,6 ± 2,1	0,970
≥ 13 mm	19,7 ± 7,4	13,6 ± 3,3	0,300
≥10 mm total	25,7 ± 7,8	20,2 ± 2,4	0,237
E2 (pg/mL)	3362 ± 1196	3719 ± 1114	0,375
Oocyte Count			
MII oosite	11,1 ± 4,8	14,4 ± 5,9	0,301
2PN oosite	8,0 ± 4,1	9,8 ± 3,4	0,336
Total oosite	15,2 ± 5,4	20,4 ± 5,0	0,554
count	15,2 ± 5,4	20,4 ±5,0	

Pregnancy Outcomes

The total pregnancy rate was found to be 44.9% in 49 cycles with embryo transfer applied. Biochemical pregnancy was observed in 7 (14.3%) patients. The anembryionic pregnancy rate was determined as 4.1% (2/49). A total of 13 (26.5%) clinical pregnancies were obtained from the cycles where embryo transfer was made. Curettage was applied to 1 patient with clinical pregnancy because of missed abortus. Comparisons of the data of the patients with and without clinical pregnancy are shown in Table V.

Table 5: the data of the patients with and without clinical pregnancy

Clinical Pregnancy-Absent (s=36)			Clinical Pregnancy- Present (s=13)			p
		Mean ±s.s./n-%	Med.(25-75 p)	Mean.±s.s./n-%	Med(25-75 p)	
Age (year)		28,5±4,4	28# -31	26,8 ±4,3	27 24 31	0,282
BMI (kg/m²)		25,6±4,7	25#-28	23,9±4,4	24 21 25	0,130
PCOS	Absent	20	55.5%	6 46,2%		0,176
	Present	16	44.4%	7 58,3%		
İnfertility Cause	Anexplained	9	24,3%	3 23,0%		
	Male FActor	13	35,1%	2 15,4%		
	PCOS	11	29,8%	3 23,0%		
	PCOS +Male Factor	2	5,6%	4 30,7%		
	Tubal Factor	1	2,8%	0 0,0%		
İnfertility Type	Primer	32	88,9%	11 84,7%		1,000
	Seconder	4	11,1%	2 15.3%		
Follicule Count						
10-12 mm		5,9±4,4	5 3 - 8	6,2 ± 4,6	6 1 11	0,624
≥ 13 mm		18,3±6,8	16 # - 25	20,6 ± 9,2	21 13 26	0,535
≥10 mm total		24,2±7,9	21 #- 0	26,8 ± 6,6	26 20 34	0,173
OOCYTE İnformation						
GV		3,5 ± 3,3	3 1 - 5	2,9 ± 2,6	2 14	0,657
MI		0,8 ± 1,3	0 0 - 1	0,8 ± 1,3	0 0 2	0,955
MII		11,2 ± 5,5	10 7 - 16	12,2 ±3,6	11 9 15	0,377
2PN oocyte		7,6 ± 4,3	7 4 - 12	10,0 ±3,0	9 8 11	0,081
Total oocyte count		15,5 ± 5,9	15 # - 20	15,9 ±4,6	16 11 20	0,839
Transferred						
Embrio Count		1,6 ± 0,6	2 1 - 2	2,0 ± 0,0	2 2 2	<0,05
Trigger Day Endometrium Thickness (mm)		10,4 ± 2,2	10 9 - 12	11,2 ± 2,5	12 9 13	0,241
Cyclus count		1,5 ± 0,7	1 9 - 12	1,7 ± 1,2	1 9 13	0,728
İnfertility Duration (year)		5,2 ±2,7	5 3 - 7	5,4 ± 2,7	5 4 7	0,792
Mann-whitney u test / Ki-kare test (Fischer test)						

Discussion

Previous studies have investigated the use of bolus GnRHa both in the search for a more physiological trigger and to reduce the risk of OHSS [5]. In small-scale studies, it has been shown that OHSS is prevented in high risk patients when final oocyte maturation is applied with GnRHa. A pilot study on this subject was published in 2000 by Itskovitz-Eldor et al [10]. In a 2006 study by Babayof et al of 28 high-risk patients, while moderate or severe OHSS developed in 4 (30.8%) of 13 patients applied with hCG to trigger ovulation, no OHSS was observed in any of the 15 patients applied with GnRHa ($p<0.05$) [11]. In a more extensive study of 66 high-risk patients, Engmann et al obtained similar results [12].

In the current study, the early OHSS rate was determined as 7.8%. Severe OHSS did not develop in any of these patients. However, the most significant difference of the current study from previous research was that patients received luteal support with 1500 IU hCG. Therefore, the early OHSS rate of the current study cannot be compared with the results of those studies that have suggested that GnRHa triggering completely eliminates early OHSS.

Moreover, despite patients in these studies having received similar intense luteal support, conflicting data have been obtained in respect of reproductive outcomes. While one study obtained good reproductive results in another study, a low rate (6%) of clinical pregnancy and a high rate (80%) of early pregnancy loss were observed [11,12]. The poor pregnancy outcomes obtained with GnRHa have increased the number of studies focusing on luteal support to provide fresh embryo transfer and it has been shown that the application of a low dose of hCG such as 1500 IU could achieve similar pregnancy rates as the classic hCG trigger without incurring a negative effect on OHSS. In the current study, 1500 IU hCG was applied subcutaneously within 1 hour of OPU. From the evening of OPU, progesterone vaginal gel and oral estrofem of 2mg/ 3 times per day were started. With the modified luteal support protocol, the pregnancy rate was found to be 44.9% and the clinical pregnancy rate 26.5%. In a study by Humaidan published in 2010, it was concluded that effect of the use of 1500 IU hCG on pregnancy outcomes was similar to that of the classic 10,000 IU hCG [8].

In contrast to other studies that reported that early OHSS was completely eliminated with GnRHa triggering and modified luteal support, a study of 6 severe OHSS cases by Seyhan et al revealed that 1500 IU hCG applied 35 hours after GnRHa trigger was sufficient to induce early OHSS [4]. In this retrospective, cohort study, the incidence of early onset OHSS was reported to be 22%. In another study of 23 patients at high risk of OHSS, the trigger day E2 values were mean 4891±2241 pg/mL and the total number of follicles >12 mm was 20±6 in patients applied with 1500 IU hCG for luteal support. Severe OHSS developed in 6 (26%) of these 23 patients. Of these, 5 patients with early onset OHSS were hospitalised as the presence of ascites required drainage and in 3 patients, ET was cancelled. In the same study, the number of follicles between 10mm and 14 mm were found to be significantly high in the patients with severe OHSS compared to the number in the patients without OHSS (34 vs 12).

A mean 39 oocytes were collected from patients who developed OHSS and fresh transfer could be made in 2 patients. The results of the current study suggest that GnRHa triggering and the application of 1500 IU hCG could reduce the incidence of OHSS in patients at risk of increased ovarian response. Currently, no optimal threshold value has been defined for the freezing of all embryos after GnRHa. In a study by Seyhan et al, as all the patients who developed severe OHSS had more than 18 follicles measuring 10-14 mm on trigger day, it was suggested that the number of follicles measuring 10-14 mm on trigger day could predict severe OHSS and that the number of follicles measuring > 12mm was not sufficient on this subject. With these predictive values, it was recommended that in women at increased risk of OHSS, all the embryos were frozen then later transferred in a natural cycle. However, the fact that the study was conducted with a low number of patients and the E2 values were higher than those of other studies may have prevented the determination of other risk factors.

In the current study, the rate of early onset OHSS was found to be 7.8% with GnRHa triggering and a single dose bolus 1500 IU hCG applied 35 hours after OPU in patients seen to be at risk of OHSS. Severe OHSS did not develop in any of these patients. The mean number of MII oocytes was determined as 11.4 ± 5 and the rate of clinical pregnancy was 26.5%. These results do not support the findings of other studies that have suggested that early OHSS is completely prevented by GnRHa triggering and a luteal support protocol with 1500 IU hCG. In the study by Seyhan et al, the study group comprised 23 patients at real risk of OHSS. In studies which have reported a high incidence of early onset severe OHSS, as it is known that there is greater expression of vasoactive mediators which have a significant place in OHSS pathogenesis, it is not surprising that there are greater numbers of small diameter follicles in the patient group that develops severe OHSS. However, in the current study, no statistically significant difference was determined between patients who developed and did not develop OHSS in respect of the total number of follicles, the number ≥ 13 mm, 10-12 mm and ≥ 10 mm (Table 4).

As severe early OHSS cases cannot be completely eliminated following GnRHa triggering, the freezing of all embryos has become a safe alternative method for patients at high risk of OHSS. The other advantages of this application are that it does not require intensive luteal support, there is no effect from endometrial problems which are widespread in patients giving an excessive response and it allows the transfer of suitable embryos in a natural cycle [13].

In the last 2 years, there have been seen to be rapid developments in the data obtained related to GnRHa triggering as a good alternative to hCG. GnRHa trigger is safe, patient-friendly and has many physiological advantages compared to hCG. Although optimal luteal phase support after GnRHa trigger is still being researched, when patient comfort and needs are considered, the concept of hCG triggering has become questionable especially in respect of preventing OHSS. To trigger ovulation in GnRH antagonist cycles, the use of GnRHa seems to be a good option in patients at high risk of OHSS. However, to confirm this effect, there is a need for further studies to shed light on subjects such as the effects on patients who give a normal response and the need for optimal luteal phase support.

Referenses

1. Polat M, Bozdag G, Yarali H (2014) Best protocol for controlled ovarian hyperstimulation in assisted reproductive technologies: fact or opinion? Semin Reprod Med 32: 262-271.
2. Mathur R, Evbuomwan I, Jenkins J (2005) Prevention and management of ovarian hyperstimulation syndrome. Current

Obstetrics and Gynaecology 15: 132-138.

3. Humaidan P, Quartarolo J, Papanikolaou EG (2010) Preventing ovarian hyperstimulation syndrome: guidance for the clinician. Fertil Steril 94: 389-400.
4. Seyhan A, Ata B, Polat M, Son WY, Yarali H, et al. (2013) Severe early ovarian hyperstimulation syndrome following GnRH agonist trigger with the addition of 1500 IU hCG. Hum Reprod 28: 2522-2528.
5. Humaidan P, Bredkjaer HE, Bungum L, Bungum M, Grondahl ML, et al. (2005) GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study. Hum Reprod 20: 1213-1220.
6. Kolibianakis EM, Schultze-Mosgau A, Schroer A, van Steirteghem A, Devroey P, et al. (2005) 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 antagonists. Hum Reprod 20: 2887-2892.
7. Humaidan P, Bungum L, Bungum M, Yding Andersen C (2006) Rescue of corpus luteum function with peri-ovulatory HCG supplementation in IVF/ICSI GnRH antagonist cycles in which ovulation was triggered with a GnRH agonist: a pilot study. Reprod Biomed Online 13: 173-178.
8. Humaidan P, Ejdrup Bredkjaer H, Westergaard LG, Yding Andersen C (2010) 1,500 IU human chorionic gonadotropin 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 93: 847-854.
9. Kol S, Humaidan P (2013) GnRH agonist triggering: recent developments. Reprod Biomed Online 26: 226-230.
10. Itskovitz-Eldor J, Kol S, Mannaerts B (2000) Use of a single bolus of GnRH agonist triptorelin to trigger ovulation after GnRH antagonist ganirelix treatment in women undergoing ovarian stimulation for assisted reproduction, with special reference to the prevention of ovarian hyperstimulation syndrome: preliminary report: short communication. Hum Reprod 15: 1965-1968.
11. Babayof R, Margalioth EJ, Huleihel M, Amash A, Zylber-Haran E, et al (2006) Serum inhibin A, VEGF and TNFalpha levels after triggering oocyte maturation with GnRH agonist compared with HCG in women with polycystic ovaries undergoing IVF treatment: a prospective randomized trial. Hum Reprod 21: 1260-1265.
12. Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, et al. (2008) The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. Fertil Steril 89: 84-91.
13. Humaidan P, Kol S, Papanikolaou EG, Copenhagen Gn RHATWG (2011) GnRH agonist for triggering of final oocyte maturation: time for a change of practice? Hum Reprod Update 17: 510-524.