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COMPARISON OF GNRH AGONIST WITH LOW-DOSE URINARY HCG FOR THE INDUCTION OF FINAL OOCYTE MATURATION IN HIGH-RISK PATIENTS UNDERGOING INTRACYTOPLASMIC SPERM INJECTION-EMBRYO TRANSFER (ICSI-ET)

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Abstract

The aim of this study is to compare clinical pregnancy rates in ICSI-ET cycles where GnRH agonist or hCG was used to induce final maturation of the oocytes.

A total of 97 women who produced more than 14 follicles following ovulation induction with recombinant FSH and GnRH antagonist were selected for randomization. Human chorionic gonadotropin (hCG, 5.000 IU, IM) or GnRH agonist (triptorelin 0.2 mg, SC) was used for the induction of final maturation. Women in GnRH agonist group received higher dose of progesterone (100 mg vs. 50 mg) and estradiol (6 mg orally per day vs. none) compared to women in hCG group in the luteal phase starting on the day of oocyte pick-up.

Age, duration of stimulation, dose of gonadotropins, peak estradiol levels were similar in both groups. The mean number of collected oocytes (14.7±2.1 vs. 13.8±4.3) and fertilization rates (70.7 ±18 vs.71.8 ±21) were not significantly different between women allocated to hCG group (n=53) and GnRH agonist group (n=44). Clinical pregnancy rates (37.7 vs. 36.3), miscarriage rates (15% vs. 18.7%) and ongoing pregnancy rates (32% vs. 29.5%) were similar between hCG group and GnRH agonist group, respectively. Two cases of moderate/severe OHSS occurred in the hCG group, and none in the GnRH agonist group.

In conclusion, GnRH-agonist triggering together with high dose steroid supplementation in the luteal phase yields similar clinical pregnancy rate to that obtained with lower dose of hCG administration for final maturation. However, lower dose of hCG was associated with a higher incidence of moderate/severe OHSS.

Introduction

Ovulation induction using either Gonadotropin Releasing Hormone (GnRH) agonist or antagonist protocol has been used to achieve multifollicular development in IVF cycles. However, ovarian hyperstimulation syndrome (OHSS) is still the major complication of ovulation induction and may lead to ovarian torsion, hydrothorax, thromboembolism and liver dysfunction in its severe form[1]. Although the incidence of severe OHSS is <2%, it may result in a life threatening condition. Thus, several strategies have been proposed to eliminate the risk of OHSS. GnRH antagonist protocol is commonly used with similar pregnancy rates and associated with a significant reduction in the incidence of severe OHSS when compared to GnRH agonist namely long-protocol[2]. Besides, GnRH agonist can also be used for triggering in GnRH antagonist protocol for high risk patients. Administration of hCG to induce oocyte maturation results in prolonged luteotropic effect and subsequently increases the risk of OHSS in high- risk patients[3]. GnRH agonist for inducing final oocyte maturation was used in many studies to reduce the risk of severe OHSS[4-6]. Nevertheless, luteal phase hormone levels may be inadequate to sustain well developed endometrium

with GnRH agonist triggering due to rapid demise of the corpus luteum. A number of protocols have been proposed to overcome impaired luteal phase in women who had agonist triggerring such as low-dose hCG administration together with agonist, low-dose hCG administration on the day of oocyte pick- up (OPU), the use of increased dose of estrogen and progesterone, administration of low-dose hCG in the mid-luteal phase[7-9]. It was even recommended to cryopreserve all of the fertilized oocytes for a later transfer to circumvent suboptimal luteal phase[10]. Thus, controversy still exists regarding the best method to obtain optimal pregnancy rates in IVF cycles with GnRH agonist triggering. The reduced risk of OHSS without affecting implantation rate with the administration of adjusted doses of estradiol and progesteron supplementation in GnRH agonist triggering cycles has been reported[8]. Steroid doses were adjusted according to serum estradiol and progesterone levels in the same study. Shapiro et. al. used aggresively enhanced steroid doses in the luteal phase and obtained similar pregancy rate with the dual trigger[9]. It is still not clear if using fixed increased doses of steroids in the luteal phase may restore an optimal endometrial environment. We therefore hypothesized that increasing the dose of progesterone and adding estradiol in the luteal phase may overcome the defective luteal endocrine/endometrial environment and restore implantation capacity after agonist triggering. In our prospective study, we compared the outcomes of ICSI-ET cycles where agonist was used for triggering combined with high dose steroidal supplementation with the low dose hCG for final maturation.

Patients and methods

A total of 97 patients undergoing ICSI-ET cycles from July 2011 to May 2012 were prospectively enrolled in this study. Inclusion criteria for women were age less than 40 years and with normal uterine cavity diagnosed with HSG or hysteroscopy and having more than 14 follicles >10 mm in diameter and estradiol level less than 4.000 pg/ml on the day of triggering final oocyte maturation. Baseline ultrasound assessment for antral follicle count and assessment of FSH level were performed prior to initiating ovulation induction. Ovarian response was monitored with serial transvaginal ultrasound and serum estradiol assessments. The starting dose of FSH (Puregon, Organon) was 150 IU per day and the dose of gonadotropins was adjusted according to response. A daily administration of cetrorelix (0.25 mg Cetrotide; Serono) was introduced in a fixed way on day 6 and continued until the day of hCG or GnRH agonist administration. All patients were triggered when at least three follicles reached to >17 mm with either hCG (5.000 IU, IM) or 0.2 mg of triptorelin SC (Decapeptyl). Randomization was performed by designed numerical chart. Coasting was carried out in women with estradiol level > 4.000 pg/ml and final oocyte maturation was administered when estradiol level dropped. Coasting was not continued for more than 3 days. Estradiol assessment was carried out by enzyme linked flourescent assay (VİDAS, Biomerıeux, France). Oocyte pick-up (OPU) was performed 34-36 hours later and oocytes were cultured in G-IVF- Plus (Vitrolife-Sweden) medium supplemented with 10 % human serum albumin (HSA) (Vitrolife-Sweden) at 37° C under 6% CO2 for 2 hours. Cumulus – corona complex was removed by pipetting to hyaluronidase (Type VIII; Sigma, St.Louis, MO) after 2 hours, and the cells of the corona radiata were removed mechanically with the aid of a 150-µm pasteur pipette in G-MOPS-Plus (Vitrolife-Sweden) medium. ICSI procedure was performed in all cases as described in detail elsewhere[11]. Fertilization was assessed 16-18 hours after ICSI, cleavage rate was checked 48-

72 hours after OPU. Embryo transfer was performed on post- OPU day 3 at the cleavage stage. In GnRH group, progesterone in oil 100 mg/day IM together with estradiol 6 mg (Estrofem tb, Novo Nordisk)) orally initiating on the day of OPU was used until the detection of fetal heart beat. In hCG group, progesterone in oil 50 mg/day IM (half of the dose used in GnRH agonist group) was administered starting on the day of OPU and continued until the presence of fetal heart beat. Estrogen supplementation was not used in the luteal phase in hCG group. Pregnancy was confirmed by assessing serum hCG level 12 days after the embryo transfer. Clinical pregnancy was defined by the presence of a gestational sac on a 7-week ultrasound. The diagnosis of OHSS was based on the criteria described previously[12] Fertilization, implantation, clinical pregnancy, miscarriage and ongoing pregnancy rates as well as moderate/severe OHSS rates were compared among two groups by using the unpaired Student's t test or X analysis as appropriate. A P value of <.05 was considered statistically significant. Values are expressed as mean ± SD.

Results

A total of 97 patients were randomized; 53 allocated to the hCG group and 44 to the GnRH-agonist group. Only the first cycle of each couple was included. There were no significant differences in the baseline characteristics between the two groups (Table I). There were also no statistically significant differences in the duration of stimulation, total dose of FSH (IU) used, estradiol level on the day of hCG administration, the number of mature oocytes, fertilization rate, clinical pregnancy rate, miscarriage rate and ongoing pregnancy rate (Table II). There were 3 cases in the hCG group and 2 cases in the GnRH agonist group for coasting. At least 3 oocytes were found in either group at OPU. In the hCG group, only two oocytes were obtained in 2 women otherwise all other women produced more than 8 oocytes. In GnRH agonist group one oocyte was recovered in one woman and at least 7 oocytes in the others. There was no ectopic pregnancy in both groups. There were 2 multiple pregnancies (twins) in the hCG group and one twins in the GnRH agonist group. Moderate/ severe OHSS developed in 2 women in the hCG group and none in the GnRH agonist group. The difference between the groups was not statistically significant (p=0.07). Clinical evidence of ascites was found in both patients. One of them was hospitalized for 5 days and ascites puncture through vagina was performed twice. Both women recovered in 10 days without any other complication.

Discussion

The present prospective study has demonstrated that the use of GnRH agonist trigger together with a high dose steroid supplementation in the luteal phase does not impair clinical pregnancy rate and reduces moderate/severe OHSS rate in ICSI-ET cycles. GnRH antagonist protocols have a number of advantages such as shorter duration of stimulation, absence of side effects caused by profound hypo-estrogenemia and avoidance of inadvertent administration of GnRH analogue in early pregnancy. Nevertheless, GnRH antagonist protocols offer less flexibility regarding cycle programming compared with GnRH agonists. A recent meta-analysis found decreased gonadotropin requirements and lower incidence of OHSS in the antagonist group[12]. Additionally, GnRH antagonist protocols allow physicians for agonist trigger instead of hCG if needed. The decreased risk of OHSS in high-risk patients following GnRH agonist trigger may be due to possibly diminished secretion of peptides responsible for causing OHSS. The most serious complication of an ovarian stimulation is the OHSS, a rare but potentially life-

threatening condition. A threshold of more than 18 follicles and/or estradiol level over 5.000 pg/ml was reported as predictors of severe OHSS by sensitivity rate of 83% and specificity rate of 84%[13]. In the present study, 85% of the patients presented with >20 follicles >10mm at the end of the follicular phase, thus representing a true high-risk population for OHSS. However, because of the increased risk of severe OHSS we did not trigger and coast the patients with estradiol level >4000 pg/ml. In our study, although it did not reach a statistical significance, moderate/severe OHSS was observed in two cases in the hCG triggered group but none in the GnRH triggered group. Several strategies have been proposed to reduce the risk of OHSS. Triggering of final oocyte maturation by GnRH analog in an antagonist cycle was recommended to decrease the risk of OHSS[5,14,15]. Embryo quality seems not to be affected by GnRH agonist trigerring since cryopreservation of all embryos followed by consecutive thaw cycles results in good pregnancy outcome[10]. However, GnRH trigger can result in abnormal endogenous LH surge and subsequently rapid luteolysis and inadequate luteal phase steroid levels[16,17]. This may cause a defective endometrial receptivity and an impair pregnancy rate[18]. The ongoing pregnancy rate was reported significantly lower in agonist trigger cycles[19,20]. Thus, several strategies have been proposed to supply luteal phase in these women, but the best approach is yet to be determined. Supplementation of LH in the form of low-dose hCG at the time of trigger[21] or at the oocyte retrieval[15] or in the midluteal phase[8] has been used to improve pregnancy rate because of the short half life of LH surge triggered by GnRH agonist. Particularly, serum LH level on the day of trigger was significantly lower when estradiol level was less than 4.000 pg/ml and this affected probability of conception. Addition of LH/hCG was recommended especially in these cases to rescue a few corpus lutea[22,23]. Nevertheless, administration of hCG, even with lower dose, may increase the risk of OHSS development. Therefore, we aimed at obtaining comparable clinical pregnancy rates without increasing the risk of OHSS and used only high dose steroids in the luteal phase.

Some studies reported the use of high dose steroids in the luteal phase without additional small dose of hCG[8,9,15,24]. However, results are conflicting probably due to differences in the dose, duration, type and the route of administration of the steroids in the luteal phase. Although optimal route of progesterone supplementation is still questionable, intramuscular administration seems to be preferable because of a defective corpus luteum following the GnRH trigger. The ongoing pregnancy rates were significanlty low in two studies using micronized vaginal progesterone and oral estradiol[7,24]. Moreover, addition of low dose of hCG (1.000 IU) to GnRH agonist for trigger improved the probability of conception over the use of GnRH analog together with 50 mg IM progesterone and 0.3 mg transdermal estradiol patches[25]. However, other studies advocated the intensive luteal support with high dose steroids to overcome the luteal phase defect. Engmann et. al. reported an unaffected implantation rate by supplementation of estradiol and progesterone in the luteal phase and early pregnancy compared to hCG trigger. They sustained the serum estradiol level above 200 pg/ml and the serum progesterone level above 20 ng/ml in the luteal phase by adjusting the dose administered[5]. Also, Shapiro et. al. found no difference in the ongoing pregnancy rate, when GnRH trigger with intensive luteal support was compared with dual trigger[10]. Estradiol patches (0.1 mg, 2-4 patches every 3 days), oral estradiol (2 mg, three times daily), injectable progesterone (100 mg IM daily) and vaginal suppositories (400

mg twice daily) were administered in the luteal phase. The findings of our study are in accordance with the studies which reported similar pregnancy rates between hCG and GnRH agonist plus high dose steroid administration in the luteal phase. Since the efficacy of a routine estradiol supplementation in the luteal phase has not been proven women who were triggerred by hCG did not use estradiol in our study[26]. In conclusion, our data confirm that a GnRH agonist trigger together with a high dose steroid supplementation in the luteal phase yields similar clinical pregnancy rate to that obtained with a lower dose of hCG administration in the high risk population.

Table I: Characteristics of women analyzed

	hCG Group	GnRH agonist group
n	53	44
Age (yr)	29.7 ± 4.1	31.2±3.8
BMI (kg/m2)	22.9± 4.8	23.4± 5.8
Baseline serum FSH (IU/L)	6.3 ± 1.9	5.9 ± 1.4
Baseline antral follicle count	17.9 ± 3.8	18.4 ± 4.1

Note: No significant differences between the two groups

Table II: Outcome of cycles according to the triggering agent

	hCG group	GnRH agonist group
No. of cycles	53	44
Duration of stimulation (days)	9.8±1.7	10.2±1.9
Total dose of FSH(IU)	2133±449	2310±390
Final E2 level (pg/ml)	2850±1115	3150±980
Number of follicles ≥10 mm	15.7 ± 4.1	16.6 ± 2.9
No of oocytes collected	14.7±2.1	13.8±4.3
No. of MII oocytes	12.8±1.8	11.9±3.2
Fertilization rate (%)	70.7± 18	71.8±21
No.of embryos transferred	1.92±1.1	1.97±1.3
Implantation rate, n(%)	23/138 (16.6)	19/116 (16.3)
Clinical pregnancy rate, n(%)	20/53 (37.7)	16/44 (36.3)
Miscarriage rate , n(%)	3/20 (15)	3/16 (18.7)
Ongoing pregnancy rate, n(%)	17/53(32)	13/44 (29.5)
No. of OHSS (moderate/severe)	2	0

Note: No significant differences between the two groups

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