FINAL OOCYTE MATURATION IN NORMORESPONDER PATIENTS UNDERGOING INTRACYTOPLASMIC SPERM INJECTION: GNRH AGONIST VS. DUAL VS. RCHG

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ABSTRACT

Problem Statement: Evidence suggests that GnRH agonist as a final oocyte maturation trigger in fresh autologous cycles is associated with a lower live birth rate, a lower ongoing pregnancy rate and a higher rate of miscarriage. GnRH agonist as an oocyte maturation trigger could be useful in terms of preventing ovarian hyperstimulation syndrome in hyperresponder patients. However, there's not enough evidence regarding the impact of dual trigger or GnRH agonist trigger in normoresponder patients. The aim of the present study was to investigate if there's a difference between cycle outcomes of normoresponder patients who were triggered by GnRH agonist alone or GnRH agonist+hCG or hCG alone?

Methods: In this retrospective cohort study data of normal responder patients who were treated by antagonist co-treated ICSI at a university-based infertility clinic between January 2016 and December 2016 were reviewed (n=200). The first study group consisted of cycles triggered by GnRH agonist alone. The second study group consisted of cycles triggered by both GnRH agonist and recombinant hCG (dual trigger). And the control group consisted of cycles triggered by recombinant hCG alone. There were 56 cycles in the GnRH agonist trigger group, 59 patients in the dual trigger group, and 85 patients in the hCG trigger group. The main outcome parameter was ongoing pregnancy rate. Demographic parameters, cycle characteristics and cycle outcome were compared between the groups. Continuous variables were analysed independently by Oneway ANOVA test and categorical variables were compared by using Fisher's exact test.

Results: There were no statistically significant differences between the study and control groups regarding age, body mass index, duration of infertility, etiology of infertility, and baseline hormonal status. Regarding the cycle characteristics total dose of gonadotropins, duration of ovulation stimulation, maximum estradiol levels, number of oocytes retrieved, MII and fertilization rates were comparable between the groups. The number of transferred embryos were 1.1±0.7, 1.2±0.6, and 1.2±0.5, respectively. The total number of good quality embryos were 3.2±2.9 in GnRH agonist trigger, 4.4±3.2 in dual trigger, and 2.9±2.1 in hCG trigger (P=0.014). The significance stems from the difference between dual trigger and hCG trigger (P=0.011). The cycle cancellation rates were 17.9% for GnRH agonist trigger, 10.2% for dual trigger, and 4.7% for hCG trigger (P=0.039). The ongoing pregnancy rates were 21.4% for GnRH agonist trigger, 30.5% for dual trigger, and 28.2% for hCG trigger (P=0.126).

Conclusion: Our results suggest that GnRH agonist or dual or hCG triggering have similar outcome in terms of ongoing pregnancy in normoresponder patients. However, dual trigger results in more good quality embryos and GnRH agonist trigger results in more cycle cancellations. Further randomized controlled studies are needed to confirm our findings.

BACKGROUND

While mature oocytes are necessary for oocyte retrieval and fertilization, final oocyte maturation is the key step in in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles. Human chorionic gonadotropin (hCG) has been used to trigger final follicle maturation, which is a prerequisite for oocyte fertilization, for many years in IVF/ICSI cycles and promoted the pregnancy rates. However, hCG administration for final oocyte maturation resulted in supra-physiologically elevated steroid levels in the luteal phase due to its long half-life. Hence, ovarian hyperstimulation syndrome (OHSS) risk is increased (1).

Recently, gonadotropin releasing hormone (GnRH) agonists have been introduced for final oocyte maturation in GnRH antagonist down-regulated cycles (2,3). It has been documented that GnRH agonists induce endogenous LH and FSH surges similar to natural mid-cycle LH surge with a shorter effect duration compared to exogenous hCG which may help to reduce the risk of OHSS (4).

Evidence suggests that GnRH agonist as a final oocyte maturation trigger in fresh autologous cycles is associated with a lower live birth rate, a lower ongoing pregnancy rate and a higher rate of miscarriage. GnRH agonist as an oocyte maturation trigger could be useful in terms of preventing OHSS in hyperresponder patients. However, there's not enough evidence regarding the impact of dual trigger or GnRH agonist trigger in normoresponder patients.

The aim of the present study was to investigate if there's a difference between cycle outcomes of normoresponder patients who were triggered by GnRH agonist alone or GnRH agonist+hCG or hCG alone?

METHODS

In this retrospective cohort study data of normal responder patients who were treated by antagonist co-treated ICSI at a university-based infertility clinic between January 2016 and December 2016 were reviewed (n=200). The first study group consisted of cycles triggered by GnRH agonist alone. The second study group consisted of cycles triggered by both GnRH agonist and recombinant hCG (dual trigger). And the control group consisted of cycles triggered by recombinant hCG alone. There were 56 cycles in the GnRH agonist trigger group, 59 patients in the dual trigger group, and 85 patients in the hCG trigger group.

The inclusion criteria were female age 18-40 years, baseline FSH level 3-15 IU/L, baseline LH level >3 IU/L, a starting dose of gonadotropin stimulation with a dose of 150 IU/day. The exclusion criteria were secondary infertility, body mass index (BMI) >30 kg/m², poor response to ovarian stimulation, presence of any untreated thyroid dysfunction/hyperprolactinemia, and/or presence of uterine abnormality. For eligible participants, all data regarding COS and clinical outcomes were extracted from the database, and the patients were divided into three groups according to final oocyte trigger.

An injection of 0.2 mg triptorelin acetate (Gonapeptyl 0.1 mg, Ferring, Istanbul, Turkey) or 1 mg (20 units in a tuberculin syringe of 5 mg/ml injectable solution) leuprolide acetate (Lucrin 5 mg, Abbott, Istanbul, Turkey) was administered for final oocyte maturation in the first group. However, in the second group in addition to one of these GnRH agonists 1500 IU hCG was administered. In the last group, 10000 IU hCG (Pregnyl; MSD, Oss, Holland) was administered for final oocyte triggering.

Ovarian stimulation was carried out with recombinant FSH (Gonal-F, Merck-Serono, Istanbul, Turkey) beginning from the second day of the menstrual cycle with a fixed starting dose of 150 IU/day when the antral follicle count was >12 per ovary. Dose adjustment was performed individually according to ovarian response. The GnRH antagonist (Cetrotide, Merck-Serono, Istanbul, Turkey) was introduced (0.25 mg/day) on the sixth day (fixed antagonist protocol) and continued throughout ovarian stimulation. When at least three follicles were ≥ 18mm, final oocyte triggering was performed. Transvaginal ultrasonography guided oocyte pick-up (OPU) was performed 35-36 hours after final oocyte trigger. Embryo transfer was performed on the 3rd day of OPU. A maximum of two embryos were transferred under ultrasound guidance due to national embryo transfer regulations. Vaginal micronized progesterone 90 mg/day (Crinone 8% gel; Merck-Serono, Istanbul, Turkey) was administered to all patients for LPS starting OPU day until the pregnancy test, and women with a positive result continued progesterone supplementation until 10 weeks of gestation.

The main outcome parameter was ongoing pregnancy rate. Demographic parameters, cycle characteristics and cycle outcome were compared between the groups. Continuous variables were analysed independently by Oneway ANOVA test and categorical variables were compared by using Fisher's exact test.

RESULTS

There were no statistically significant differences between the study and control groups regarding age, body mass index, duration of infertility, etiology of infertility, and baseline hormonal status (Table 1). Regarding the cycle characteristics total dose of gonadotropins, duration of ovulation stimulation, maximum estradiol levels, number of oocytes retrieved, MII and fertilization rates were comparable between the groups. The number of transferred embryos were 1.1±0.7, 1.2±0.6, and 1.2±0.5, respectively. The total number of good quality embryos were 3.2±2.9 in GnRH agonist trigger, 4.4±3.2 in dual trigger, and 2.9±2.1 in hCG trigger (P=0.014). The significance stems from the difference between dual trigger and hCG trigger (P=0.011). The cycle cancellation rates were 17.9% for GnRH agonist trigger, 10.2% for dual trigger, and 4.7% for hCG trigger (P=0.039). The ongoing pregnancy rates were 21.4% for GnRH agonist trigger, 30.5% for dual trigger, and 28.2% for hCG trigger (P=0.126) (Table 2).

Table 1	GnRH agonist N=56	Dual N=59	rHCG n=85	P
Age, years	30.6±4.7	31.4±4.2	32.1±4.5	0.188
BMI, kg/m ²	23.5±4.2	24.8±3.5	24.9±3.7	0.166
Bazal E ₂ ,pg/ml	42.2±21.4	53.4±38.0	48.7±20.2	0.092
FSH, IU/L	8.2±4.4	7.5±4.5	8.2±3.7	0.571
LH, IU/L	4.7±2.7	4.4±2.3	4.4±2.1	0.761
Duration of infertility, years	6.4±3.5	6.1±2.8	5.8±2.4	0.508
Etiology of infertility				0.062
Female	9 (%16.1)	15 (%25.4)	20 (%23.5)	
Male	31 (%55.4)	17 (%28.8)	38 (%44.7)	
Unexplained	16 (%28.6)	27 (%45.8)	27 (%31.8)	

Table 2	GnRH agonist N=56	Dual N=59	rHCG n=85	P
Total dose of gonadotropins,IU	2442±975	2390±1049	2725±932	0.086
Duration of stimulation, days	9.4±1.3	9.5±2.4	9.3±1.7	0.913
Max E ₂ , pg/ml	1640±1205	1916±1128	1406±928	0.026
Endometrial thickness on day of ET	10.4±1.7	10.4±1.8	10.7±1.6	0.490
Oocytes retrieved, n	7.4±4.9	9.2±5.3	7.6±4.5	0.087
MI, n	6.2±4.2	7.2±4.7	5.6±3.7	0.095
Fertilization rate, %	69±42	70±33	62±29	0.500
Number of Grade 1-2 embyos, n	3.2±2.9	4.4±3.2	2.9±2.1	0.014 ^a
Number of embryos transferred, n	1.1±0.7	1.2±0.6	1.2±0.5	0.291
Cycle cancellation, n (%)	10 (%17.9)	6 (%10.2)	4 (%4.7)	0.039
Pregnancy, n (%)	15 (%26.8)	20 (%33.9)	31 (%36.5)	0.141
Clinical pregnancy, n (%)	13 (%23.2)	20 (%33.9)	26 (%30.6)	0.112
Miscarriage, n (%)	1 (%1.8)	2 (%3.4)	2 (%2.4)	0.148
Ongoing pregnancy, n (%)	12 (%21.4)	18 (%30.5)	24 (%28.2)	0.126
OHSS, n (%)	0	0	0	

CONCLUSION

In assisted reproductive technology (ART), it is important to seek a balance between optimum ovarian stimulation and good clinical outcome with high pregnancy and minimal moderate/severe OHSS rates.

Our results suggest that GnRH agonist or dual or hCG triggering have similar outcome in terms of ongoing pregnancy in normoresponder patients. However, dual trigger results in more good quality embryos and GnRH agonist trigger results in more cycle cancellations. Further randomized controlled studies are needed to confirm our findings.

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