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Does the Modification of Starting Gonadotropin Dose During Intracytoplasmic Sperm Injection Cycle Have Any Significant Impact on Cycle Outcome?

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ABSTRACT

OBJECTIVE: The aim of this study was to figure out the impact of gonadotropin dose alteration requirements due to high response or unresponsiveness on intracytoplasmic sperm injection cycle outcomes in a standard group of patients.

STUDY DESIGN: One hundred cycles with same gonadotropin dosage along the stimulation were compared with 100 cycles in which gonadotropin dose alterations were needed due to high response or unresponsiveness. Groups were compared in terms of age, body mass index, serum follicle stimulating hormone and estradiol levels, antral follicle count, gonadotropin dosage, duration of stimulation, endometrial thickness at trigger day, number of total, mature and immature oocytes and finally the clinical pregnancy rates.

RESULTS: There were significant differences between groups with regard to gonadotropin starting dose, total gonadotropin dose, duration of stimulation, estradiol level at trigger day, number of total oocytes and metaphase 1 oocyte number. Clinical pregnancy rates were similar between groups.

CONCLUSION: Dose alteration requirement along intracytoplasmic sperm injection cycle result in high number of total and metaphase 1 oocyte yields, higher starting gonadotropin and total gonadotropin dose, duration of stimulation and estradiol level at trigger day, however clinical pregnancy rates were similar between groups.

Keywords: Follicle stimulating hormone threshold, Ovarian reserve, In vitro fertilization cycle, Follicle stimulating hormone, Anti-Müllerian hormone, Antral follicle count

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Introduction

In assisted reproductive technology (ART) cycles, clinicians try to estimate the individual gonadotropin dose threshold by the utilization of anamnesis, clinical criteria, age, body mass index (BMI) and ovarian reserve markers to obtain optimal result (1,2).

Nowadays, follicle stimulating hormone (FSH), anti-Müllerian hormone (AMH) and antral follicle count (AFC) are proposed to be the most reliable markers to predict ovarian response to exogenous FSH (3-5). Individualized starting gonadotropin dose based on these markers was reported to result in reduction of both excessive response and cancelled cycles (6,7). A CONSORT calculated has been introduced to estimate starting gonadotropin dose and considered to have potential for use in routine clinical practice (8).

Individualization of treatment depend on potential ovarian response allow a safer and more effective in vitro fertilization (IVF) / intracytoplasmic sperm injection (ICSI) practice (9). Previous study indicated the uncertain predictive value of ovarian reserve tests for the cycle outcome and the authors concluded that AFC and AMH clearly add to age in predicting poor response and as single tests, AFC and AMH both fully cover the prediction of poor ovarian response however, none of the ovarian reserve tests add any information to the limited capacity of female age to predict ongoing pregnancy after

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IVF/ICSI. The clinical usefulness of ovarian reserve tests prior to IVF/ICSI will be limited to the prediction of ovarian response (10).

The aim of this study was to evaluate the impact of gonadotropin dose alteration requirements due to high response or unresponsiveness on ICSI cycle outcomes in which optimal gonadotropin starting dose was failed to be predicted by the utilization of ovarian reserve tests.

Material and Method

We retrospectively analyzed the database containing clinical and laboratory information on IVF/ICSI treatment cycles carried out at the IVF unit of Zeynep Kamil Women and Children's Health Training and Research Hospital. Patients who underwent first cycle of the IVF/ICSI treatment with an indication of unexplained or tubal factor infertility, women under 40 years of age were included in this study. One hundred cycles with same gonadotropin dosage along the stimulation were compared (control group) with 100 cycles in which gonadotropin dose alterations were needed due to high response or unresponsiveness (study group). Exclusion criteria were male factor infertility, history of previous ovarian surgery, diagnosis of endometriosis, basal level of day 3 FSH >15IU/L, serum AMH value <1 ng/mL, total number of AFC <4, BMI > 30 kg/m^2, presence of ovarian cysts, history of pelvic inflammatory disease, any known metabolic or endocrinological disease. All patients had been trying to conceive for at least 12 months and had undergone a fertility workup.

During database screening, randomly selected one hundred cycles with stable gonadotropin dosage along stimulation were compared with randomly selected 100 cycles in which gonadotropin dose alterations were needed due to high response or unresponsiveness. Randomization of selected files was achieved by random number generator. Database was screened by an independent staff blinded for the study design. Two groups were compared in terms of age, BMI, serum FSH and estradiol levels, AFC, gonadotropin dosage, duration of stimulation, endometrial thickness at trigger day, number of total, mature and immature oocytes and finally the clinical pregnancy rates.

For all participants, a gonadotropin-releasing hormone (GnRH) antagonist protocol was used for IVF/ICSI. A regimen of daily recombinant follicle-stimulating hormone (rFSH; Gonal-F, Merck-Serono, Geneva, Switzerland) was started on the second day of the menstrual cycle. The dose used ranged from 150 IU to 300 IU, and was determined by each patient's basal clinical characteristics. Mean follicular growth was monitored every 2-3 days via two-dimensional transvaginal sonography. The daily dose of rFSH was adjusted from day 5 of stimulation according to the ovarian response. Additionally for each participant, on the fifth day of ovarian stimulation and the following days when follicular growth was monitored, 3-5 mL of venous blood was taken between 8:00 AM and 10:00 AM, and the concentration of estradiol was determined. Estradiol levels were measured using a microparticle enzyme immunoassay, using the ECL2012 system (Siemens, Munich, Germany) in accordance with the manufacturer's protocol. The GnRH antagonist (Cetrorelix, Merck-Serono, Geneva, Switzerland) was administered at a dose of 0.25 mg/day when the follicular size reached 12 mm. When the follicular size reached 18 mm, recombinant chorionic gonadotropin alpha 250 mg (Ovitrelle, Merck-Serono, Geneva, Switzerland) was administered subcutaneously, and follicular puncture was performed after 34-36 hours. From the day of ovum retrieval, the luteal phase was supported by vaginal progesterone gel (Crinone gel 8%; Merck-Serono, Geneva, Switzerland) twice a day. ICSI was applied for each oocyte obtained by follicular puncture. Elective transfer of one grade-1 embryo was performed either at cleavage (day 3) or blastocyst (day 5) stage, according to the developmental characteristics of the embryo. Serum levels of the β-subunit of hCG (β-hCG) were measured after 2 weeks. If they were more than or equal to normal levels (5 IU/L) in pregnancy, the patient was considered to have successful implantation, and ultrasonography was performed to detect the pulse of fetus and confirm a clinical pregnancy.

Statistical analyses

Data was entered to SPSS version 15 (Chicago, USA, 2006). Continuous variables were compared by student-t test. P <0.05 was accepted to be statistically significant.

Results

Mean age, BMI and duration of infertility were 31.7 (23-39) years, 23.4 (18-26) kg/m^2, 5.8 (1-19) years respectively. Mean, minimum and maximum levels of basal ovarian reserve test results were as follows: FSH=6.3 (3-12 IU/L), estradiol=44.2 (10-78 pg/mL), AMH=4.1 (1-14 ng/mL), AFC=11.7 (4-24). Minimum and maximum starting gonadotropin dose was 75 and 300 respectively with a mean value of 243.8. Mean duration of stimulation was 8.9 (6-15 days) and mean total gonadotropin dose was 2228.7 (575-4800 IU). Cycle outcome characteristics of whole study population were as follows: Peak estradiol level =1903.1 (255-4643 pg/mL), number of total [8.7(5-30)], mature [7.3(2-18)], immature [0.61(0-5)], gv [0.86(0-10)] oocytes. There were 9 cases underwent coasting in dose altered group while 1 cases in control (<0.05). There were 33 (33%) cases with clinical pregnancy in study group while 30 (30%) cases in control (>0.05). There were 3 clinical pregnancies among 10 (30%) cases underwent coasting. There was no cycle cancellation due to hyper or unresponsiveness to gonadotropin stimulation. Comparison of groups with and without dose adjustments during stimulation was summarized in table 1 which showed significant difference between groups in terms of number of total and metaphase 1 oocyte yields, starting gonadotropin and total gonadotropin dose, duration of stimulation and estradiol level at

trigger day. There were 24 cases who required dose increment due to unresponsiveness while majority of the cases underwent dose decrement to avoid hyperresponsiveness.

Table 1: Comparison of cycles with and without gonadotropin dose adjustments

	Groups	Mean	Std. Deviation	P Value
Age (Years)	No DA	31.7	4.1	NS
	DA	31.5	4.2	
BMI (kg/m^2)	No DA	24.8	3.8	NS
	DA	25.3	3.9	
DOI (Years)	No DA	5.73	3.6	NS
	DA	5.84	3.7	
FSH (IU/L)	No DA	6.03	1.7	NS
	DA	6.5	2.2	
Estradiol (pg/mL)	No DA	44.4	15.2	NS
	DA	44.5	16.5	
AMH (ng/mL)	No DA	3.3	2.3	NS
	DA	4.7	4.3	
AFC	No DA	11.8	4.4	NS
	DA	11.5	5.1	
GSD (IU)	No DA	229	60.8	< 0.05
	DA	257	62.2	
TGD (IU)	No DA	2031.1	738.1	< 0.05
	DA	2425.7	962.5	
DS (Days)	No DA	8.6	1.5	< 0.05
	DA	9.2	1.7	
Estradiol at T (pg/mL)	No DA	1570.1	703.6	< 0.05
	DA	2236.1	1108.6	
No of TO	No DA	8.2	2.9	< 0.05
	DA	9.2	4.2	
No of IMO	No DA	0.38	0.88	<0.05
	DA	0.83	1.1	
No of MO	No DA	7.01	2.7	NS
	DA	7.6	3.5	
No of GVO	No DA	0.87	1.3	NS
	DA	0.85	1.5	
MR	No DA	0.88	0.15	NS
	DA	0.84	0.18	

DA: Dose adjustment, No: Number, DOI: Duration of infertility, BMI: Body mass index, FSH: Follicle stimulating hormone, AMH: Anti mullerian hormone, AFC: Antral follicle count, GSD: Gonadotropin starting dose, TGD: Total gonadotropin dose, DS: duration of stimulation, T: Trigger, TO: Total oocyte, IMO: Immature oocyte, MO: Mature oocyte, GVO: GV oocyte, MR: Maturity rate

Discussion

In this study, we tried to figure out the impact of gonadotropin dose alteration requirements due to high response or unresponsiveness on ICSI cycle outcomes. Our data revealed that majority of the cases required dose decrements and dose alteration requirement along ICSI cycle resulted in high rate of metaphase 1 oocyte yields, higher starting gonadotropin and total gonadotropin dose, duration of stimulation and estradiol level at trigger day, however clinical pregnancy rates were similar between two groups.

Personalized IVF/ICSI has several benefits; it lets clinicians give women more accurate information on their prognosis thus facilitates counselling especially in cases of extremes of ovarian response. Individualism of IVF/ICSI treatment provides a safer and more effective IVF/ICSI practice (9). In some cases, it is difficult to achieve correct balance between under and over-stimulation with gonadotropins due to wide inter-individual variation, variable FSH threshold. Multifollicular development is the main goal in IVF/ICSI protocols while avoiding ovarian hyperstimulation syndrome (OHSS).

It is possible to minimize possible complications by the modification of stimulation protocol. AMH was proposed to be a serum marker of ovarian response that can be measured on any day of the menstrual cycle (11). Previous study showed ovarian reserve tests to have modest predictive value for poor ovarian response, and AFC and basal FSH were found to have the best sensitivity and specificity for predicting ovarian response among all clinical and laboratory parameters (12). Broekmans et al. suggested not to use ovarian reserve tests routinely in all patients. Therefore, first cycle of IVF/ICSI treatment was proposed to be a surrogate ovarian response test (13). Although it has no clinical applicability due to the lack of data from prospective studies, it may be an alternative to overcome disadvantages of variability between ovarian reserve test results (14,15). Optimal gonadotropin starting dose is still a concern and has not been established (16). Majority of the physicians prefer trying standard doses of gonadotropins ranging between 100 and 250 IU/day for the patients who is defined as younger than 40 years of age, having two ovaries, a normal menstrual cycle (21-35 days) and a normal basal FSH level. Comparison of variable starting gonadotropin doses ranging between 100 to 225 revealed harvesting of more oocytes but similar pregnancy rates, and increased dose did not compensate for the age-related decline in ovarian function (17,18). These studies also confirmed the high variability of responses in women with standard ovarian reserves. Number of oocytes harvested in these studies varied between 1 to ≥30.

Main goal to determine the optimal starting gonadotropin dose is to have best efficacy (to retrieve an adequate number of oocytes) while avoiding risks (to avoid OHSS and cycle cancellation due to insufficient response). Optimal number of

oocyte to be harvested in a standard case has been accepted to be 5-14 oocytes per patient (19). Besides harvesting of optimal number of oocytes, it is more favorable if they are mature and good quality for higher rate of fertilization capacity, therefore effect of maturation index was emphasized in a recently published study indicating a cut off value of 40 % maturity rate for optimal embryological and clinical pregnancy outcomes, and authors concluded that "The selection of patient-specific COS strategies should take into consideration outcomes affecting oocyte maturation as well as oocyte number" (20).

Live birth rates were shown to decrease with increasing gonadotropin doses, this association was free from the effect of number of oocytes retrieved. This observation was restricted for the cases with good prognosis (21).

Harvesting of low number of immature oocytes resulted in increased rates of fertilization and incidence of wide perivitellin space, immature oocytes was not found to have negative impact on early embryo development (22). Consistent with these aforementioned data, we found significantly higher number of immature oocytes in group needed dose alterations during stimulation however, clinical pregnancy rates were comparable between groups. Although we utilized most commonly suggested predictors for optimal starting gonadotropin dose, in a proportion of cycles dose adjustments were needed, however failure of this prediction did not affect cycle outcome despite the non-significant decreased maturity rate and increased number of immature oocytes in group underwent dose adjustment.

Individualized and standard dose protocols were compared in a previous randomized study, authors stated that individual dose regimen in a well-defined 'standard' patient population was associated with better outcome with regard to ongoing pregnancy rate, dose adjustments were needed in fewer cases in this group compared to cycles with standard dose regimen (23).

In conclusion, in a standard population, possible minimum dose of gonadotropin should be determined before starting stimulation. Clinical and ovarian reserve test seem to have minimal value to determine FSH threshold. Failed prediction of optimal starting dose seems not to have any significant impact on cycle outcome in terms of clinical pregnancy rates, but result in high number of total and metaphase 1 oocyte yields, higher starting gonadotropin and total gonadotropin dose, duration of stimulation and estradiol level at trigger day in cases who needed dose alterations during stimulation.

References

1. Evian Annual Reproduction Workshop Group 2007, Fauser BC, Diedrich K, Devroey P. Predictors of ovarian response: progress towards individualized treatment in ovulation induction and ovarian stimulation. Hum Reprod Update 2008 Jan-Feb;14(1):1-14.
2. Alviggi C, Humaidan P, Ezcurra D. Hormonal, functional and genetic biomarkers in controlled ovarian stimulation: tools for matching patients and protocols. Reprod Biol Endocrinol 2012 Feb 6;10:9.
3. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF/ICSI outcome. Hum Reprod Update 2006 Nov-Dec;12(6):685-718.
4. La Marca A, Sighinolfi G, Radi D, Argento C, Baraldi E, Artenisio AC et al. Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update 2010 Mar-Apr;16(2):113-30.
5. Nelson SM, Yates RW, Fleming R. Serum anti-Mullerian hormone and FSH: prediction of live birth and extremes of response in stimulated cycles– implications for individualization of therapy. Hum Reprod 2007 Sep;22(9):2414-21.
6. Nelson SM, Yates RW, Lyall H, Jamieson M, Traynor I, Gaudoin M et al. Anti-Müllerian hormone-based approach to controlled ovarian stimulation for assisted conception. Hum Reprod 2009 Apr;24(4):867-75.
7. Yates AP, Rustamov O, Roberts SA, Lim HY, Pemberton PW, Smith A et al Anti-Mullerian hormone-tailored stimulation protocols improve outcomes whilst reducing adverse effects and costs of IVF/ICSI. Hum Reprod 2011 Sep;26(9):2353-62.
8. Pouly JL, Olivennes F, Massin N, Celle M, Caizergues N, Contard F. Usability and utility of the CONSORT calculator for FSH starting doses: a prospective observational study. Reprod Biomed Online 2015 Sep;31(3):347-55.
9. La Marca A, Sunkara SK. Individualization of controlled ovarian stimulation in IVF/ICSI using ovarian reserve markers: from theory to practice. Hum Reprod Update 2014 Jan-Feb;20(1):124-40.
10. Broer SL, van Disseldorp J, Broeze KA, Dolleman M, Opmeer BC, Bossuyt P et al. Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: an individual patient data approach. Hum Reprod Update 2013 Jan-Feb;19(1):26-36.
11. Seifer DB, Maclaughlin DT. Mullerian Inhibiting Substance is an ovarian growth factor of emerging clinical significance. Fertil Steril 2007 Sep;88(3):539-46.
12. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF/ICSI outcome. Hum Reprod Update 2006 Nov-Dec;12(6):685-718.
13. Hendriks DJ, Mol BW, Bancsi LF, Te Velde ER, Broekmans FJ. Antral follicle count in the prediction of poor ovarian response and pregnancy after in vitro fertilization: a meta-analysis and comparison with basal follicle-stimulating hormone level. Fertil Steril 2005 Feb; 83(2):291-301.
14. Hansen KR, Morris JL, Thyer AC, Soules MR.

Reproductive aging and variability in the ovarian antral follicle count: application in the clinical setting. Fertil Steril 2003 Sep;80(3):577-83.

15. Elter K, Sismanoglu A, Durmusoglu F. Intercycle variabilities of basal antral follicle count and ovarian volume in subfertile women and their relationship to reproductive aging: a prospective study. Gynecol Endocrinol 2005 Mar;20(3):137-43.
16. van Hooff MH. The human menopausal gonadotropin (hMG) dose in in vitro fertilization (IVF/ICSI): what is the optimal dose? J Assist Reprod Genet 1995 Apr; 12(4):233-5.
17. Hoomans EH, Mulder BB. A group-comparative, randomized, double-blind comparison of the efficacy and efficiency of two fixed daily dose regimens (100-and 200-IU) of recombinant follicle stimulating hormone (rFSH, Puregon) in Asian women undergoing ovarian stimulation for IVF/ICSI/ICSI. J Assist Reprod Genet 2002 Oct;19 (10):470-6.
18. Yong PY, Brett S, Baird DT, Thong KJ. A prospective randomized clinical trial comparing 150 IU and 225 IU of recombinant follicle-stimulating hormone (Gonal-F*) in a fixed-dose regimen for controlled ovarian stimulation in in vitro fertilization treatment. Fertil Steril 2003 Feb; 79(2):308-15.
19. Popovic-Todorovic B, Loft A, Lindhard A, Bangsboll S, Andersson AM, Andersen AN. A prospective study of predictive factors of ovarian response in 'standard' IVF/ ICSI/ICSI patients treated with recombinant FSH. A suggestion for a recombinant FSH dosage normogram. Hum Reprod 2003 Apr;18(4):781-7.
20. Ozgura K, Buluta H, Berkkanoğlu M, Coetzee K. Oocyte maturation-index as measure of oocyte cohort quality; a retrospective analysis of 3135 ICSI cycles. Middle East Fertil Soc J 2015;20(1):37-42.
21. Baker VL, Brown MB, Luke B, Smith GW, Ireland JJ.Gonadotropin dose is negatively correlated with live birth rate: analysis of more than 650,000 assisted reproductive technology cycles. Fertil Steril 2015 Nov;104 (5):1145-52.
22. Halvaei I, Ali Khalili M, Razi MH, Nottola SA. The effect of immature oocytes quantity on the rates of oocytes maturity and morphology, fertilization, and embryo development in ICSI cycles. J Assist Reprod Genet 2012 Aug; 29(8):803-10.
23. Popovic-Todorovic B, Loft A, Bredkjaeer HE, Bangsbøll S, Nielsen IK, Andersen AN. A prospective randomized clinical trial comparing an individual dose of recombinant FSH based on predictive factors versus a 'standard' dose of 150 IU/day in 'standard' patients undergoing IVF/ ICSI/ICSI treatment. Hum Reprod 2003 Nov;18(11): 2275-82.