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Doctors' Preferences for Controlled Ovarian Stimulation Protocols in Intrauterine Insemination

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ABSTRACT

Introduction: Intrauterine insemination (IUI) is an important treatment for infertility. IUI combined with controlled ovarian stimulation (COS) is widely used because of the higher pregnancy rates compared to IUI cycles without COS. **Material and methods:** We retrospectively analyzed a single center data from 458 patients underwent the first IUI cycle and had only 1 mature follicle from May 2009 to January 20144. 48 cycles were performed with Clomiphene citrate/Letrozole (CC/LE), 244 cycles with gonadotropins (Gn), 71 cycles with CC/LE+Gn, and 95 cycles in NC group. **Results:** Results showed that doctors preferred Gn protocol (53.3%) ($p<0.05$). Older patients were more likely to be allocated to CC/LE or NC group. 98.95% patients in NC group had regular menstruation cycle, with only 49.3% in CC/LE+Gn group ($p<0.05$). Estradiol (E2) level was much higher in COS groups than in NC group ($p<0.05$, for one mature follicle patients), and no significant differences were found within the COS groups. Duration of reaching follicles maturation was the shortest in Gn group and the longest in NC group, and NC group has the smallest follicular diameter ($p<0.05$). **Conclusion:** No significances were found regarding the IUI outcomes. To sum up, doctors prefer COS for IUI. Patients' age, menstruation cycle, infertile etiology and ovary function were the main factors affecting doctors' selection of COS protocols.
Key words: natural cycle; controlled ovarian stimulation; intrauterine insemination; pregnancy outcomes.

1. INTRODUCTION

Intrauterine insemination (IUI) is an important treatment for infertility (1). IUI combined with controlled ovarian stimulation (COS) is widely used because of the higher pregnancy rates compared to IUI cycles without COS. Effectiveness and costs were the most important determinants of patients' preferences, followed by safety and information sharing with physicians (2). It is assumed that doctors always choose COS protocol basing on patient's overall situation. Here the study aims to explore what are the factors affecting doctors' preferences in IUI treatment.

2. MATERIALS AND METHODS

2.1. Patients

This was a retrospective study conducted in Center for Reproductive Medicine, The Third Affiliated Hospital, Sun Yat-Sen University, from May 2009 to January 2014. All couples came for IUI were assigned a diagnosis of infertility after the standard infertility evaluation workup of semen analysis, assessment of ovulation, hysterosalpingogram (HSG), and, if indicated, tests for ovarian reserve and laparoscopy (3). Ac-

cording to COS protocol, patients were allocated into 4 groups: clomiphene citrate/letrozole (CC/LE) group, gonadotropins (Gn) group, CC/LE+Gn group, and natural cycle (NC) group. Only data of the first IUI cycle and with only 1 mature follicle were analyzed. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Reproductive Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University.

2.2. Controlled ovarian stimulation, monitoring ovulation and luteal support

Criteria for COS: Ovulation induction was started between day 2 and day 5 of menstruation cycle in patients who had no residual cysts larger than 20 mm by basal transvaginal ultrasound monitor.

CC/LE group and CC/LE+Gn group: Initial dose was CC 50 mg/day or LE 2.5mg/day for 5 days. 5 days later, if ultrasound monitoring showed no follicles reaching 10mm or bigger, HMG 75U was used every day until human chorionic gonadotropin (HCG, LizhuPhamacy, China) injection day.

Gn group: The initial dose was human menopausal gonadotropin (hMG, LizhuPhamacy, China) 75IU/day for 5 days. Fol-

licle growth was measured by ultrasonography every 1-5 days. Dose was increased or decreased 37.5-75 IU/day basing on the number of leading follicles.

HCG injection day: HCG 10,000 IU was administered to trigger ovulation when 1-3 follicles reached 16-20 mm in diameter, basing on urine luteinizing hormone (LH), blood LH, E2 and progestational hormone (P) level. Cycle was cancelled when more than 3 mature follicles were observed. Patients conducted IUI 24-36 hours after the HCG injection. Blood E2, LH and P levels were tested on HCG injection day (Only those with 1 mature follicle were recorded).

Luteal support: Dydrogesterone Tablets (Solvay Pharmaceuticals) were administered to support the luteal phase for 12 days. Test of HCG in blood or urine was performed 14 days after insemination. If the result was positive, the assay was repeated 48 hours later to check the increase of HCG. Clinical pregnancy was defined as that the gestational sac was found through vaginal ultrasound in 4 to 5 weeks after insemination. Biochemical pregnancy was that HCG being positive, but without visualization of a gestational sac through ultrasonographic check. Patients confirmed with pregnancy continued luteal support by Dydrogesterone Tablets until twelve weeks of gestation.

2.3. Sperm Preparation and Intrauterine Insemination
Semen was collected by masturbation. Sperm was separated by density gradient centrifugation and resuspended to 0.5ml. After number and motility evaluation, the sperm solution was injected slowly into the uterine cavity.

2.4. Statistical Analysis
SPSS 13.0 software was used for statistical analysis. Quantitative data were analyzed by one-way and crosstabs analysis of variance, and qualitative data were compared using chi-square. $P < 0.05$ was considered statistically significant.

3. RESULTS
- Patients' features of our study were shown in Table 1. A total of 458 patients were included in the study, with 48 cases in CC/LE group, 244 cases in Gn group, 71 cases in CC/LE+Gn group and 95 in NC group. 79.26% of patients were assigned COS, more than half of them accepted Gn protocol from the right beginning. Significant differences were found regarding doctors' preference of selecting protocol relating to the age, menstruation cycle, infertile etiology and ovary function, etc.
- Characteristics of clinical data on HCG day were shown

Items	CC/LE group	Gn group	CC/LE+Gn group	NC group
Cases	48	244	71	95
Age (y)[a1]	31.81±3.39	30.87±4.28	29.49±3.33	31.12±3.78
Age of menarche(y)[a2]	13.60±1.07	14.00±1.59	13.86±1.17	13.42±2.30
regular menstruation rate (%)[b]	36(75.00%)	191(78.28%)	35(49.30%)	94(98.95%)
Duration of infertility(y)[a3]	4.04±3.08	3.49±2.57	3.04±1.74	3.02±2.21
Cause of infertility case(%)[b]				
Male infertility	25(52.08%)	106（43.44%）	18（25.35%）	59（62.11%）
Female infertility	5(10.42%)	35（14.34%）	14（19.72%）	4（4.21%）
Mixed infertility	17（35.42%）	100（40.98%）	38（53.52%）	25（26.3%）
Unexplained infertility	1（2.08%）	3（1.23%）	1（1.41%）	7（7.37%）
Basal FSH(IU/L)[a4]	6.77±1.44	6.70±2.12	6.17±1.67	7.19±2.17
Basal LH(IU/L)[a5]	6.15±4.38	5.83±5.10	6.80±3.85	4.84±2.55
Basal FSH/LH[a6]	1.46±0.74	1.81±3.96	1.13±0.56	1.83±1.01
Basal E2(pmol/l)[a7]	237.28±149.04	214.48±143.67	210±114.33	204.17±99.72

a:one-way analysis, Pa1=0.01,Pa2=0.027,Pa3=0.062,Pa4=0.015,Pa5=0.039,Pa6=0.327,Pa7=0.579,;
b:Chi-square test, P<0.001,;

Table 1. Patients features of the 4 groups.

Items	CC/LE group	Gn group	CC/LE+Gn group	NC group
E2 with single follicle (pmol/l)[a]	1544.72± 749.85[f]	1701.14± 882.85[f]	1629.06± 825.26[f]	1184.59± 626.83
Duration of stimulation (days)[b]	11.96±2.04[d]	9.12±3.17	12.55±3.35[d]	13.25±3.82[c,d]
≥18mmfollicles[b]	1.08±0.45[d,e]	1.65±0.92	1.66±0.88	0.94±0.35[d,e]
Mean of largest follicular diameter (mm)[b]	21.81±2.22[f]	21.12±2.21[e,f]	22.03±2.35[f]	20.16±2.31
Endometrial thickness (mm)[b]	8.14±1.95	9.79±2.14[c,e]	9.01±2.15[c]	9.53±1.76[c]

Table 2. Data on HCG day.

Parameter	CC/LE group	Gn group	CC/LE+Gn group	NC group
Total motile sperm after washing (million)[a1]	29.37±18.27	35.97±20.52	31.34±18.83	33.71±17.01
Clinical pregnancy(%)[b1]	12.50	16.39	16.90	17.89
Biochemical pregnancy(%)[b2]	4.17	2.04	1.41	0
Abortion(%)[b3]	0	2.04	2.82	3.16
Ectopic pregnancy(%)	0	0.82	0	0
Multiple pregnancy(%)	0	3.28	0	0
Gestational age (weeks)[a2]	38.95±1.07	38.04±1.92	39.23±0.55	38.77±1.29
Neonatal weight(kg)[a3]	3.08±0.52	2.76±0.69	3.03±0.50	3.21±0.44

a: one-way analysis, Pa1=0.086, Pa2=0.376, Pa3=0.267;
b:Chi-square test, Pb1=0.873,Pb2=0.320,Pb3=0.649.

Table 3. Semen parameters and IUI results.

in Table 2. Significant differences were found between COS groups and NC groups regarding serum estradiol, but no significant differences were found within the COS groups. Duration of stimulation, mature follicles, follicle diameter and endometrial thickness were found with significant difference.
- Semen parameters and IUI outcomes were shown in Table 3. There were no significant differences found.

4. DISCUSSION
Through analysis, we found some features about doctors' preference and the outcomes of different protocol.

Doctors preferred COS for IUI, but pregnancy rate did not increase with only 1 mature follicle. There were 79.3% (363/458) patients allocated to COS cycles, and most were Gn protocol. Only 20.7% patients were allocated to NC cycle. Doctors believed that IUI combined with COS would yielded higher pregnancy than natural cycle. Actually, hormonal stimulation using clomiphene citrate and/or human menopausal gonadotrophin yielded a significant higher pregnancy rate compared to IUI in natural cycles (10.3% versus 3.3%) (4). The underlying mechanism is based on the increase number of available ova at the site of fertilization (5). In unexplained subfertility group, CC/IUI increases cycle fecundity two- to three-fold, and FSH/IUI, three- to five-fold over the baseline chance of pregnancy (6). Doctors might take it for granted that the COS cycles certainly led to higher pregnancy than natural cycles. We found no significant differences between the 4 groups regarding pregnancy rate per cycle, and surprisingly, the pregnancy rate was 17.89% in natural cycle group, which was a little higher than other 3 groups. We thought it due to our strict criteria

that only those patients underwent the first IUI cycle and had only 1 mature follicle were included. CC/LE+Gn was second choice of doctors. Basically doctors selected CC/LE as COS protocol, they usually combined CC/LE and Gn only because of poor follicular growth (7). Oral stimulation medicines, such as CC or LE, usually led to lower E_2 level, smaller follicular accounts, thinner endometrium. These findings driven doctors to choose Gn priority, but per cycle, pregnancy rates for CC/IUI and FSH/IUI cycles were not significantly different (8, 9). Now CC plus HMG is thought to be a more suitable and cost-effective regimen than CC plus rFSH in IUI cycles in patients with unexplained or male factor infertility (5). The addition of LE to gonadotrophins decreases gonadotrophins requirements and improves endometrial thickness, without a significant effect on pregnancy rates (10). Patients' age, menstruation cycle, infertile etiology and ovary function were the main factors affecting doctors' selection of COS protocols. Older patients were more possible allocated to CC/LE group or NC group ($p<0.05$). 98.95% patients bore regular menstruation in NC group and only 49.30% in CC/LE+Gn ($p<0.05$). As a common impression, the pregnancy was much lower in older women. In women with unexplained infertility aging 38-42 years, treatment of immediate IVF obtained higher cumulative pregnancy rates than treatment with two cycles of controlled ovarian hyperstimulation/IUI (11). Doctors may select CC/LE cycle or NC cycle in thought of economic-efficiency ratio. And for those patients with regular menstruation, they would prefer NC for the first cycle. COS accelerate the follicle growth. The cycle length is determined by follicular growth and by the fixed life span of the corpus luteum (12). Duration of gonadotropin therapy was significantly shorter in CC plus rFSH than CC +hMG (5.1±0.84 vs. 4.7±0.8 days, CI=95%, P<0.001) [13]. Here we also found the same feature regarding follicle growth. Basing on the same criteria for HCG injection, we found the stimulation duration was the shortest in Gn group, NC group bore the longest duration. E2 in COS group was much higher than in NC cycle. The "ideal" stimulation cycle enables the recruitment of two follicles measuring >16 mm with an E2 concentration >500 pg/mL on the day of HCG administration (14). Here in our study, E2 of these patients with 1 mature follicles were recorded. NC group had the lowest E2 level, significantly different from COS groups, and no significant differences were found within the 3 COS groups.

5. CONCLUSION

Here we concluded that doctors prefer COS for IUI, especially Gn protocol. Patients' age, menstruation cycle, infertile etiology and ovary function were the main factors affecting doctors' selection of COS protocols. No significant were found regarding pregnancy rate between COS group and NC group when there was only 1 mature follicle.

REFERENCES

1. Reindollar RH, Goldman MB. Gonadotropin therapy: a 20th century relic. Fertil Steril. 2012; 97: 813-818.

2. Palumbo A, De La Fuente P, Rodríguez M, Sánchez F, Martínez-Salazar J, Muñoz M, et al. Willingness to pay and conjoint analysis to determine women's preferences for ovarian stimulating hormones in the treatment of infertility in Spain. Hum Reprod. 2011; 26(7): 1790-1798.

3. The Practice Committee of the American Society for Reproductive Medicine. Effectiveness and treatment for unexplained infertility. Fertil Steril. 2006; 86(5 suppl): S111- S114.

4. Karuppaswamy J, Smedley M, Carter L. Intra-uterine insemination: pregnancy rate in relation to number, size of pre-ovulatory follicles and day of insemination. J Indian Med Assoc. 2009; 107(3): 141-143, 147.

5. Azargoon A, Bahrami M, Alavy Toussy J. Comparing clomiphen citrate plus HMG with clomiphen citrate plus rFSH in IUI cycles in couples with unexplained or male factor infertility: A prospective randomized study. Iran J Reprod Med. 2013; 11(3): 243-248.

6. Hughes EG. Stimulated intra-uterine insemination is not a natural choice for the treatment of unexplained subfertility. 'Effective treatment' or 'not a natural choice'? Hum Reprod. 2003; 18(5): 912-914.

7. Katz P, Showstack J, Smith JF, Natchtigall RD, Millstein SG, Wing H, et al. Costs of infertility treatment: results from an 18-month prospective cohortstudy. Fertil Steril. 2011; 95: 915-921.

8. Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, et al. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network. N Engl J Med. 1999; 340(3): 177-183.

9. Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril. 2010; 94(3): 888-899.

10. Haqnawaz F, Virk S, Qadir T, Imam S, Rizvi J. Comparison of Letrozole and Clomiphene Citrate Efficacy along with Gonadotrophins in Controlled Ovarian Hyperstimulation for Intrauterine Insemination Cycles. J ReprodInfertil. 2013; 14(3): 138-142.

11. Goldman MB, Thornton KL, Ryley D, Alper MM, Fung JL,Hornstein MD, Reindollar RH. A randomized clinical trial to determine optimal infertility treatment in older couples: the Forty and Over Treatment Trial (FORT-T). Fertil Steril. 2014; 101(6): 1574-1581.

12. Chabbert Buffet N, Djakoure C, Maitre SC, Bouchard P. Regulation of the human menstrual cycle. Front Neuroendocrinol. 1998; 19(3): 151-186.

13. Rashidi M, Aaleyasin A, Aghahosseini M, Loloi S, Kokab A, Najmi Z. Advantages of recombinant follicle-stimulating hormone over human menopausal gonadotropin for ovarian stimulation in intrauterine insemination: a randomized clinical trial in unexplained infertility. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2013; 169: 224-247.

14. Merviel P, Heraud MH, Grenier N, Lourdel E, Sanguinet P, Copin H. Predictive factors for pregnancy after intrauterine insemination (IUI): an analysis of 1038 cycles and a review of the literature. Fertil Steril. 2010; 93: 79-88.