

The pregnancy outcomes of intrauterine insemination with husband's sperm in natural cycles versus ovulation stimulated cycles: A retrospective study

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Summary

To compare the clinical outcomes of intrauterine insemination (IUI) with or without ovulation induction (OI), IUI cycles from January 2008 to December 2017 in Zhoushan Maternity and Child Healthcare Hospital were included, consisting of 455 natural cycles and 536 OI cycles. The overall clinical pregnancy rate did not differ between the two groups ($P > 0.05$). Stratified by OI medications such as clomiphene (CC), human menopausal gonadotropin (HMG) and follicle stimulating hormone (FSH), the pregnancy rates in HMG, CC, CC+HMG, and FSH/FSH+HMG groups were 11.70%, 13.58%, 15.95%, and 13.46%, respectively, but the difference was not significant compared with natural cycles ($P > 0.05$). Stratified by infertility etiology, the pregnancy rate was significantly higher in stimulated cycles than natural cycles with ovulation disorders ($P < 0.01$) and unexplained factors ($P < 0.01$) while it was significantly lower regarding cervical factors ($P < 0.01$), endometriosis ($P < 0.05$), male factor ($P < 0.01$) and other female factors. There was no strong difference of pregnancy rate for biparental causes ($P > 0.05$). Stratified by age category, women over 35 had higher pregnancy rate in stimulated cycles compared with natural cycles (18.75 vs. 12.24%; $P < 0.05$), while women under 35 had no significant difference of pregnancy rate between the two groups (13.65 vs 13.05%; $P > 0.05$). However, there was no significant difference between each ovarian stimulation group and natural cycle group regardless of the infertility causes or age categories. To conclude, IUI-OI could achieve a higher overall pregnancy rate for women over 35 and infertile patients with ovulation disorders and unexplained factors.

Keywords: Intrauterine insemination (IUI), ovulation induction (OI), stimulated cycles, natural cycles, clinical pregnancy rate

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1. Introduction

Intrauterine insemination (IUI) is an assisted conception technique offering hope to many infertile couples based on the finding of a striking reduction in sperm

number with the length of the female reproductive tract after intercourse (I). It is performed by transferring a processed motile semen sample into a female's uterus, which increases the number of sperm that reaches the oviduct and subsequently increases the chances of in vivo fertilization.

IUI with or without ovulation induction (OI) is a relatively cost-effective and noninvasive treatment, indicated for selected couples with infertility due to female factors including ovulation disorders and cervical factor, mild male factor, ejaculatory disorders, immunological factor and unexplained factors with an unfavorable prognosis for natural conception. As the effectiveness of IUI-OI is a result of multiple ovulations compared with natural cycles, concerns exist about the associated OI complications such as ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies, leading to maternal and perinatal risks. Predictive indicators of IUI success include maternal age, infertility etiology, infertility duration, stimulation medications, follicle number, endometrial thickness, semen characteristics, timing of insemination, number of cycles, *etc.* (2).

In order to address the question of whether and when OI is required in IUI, a retrospective study was conducted to provide evidence regarding the fertility treatment.

2. Materials and Methods

2.1. Study design

The clinical data of 991 IUI cycles with husband's sperm present at the Reproductive Center of Zhoushan Maternity and Child Healthcare Hospital in China from January 2008 to December 2017 were reviewed retrospectively. A complete couple workup was performed, including health history, physical examination, laboratory and radiological investigations. Semen analysis was repeated three times if an abnormal sperm result occurred. Inclusion criteria consisted of: 1) married couples failing to achieve a clinical pregnancy after one-year (or longer) of regular unprotected sexual intercourse; 2) patency of at least one fallopian tube confirmed by hysterosalpingography, laparoscopy or ultrasound-guided hydrotubation. Exclusion criteria included: 1) failed ovulation after IUI under ultrasound monitoring; 2) total motile sperm count $< 5 \times 10^6$ (grade a+b) after semen processing. The study was approved by the ethics committee of Zhoushan Maternity and Child Healthcare Hospital (No. 2018-004).

2.2. Natural or stimulated IUI cycles

Females with regular menstrual cycles could adopt IUI in natural cycles. Follicular development was monitored by transvaginal ultrasound from day 10-12 of the cycle

onward according to the menstrual cycle length.

Patients with ovulation disorders, irregular menstruation or abnormal follicle development received ovarian stimulation medications from cycle day 3-5 under the monitoring of transvaginal ultrasonography.

Human menopausal gonadotropin (HMG): daily injection of 75-150 IU HMG from day 3-5 of the menstrual cycle for 4-5 days consecutively. The dosage was adjusted according to the ultrasonic monitoring of follicle and endometrial development.

Clomiphene Citrate (CC): daily oral administration of 50-100 mg CC starting from day 5 of the cycle for 5 days with subsequent ultrasonic monitoring.

CC+HMG: CC 100 mg/day (cycle day 5) for 5 days, followed by daily injection of 150 IU HMG for 2 days. According to the ultrasonic monitoring for ovary response and dominant follicle size, CC/HMG could be administered repeatedly.

Follicle stimulating hormone (FSH)/FSH+HMG: daily injection of 150 IU FSH from day 3 of the cycle. To prevent OHSS, the dosage was adjusted accordingly.

2.3. Operative time of IUI

Urinary luteinizing hormone (LH) test paper (Yunnan University Biopharmaceutical Co., Ltd.) and vaginal ultrasound were measured day by day from when the lead follicle diameter reached 16-18 mm. Ovulation was triggered with 5000-10000 IU of human chorionic gonadotropin (HCG) when a follicle with a diameter of 18 mm was observed and the number of dominant follicles was controlled at ≤ 3 . IUI was implemented based on the detection of LH surge or at 24-36 hours post HCG. If the follicle diameter was over 20 mm without the presence of a urinary LH peak, HCG 10000 IU was injected and IUI was planned 24-36 hours thereafter. Non-ovulators detected by ultrasound at 24 hours after operation required a second IUI.

2.4. Semen collection and processing

In accordance with laboratory guidelines of the World Health Organization (WHO) for sperm collection and preparation, semen was collected by masturbation after abstinence for 3-7 days, placed in CO₂ incubator at 37°C and liquefied for about 30 minutes. After semen analysis, the upstream or density gradient centrifugation method was adopted to yield 0.5 mL of semen suspension.

2.5. Insemination

The patient was placed in a lithotomy position. After routine disinfection of the vulva and placement of a sterile towel, the cervix was exposed with a vaginal speculum and wiped with a cotton ball containing saline. 0.5 mL of semen suspension was injected into

the uterine cavity through a disposable syringe. The patient was instructed to immobilization in a supine position for 30 minutes after the operation.

2.6. Postoperative corpus luteum support and follow-up

Routine corpus luteum support for all patients started from the third day after ovulation with oral administration of dydrogesterone tablets 10 mg, twice a day, and continued up to postoperative day 15. A clinical pregnancy was confirmed by HCG level with urine test and detection of a gestational sac and embryonic heartbeat via ultrasound on postoperative day 15 and day 30, respectively. Patients were followed up to the time of delivery.

2.7. Statistical analysis

Data were expressed as mean ± standard deviation (SD). Statistical Package for the Social Sciences (SPSS) 13.0 software was used for statistical analysis. Student's *t* test was used for measurement data, and chi-square test was used for count data. A *p*-value < 0.05 was considered statistically significant.

3. Results

3.1. Study demographics

A total of 991 IUI cycles with husband's sperm present at the Reproductive Center of Zhoushan Maternity and Child Healthcare Hospital from 2008 to 2017 were reviewed. The average age of women was 30.48 ± 3.29 years (range: 22-43 years), and the average infertility period was 3.69 ± 2.48 years (range: 1-13 years). 547 cycles (55.2%) were diagnosed as primary infertility and 444 cycles were secondary infertility. Female infertility etiology included ovulation disorders (*N* = 245), cervical factor (*N* = 100), endometriosis (*N* = 40) and other female factors (*N* = 33). In addition, male

factor contributed to 188 cycles of infertility; biparental factor caused 196 cycles of infertility; and there were 189 cycles of unexplained causes. From a total of 991 IUI cycles, the clinical pregnancy rate was 13.32%.

3.2. Natural cycles versus stimulated cycles

In natural cycles (*N* = 455), the average female age was 30.59 ± 3.59 years and the average infertility period was 3.65 ± 2.57 years. 536 were stimulated cycles with an average female age of 30.39 ± 3.03 years and an average infertility period of 3.73 ± 2.41 years. The two groups were comparable for baseline characteristics regarding female age, body mass index (BMI), infertility period and infertility type (*P* > 0.05) (Table 1). The overall clinical pregnancy rate did not differ between stimulated cycles and natural cycles (13.62 vs. 12.97%; *P* > 0.05).

The pregnancy outcomes of different ovarian stimulation protocols are shown in Table 2. The pregnancy rates in HMG, CC, CC+HMG, and FSH/FSH+HMG groups were 11.70%, 13.58%, 15.95%, and 13.46%, respectively. However, the difference was not statistically significant as compared with the natural cycle group (*P* > 0.05).

3.3. Pregnancy outcomes stratified according to infertility etiology

The pregnancy outcomes pertaining to different causes of infertility are shown in Table 3. Stratified according to infertility etiology, the clinical pregnancy rate significantly increased in stimulated cycles compared to natural cycles with ovulation disorders (14.22 vs. 9.76%; *P* < 0.01) and unexplained factor (14.08 vs. 10.17%; *P* < 0.01) while it decreased regarding cervical factor (7.27 vs. 15.56%; *P* < 0.01), endometriosis (19.05 vs. 21.05%; *P* < 0.05), other female factors (0.00 vs. 12.00%) and male factor (7.84 vs. 13.14%; *P* < 0.01), in contrast with a lack of a strong difference of pregnancy

Table 1. Comparison of natural cycles versus stimulated cycles

Groups	Female age, years, mean ± SD	Infertility period, years, mean ± SD	Body mass index (BMI), mean ± SD	Primary infertility, N (%)	Secondary infertility, N (%)
Natural cycles (<i>N</i> = 455)	30.59 ± 3.59	3.65 ± 2.57	21.03 ± 2.39	284 (62.4)	171 (37.6)
Stimulated cycles (<i>N</i> = 536)	30.39 ± 3.03	3.73 ± 2.41	23.60 ± 4.23	263 (49.1)	273 (50.9)

Table 2. Pregnancy outcomes of ovulation induction regimens

Groups	Cycles, N	Pregnancy, N	Pregnancy rate, %
Natural cycles	455	59	12.97
Stimulated cycles	536	73	13.62
HMG	188	22	11.70
CC	81	11	13.58
CC+HMG	163	26	15.95
FSH/FSH+HMG	104	14	13.46

Table 3. Pregnancy outcomes stratified according to infertility etiology

Infertility etiology	Stimulated cycles																	
	Natural cycles			HMG			CC			CC+HMG			FSH/FSH+HMG			Total		
	Cycles, N	Pregnancy rate, N (%)		Cycles, N	Pregnancy rate, N (%)		Cycles, N	Pregnancy rate, N (%)		Cycles, N	Pregnancy rate, N (%)		Cycles, N	Pregnancy rate, N (%)		Cycles, N	Pregnancy rate, N (%)	
Female factors	130	18 (13.85)		82	10 (12.20)		57	8 (14.041)		62	8 (12.90)		87	11 (12.64)		288	37 (12.85)	
Cervical factor	45	7 (15.56)		21	2 (9.52)		18	2 (11.11)		8	0 (0.00)		8	0 (0.00)		55	4 (7.27)**	
Endometriosis	19	4 (21.05)		0	0 (0.00)		5	1 (20.00)		10	2 (20.00)		6	1 (16.67)		21	4 (19.05)*	
Ovulation disorders	41	4 (9.76)		58	8 (13.80)		33	5 (15.15)		40	6 (15.00)		73	10 (13.70)		204	29 (14.22)**	
Others	25	3 (12.00)		3	0 (0.00)		1	0 (0.00)		4	0 (0.00)		0	0 (0.00)		8	0 (0.00)	
Male factor	137	18 (13.14)		16	2 (12.50)		10	0 (0.00)		20	2 (10.00)		5	0 (0.00)		51	4 (7.84)**	
Biparental factor	70	11 (15.71)		48	6 (12.50)		10	2 (20.00)		60	11 (18.33)		8	3 (37.50)		126	22 (17.46)	
Unexplained causes	118	12 (10.17)		42	4 (9.52)		4	1 (25.00)		21	5 (23.81)		4	0 (0.00)		71	10 (14.08)**	

Note: * $P < 0.05$ compared with natural cycle group, ** $P < 0.01$ compared with natural cycle group.

Table 4. Pregnancy outcomes stratified according to age categories

Age category	Stimulated cycles																	
	Natural cycles			HMG			CC			CC+HMG			FSH/FSH+HMG			Total		
	Cycles, N	Pregnancy rate, N (%)		Cycles, N	Pregnancy rate, N (%)		Cycles, N	Pregnancy rate, N (%)		Cycles, N	Pregnancy rate, N (%)		Cycles, N	Pregnancy rate, N (%)		Cycles, N	Pregnancy rate, N (%)	
Aged ≤ 35	406	53 (13.05)		179	20 (11.17)		80	11 (13.75)		158	25 (15.82)		103	14 (13.59)		520	70 (13.65)	
Aged > 35	49	6 (12.24)		9	2 (22.22)		1	0 (0.00)		5	1 (20)		1	0 (0.00)		16	3 (18.75)*	

Note: * $P < 0.05$ compared with natural cycle group.

rate for biparental causes (17.46 vs. 15.71%; $P > 0.05$). Further stratified according to OI regimes, there was no significant difference between each ovarian stimulation group and natural cycle group regardless of the infertility causes ($P > 0.05$).

3.4. Pregnancy outcomes stratified according to age categories

The pregnancy outcomes of different age categories are shown in Table 4. The overall pregnancy rate did not differ between the over-35s and the under-35s (13.85 vs. 13.28%; $P > 0.05$). Women over 35 years old had a higher pregnancy rate in stimulated cycles compared with natural cycles (18.75 vs. 12.24%; $P < 0.05$), while women under 35 had no significant difference of pregnancy rate between the two groups (13.65 vs. 13.05%; $P > 0.05$). Further stratified according to OI regimes, there was no significant difference between each ovarian stimulation group and natural cycle group regardless of the age categories ($P > 0.05$).

4. Discussion

IUI with or without OI is currently one of the most common assisted conception technologies for the treatment of infertility. Compared with monofollicular growth in natural cycles, the rationale of OI prior to IUI was to achieve multifollicular growth, which resulted in a notably higher pregnancy rate (3). IUI-OI treatment could increase the number of mature follicles and improve the development of follicles. In addition, the non-synchronous rupture of multiple follicles by HCG as well as the optimal timing of insemination could increase the fertilization rate and thus increase the pregnancy rate of IUI. Ovarian stimulation therapy might correct the unfavorable factors in the process of follicular maturation, fertilization and implantation. Researchers who held this view believed that the pregnancy rate of IUI in the stimulated cycles was higher than that in the natural cycles, which was verified in a meta-analysis (OR: 1.47, 95% CI: 1.26-1.72; $P < 0.00001$) (4) and a randomized clinical trial (13.7 vs. 9.5%; $P < 0.05$) (5).

However, a recent retrospective study discovered that the pregnancy rate did not differ between IUI and IUI-OI ($\chi^2=1.55$; $P > 0.05$) and suggested that natural cycles would be a more reasonable treatment in prevention of multiple pregnancies (6). Agreeing with this finding, our study also showed that the difference of overall clinical pregnancy rate between the stimulated cycles and the natural cycles was not significant. Subdividing stimulated cycles into HMG, CC, CC+HMG and FSH/FSH+HMG groups according to different OI regimens, still, no strong difference was found as compared with the natural cycle group. Opposed to the idea that OI induced multifollicular

growth, the current ovarian stimulation medications could control the number of dominant follicles. Meanwhile, the developmental motivation of follicles in IUI-OI was due to exogenous drug stimulation, which was different from the natural physiological condition, therefore the risk of abnormal follicle development remained. The endocrine environment altered by OI might impair fertilization potential and endometrial receptivity as well.

We therefore recommended that the indications for IUI-OI be strictly controlled and natural cycle-IUI be the preferred choice for females with normal ovulation. For patients with abnormal ovulation or repeated failures of getting pregnant in natural cycle-IUI, OI prior to IUI could be adopted with reasonable regimen, mild doses and optimal timing of HCG. It was appropriate to have one or two dominant follicles developed in OI cycles to avoid multiple pregnancies. Ovulation trigger and IUI would be withheld or shifted to oocyte retrieval and in vitro fertilization-embryo transfer (IVF-ET) when more than 3 follicles with a diameter of 16 mm or more than 5 follicles with a diameter of 12 mm were present.

Our study showed that the clinical pregnancy rate significantly increased in stimulated cycles compared to natural cycles for females presenting with ovulation disorders while it decreased regarding cervical factor, endometriosis and other female factors. It was further strengthened by a retrospective study in 2014 that higher clinical pregnancy rates per cycle were observed in patients with ovulation disorders versus other female indications ($P = 0.03$) (7). For infertility caused by cervical factors, our study found a significant difference in favor of natural cycles. However, Fu *et al.* believed that OI combined with IUI positively influenced the pregnancy outcomes (22.40 vs. 14.62%; $P < 0.05$) because the ovarian stimulation treatment increased the follicle number and estrogen level and improved cervical mucus, subsequently increased the pregnancy rate (8), which was inconsistent with Steures's results in terms of ongoing pregnancy rate (21 vs. 17%; RR: 1.2, 95% CI: 0.75-2.0) (9). Endometriosis could affect pregnancy by disturbing ovulation, endometrial receptivity, uterus microenvironment and luteal function. Surgery remained an important option to reduce ectopic lesions, restore normal anatomy, prevent recurrence of ectopic lesions and relieve symptoms. Some believed that IUI combined with FSH could obtain a better pregnancy rate than anti-estrogens for infertile females with mild endometriosis, mild male infertility and unexplained factor (OR: 1.8, 95% CI: 1.2-2.7) (10). However, our study showed a significant benefit of natural cycles for patients with endometriosis, which required further investigation.

IUI-OI has been routinely offered as a first-line treatment for couples with unexplained infertility in most fertility clinics of China. Our findings showed that clinical pregnancy rate significantly increased in

stimulated cycles compared to natural cycles regarding unexplained factor, consistent with an updated Cochrane review by Veltman-Verhulst in 2016, which reported a beneficial effect of IUI-OI on live birth rate compared to the natural cycles (OR: 0.48, 95% CI: 0.29-0.82) (11). However, because there was still a chance of natural conception through expectant management in couples with unexplained infertility and a good prognosis, the 2013 guideline from the UK National Institute for Health and Care Excellence recommended extended expectant management instead of IUI-OI for these patients. More recently, a randomized, controlled, two-center study in New Zealand in 2018 revealed that IUI-OI had a higher cumulative livebirth rate than three cycles of expectant management (31 vs. 9%; RR: 3.41, 95% CI: 1.71-6.79; $p = 0.0003$) in this particular population (12). Large multi-center trials comparing IUI in natural unstimulated cycles or stimulated cycles to extended expectant management were necessary to draw a firm conclusion.

IUI for male infertility was under huge debate because large high-quality randomized studies were lacking. There was neither a strict cut-off value of sperm quality nor a clear definition of mild, moderate and severe male infertility (13). Our study showed that the clinical pregnancy rate significantly decreased in stimulated cycles compared to natural cycles regarding male factor, which was insufficient evidence to recommend for or against IUI-OI in couples with poor sperm parameters. In patients with unexplained or mild male infertility and an unfavorable prognosis, IVF with elective single embryo transfer was as effective as IUI-OI in terms of livebirth rate per couple (52 vs. 47%), demonstrated by Bendsorp *et al.* in 2015 (14).

Age is one of the most important factors of pregnancy achievement in IUI. Women's fertility potential declined with advancing reproductive age (15). As aging, there was a decrease in women's ovarian reserve, follicle number, oocyte quality, endometrial receptivity, function of corpus luteum and uterine blood flow, while an increase in the incidence of chromosomal abnormalities in oocytes was noted, leading to compromised capability of fertilization, development and implantation (16). The prolonged infertility duration and repeated failures in IUI brought psychological stress, depression and iatrogenic injuries, which seriously affected the success rate of IUI (17).

Our study revealed that the overall pregnancy rate did not differ between the over-35s and the under-35s, which might be explained by the individual treatment plans chosen for each patient from different age groups. Women over 35 years old had higher pregnancy rate in stimulated cycles compared with natural cycles, while women under 35 had no significant difference of pregnancy rate between the two groups. It was contradicted by another retrospective cohort study that females younger than 38 years old obtained a

better clinical pregnancy rate in the stimulated cycles than their older counterparts ($P = 0.02$) (18). It argued that due to the irreversibility of ovarian function that accompanied aging, it would be impossible to yield high-quality oocytes and improve endometrial receptivity with ovulation induction, resulting in an unfavorable clinical pregnancy rate.

With a lack of high quality studies on pregnancy outcomes comparing IUI with or without OI in different age groups, the question of whether IUI-OI should be recommended for or against in the aged population deserved consideration and a clear age cut-off level was needed. With failed attempts of assisted reproductive technologies, women with age-related infertility probably labeled with unexplained infertility which led to inappropriate therapies (19). We therefore suggested that infertile women should be treated as early as possible and ovulation induction in females above 35 years should be used with caution.

Our study retrospectively reviewed all the IUI cycles with husband's sperm at our center in a ten-year period. It was noteworthy that the outcome measure in the study was solely pregnancy rate, whereas the European Society for Human Reproduction and Embryology (ESHRE) recommended birth of a single healthy child as the primary outcome (20). Our study was strengthened by complete data, strict criteria for clinical pregnancy, standard clinical routine and laboratory procedures. Pregnancies achieved with natural conception or additional interventions were carefully identified and excluded from the analysis.

5. Conclusion

To conclude, IUI-OI could achieve a higher overall pregnancy rate for women over 35 and infertile patients with ovulation disorders and unexplained factors. Natural cycle-IUI had better performance in the pregnancy outcome for patients with cervical factor, endometriosis, other female factors and male infertility. Our study provided draft recommendations for answering whether and when to provide ovulation induction in IUI.

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