The Impact of the Time Interval Between Cycles on Pregnancy Outcome of Intrauterine Insemination

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Abstract

Objective: The objective of this study was to estimate whether the time interval between two intrauterine inseminations (IUI) treatments needs to be extended by one menstrual cycle or more, and whether this will have an impact on the clinical pregnancy rate (CPR).

Study Design: Retrospective cohort study.

Study site: The study site was the reproductive medicine center of a teaching hospital.

Patient(s): The subjects were women and their husbands who received two or more intrauterine insemination in our reproductive medicine center due to mild infertility in the period from January 2014 to December 2020. Patients were divided into 2 groups according to the number of days between the last menstrual day(LMD)and the previous IUI operation day(POD), continuous group (the time from the LMD to POD ≤ 34 days) and delayed group (the time from the LMD to POD ≥ 35 days). If the previous cycle was a pregnancy or abortion cycle, the next cycle immediately adjacent to it was defined as a new cycle, and the days between the two cycles were not included in the study.

Intervention(s):No intervention.

Main Outcome Measure(s): A total of 1491 cycles were finally included in the study.990 cycles followed by the second IUI cycle after the previous failure,501 cycles at least one menstrual cycle was separated between two IUI treatments. The primary outcome measure was clinical pregnancy rate (CPR), with secondary outcomes including abortion rate and live birth rate. Differences in clinical pregnancy rate (CPR)、abortion rate and live birth rate were compared between the two groups.

Result: No significant differences with regard to baseline demographic and the number of treatment cycles, the duration of infertility, the type of infertility, the mode of treatment, and the cause of infertility were observed between the two groups.There were no statistical differences between the delayed group vs continuous group regarding the clinical pregnancy rate(15.0% *vs* 13.7%), live birth rate(78.7% *vs* 74.3%), and abortion rate(17.3% *vs* 18.4%)（P＞0.05）.The above factors were included for binary logistic regression analysis. The observed difference in clinical pregnancy rate between the groups was not statistically significant after adjustment(OR = 1.101,95%CI 0.807-1.499, P=0.546）.The all cycles were divided into four groups based on female age. results showed that when the female's age was ≤ 25 years old, the pregnancy rate in the continuous group was 16.5%, which was significantly higher than that in the delayed group by 5.8% (difference 0.107, 95% CI 0.016-0.198, P = 0.055), approached, but did not reach, statistical significance. When the female was 30-35 years old, the pregnancy rate in the delayed group was 19.4%, which was significantly higher than 10.9% in the continuous group (difference 0.085, 95% CI 0.016-0.154, P = 0.011). The difference between the two groups was statistically significant. The all cycles were divided into three groups based on years of infertility. Our results show that when the number of years of infertility was≤2 years, the clinical pregnancy rate was 20.7% in the delayed group and 12.5% in the continuous group (difference 0.107, 95% CI 0.150-0.014, P = 0.013), statistical

significance was maintained. Based on the number of treatment cycles, it is divided into 2 cycles, 3 cycles, and≥4 cycles. The results showed that when≥4 cycles, the pregnancy rate in the continuous group were 19.4%, which was significantly higher than 6.1% in the delayed group (difference 0.133, 95% CI 0.246-0.020, $P = 0.038$). Statistical significance was maintained at $P < 0.05$.

Conclusions: Overall, prolonging the interval between two IUI did not significantly improve pregnancy outcomes. Yet, for different age stages, duration of infertility, and the number of treatment cycles, we suggest that more flexible treatment strategies can be tried to improve the clinical pregnancy rate.

Introduction

Intrauterine insemination (IUI) has the advantages of less damage and low price, contributed it to become a highly used pregnancy aid technology in clinics[1].IUI is the therapeutic process of placing screening out excellent sperm after removing the seminal plasma from the husband's semen transcervically into the uterine cavity for the treatment of infertility. However, So far, compared with in vitro fertilization and embryo transfer (IVF-ET), the pregnancy rate by IUI has been maintained at a lower level, and the vast majority of patients need to continuously try multiple attempts before they can get pregnant. For those patients who are destined to receive multiple IUI treatments, it is very especially urgent and important to use what way to improve their pregnancy rate. Within recent years, studies of the whether IVF-ET treatment needs to delay frozen embryo transfer have gradually increased[2−5], but the conclusions are inconsistent. Nevertheless, do need to rest after IUI treatment failure? Be here any benefit in doing so? To date, there is no clear answer to this question. Thus, this study aimed to try to analyze whether the interval between two IUI will have an impact on the clinical pregnancy rate, aiming to provide a reference for the clinical treatment of IUI.

Materials And Methods

Study Population and Design

In this study, we retrospectively reviewed all cycles of intrauterine artificial insemination for infertility between January 1, 2013, and December 31, 2020. Indications for IUI treatment included tubal problems, unexplained infertility, infertility caused by cervical factors, ovulation disorders (refer to Rotterdam standard [6]), and infertility caused by mild to moderate male low fertility (refer to WHO standard [7]). The inclusion criterion were at least two or more consecutive IUI cycles. In order to avoid the increase of bias factors caused by too long interval and the adverse impact of the increase of age on pregnancy outcome, we prescribed that the interval between two adjacent cycles should be kept within 180 days. To avoid any interference caused by pregnancy or abortion, we also prescribed that if the previous cycle is the outcome of pregnancy or abortion, the next cycle immediately after this cycle is a new start, and the time between them is also excluded from this study. We acquired information on the relevant information of each cycle from the clinical database. and made statistical analysis with reference to the above standards in the next stage. The study was approved by the hospital ethics committee.

IUI treatment procedure

Natural IUI cycles treatment were first used for women with regular menstrual cycles. For those with sparse menstruation, natural cycle follicular dysplasia, ovulation disorder, or previous natural cycle IUI who are not pregnant, ovulation induction treatment shall be performed.ovulation-induction protocols include:clomiphene (CC), letrozole (LE), human menopausal gonadotropin (HMG), CC + HMG, LE + HMG.The follicular and intima growth was monitored using transvaginal ultrasound in all patients. combined with the level of blood or urinary luteinizing hormone (LH), the growth and development status of ovarian folliculars were evaluated. the individualized medication was adjusted in time and controlled < 3 dominant follicles.5000 IU human chorionic gonadotropin (hCG) trigger was injected when the diameter of one follicle was ≥ 18 mm.

Semen collection and treatment

we generally require them to ejaculate once 2-7 days before the operation day of IUI, and then tell them to avoid sex during this period, through thiswere performed to guarantee the quality of the semen quality of male spouses on the day of IUI. To avoid the adverse effects of ambient temperature fluctuation on sperm, All male partners were asked to collect semen in a private room next to the laboratory. Semen samples were collected by masturbation and purified from using density gradient centrifugation after liquefaction for 30 min at 37°C.

Timing of insemination

Ordinary circumstances, IUI was scheduled on the 24-36 hours after the hCG injection. B-ultrasound reexamination the next day and to assess ovulation.If the B-ultrasound finds that the follicles have been discharged before the trigger, the IUI operation will be conducted in the afternoon of the same day.

Luteal support and follow-up

The patient starts oral progesterone for luteal support began on day 1 after the operation. Serum β-hCG was assessed on day 14 after the IUI operation and the β-hCG level was evaluated to discover pregnancy. If not pregnant, stop luteal support. If the blood β-HCG is > 20 IU/ L, the Cases were diagnosed as biochemical pregnancy, for which luteal support was continued to 10-12 weeks of pregnancy.

Time Intervals

We conducted systematic database searches and determined the date of the last menstrual before this IUI treatment, the date of this IUI operation, and the date of the previous IUI operation. Grouping situations were identified by exploring the links between the three-date relationships. Patients were divided into 2 groups according to the number of days between the last menstrual day(LMD)and the previous IUI operation day(POD), continuous group (the time from the LMD to POD ≤ 34 days) and delayed group (the time from the LMD to POD ≥ 35 days). Typically, the normal menstrual level of women was defined as a spontaneous cycle length of 21 to 35 days[5].Serum β-hCG was assessed on day 14 after the IUI

operation and the hCG level was evaluated to discover pregnancy. Therefore, if the cycle belongs to the Delayed group (IUI treatment after at least 1 menstrual cycle), then, it takes at least 14 + 21 days from LMD before this cycle to POD. cycles beyond this time interval belong to the Delayed group. Otherwise, it is a continuous group. By using the method described above, we broadly separated the samples into:1) Continuous group: the period of IUI treatment immediately; 2) Delayed group: waiting for at least one menstrual cycle before receiving IUI treatment, This is illustrated in Figure 1.

Figure 1. Continuous group (defined as the time from the last menstrual day(LMD) to the previous IUI operation day(POD)≤34 days) and delayed group (defined as the time from the last menstrual day (LMD)to the previous IUI operation day(POD)≥ 35 days).

Primary and secondary outcome measures

The primary outcome measure was clinical pregnancy rate (CPR), with secondary outcomes including abortion rate and live birth rate. Clinical pregnancy will be defined as the observed of an intrauterine gestation sac at 7 weeks of gestation by transvaginal ultrasound. Pregnancy rate: defined as all pregnancy reported in the study. Termination of pregnancy under any circumstances after confirmation of clinical pregnancy is considered as abortion, and the abortion rate = the number of abortion cycles/number of clinical pregnancy cycles. Deliveries occurring after 24 weeks of gestation are considered live births. Live birth rate = the number of live birth cycles/number of clinical pregnancy cycles.

Statistical analysis:

All statistical analyses were performed using SPSS Statistics 26.0 (IBM, Inc.) and Graphpad Prism 9 (Graphpad Software, LLC). Firstly, the data were tested for normality using Shapiro-Wilk's statistics. and the results were expressed as means±standard deviations (Mean±SD). Categorical variables are expressed as a percentage(n%); comparisons between groups were made using the chi-square test($\chi 2$) or Fisher exact probability method. Considering that the retrospective study included many important unmeasured confounders that may exist, binary logistic regression analysis was used to evaluate the relationship between IUI interval and clinical pregnancy. And estimate the odds ratio (OR) with a corresponding bilateral 95% confidence interval (CI). The confounding factors included the age of the woman, the age of the man, the number of treatment cycles, the duration of infertility, the type of infertility, the mode of treatment, and the cause of infertility. In addition, We also conducted stratified analyses of these variables. Repeat procedures cycles on the same patient were assumed to be independent in the study. $P<0.05$ was defined as the difference was statistically significant.

Results

Basic information

Between January 2013 and December 2020, a total of 3118 IUI cycles were performed in our reproductive center department, a total of 1626 cycles received 2 or more IUI treatments. 86 cycles were excluded because the interval times were > 180 days, and 49 cycles were excluded because the previous cycle was the outcome of pregnancy or abortion. A total of 1491 cycles met the study criteria and were finally enrolled for integrated analyses.

Among these cycles, A total of 990 (66.4%) cycles met the criteria for the continuous group, and 501 (33.6%) cycles met the criteria for the delayed group. Table 1 shows the baseline characteristics of the groups, baseline characteristics of patients were similar between the two cohorts ($P > 0.05$). 66.7% of women were primary infertility and 33.3% were secondary infertility; 12.3% of patients were treated with natural cycle protocol. and 87.7% of patients were treated with ovarian stimulation regimen. The cause of infertility among these couples can be attributed to 10.0% male factors, 43.3% female factors, 36.9% unexplained infertility, and 9.9% due to the factors of both husband and wife. As reported in Table 1, no significant differences were found between the two groups with regard to age, type of infertility, number of treatments, treatment mode, duration of infertility, and causes of infertility.

Pregnancy outcome

By contrast, no significant differences were found between the continuous group and delayed group in the clinical pregnancy rate (13.7% *vs.* 15.0%, respectively; P= 0.519).The abortion rate(18.4 % *vs.* 17.3%, respectively; P=0.849),the live birth rate(74.3% *vs.* 78.7%, respectively; P= 0.475).Again, this difference was not statistically significant.Table 2.

Multivariate analysis.

The age of the woman, the age of the man, the number of treatment cycles, the duration of infertility, the type of infertility, the mode of treatment, and the cause of infertility were included for binary logistic regression analysis, the results showed that the effect of IUI interval on clinical pregnancy was not statistically significant (OR = 1.101,95% CI 0.807-1.499, P=0.546.Table 3.

Subgroup analysis

Stratified analysis was conducted in this study, to study the difference of clinical pregnancy rate between the continuous group and delayed group under different conditions. Stratified analysis showed that there were significant differences in Female age, duration of infertility, and the number of treatment cycles between the two groups ($P < 0.05$). However, no significant differences were found for male age, infertility type, treatment method, and Causes of infertility ($P > 0.05$).

Female age

All cycles were divided into four groups according to female age, ≤ 25 years old, 25-30 years old, 30-35 years old, and over 35 years old. female age-stratified analysis showed that when the woman's age was ≤ 25 years old, the pregnancy rate in the continuous group was 16.5%, which was significantly higher

than that in the delayed group by 5.8% (difference 0.107, 95% CI 0.198-0.016, $P = 0.055$).with a concomitant increase in woman's age, the pregnancy rate a gradual decline was noted for the continuous group, while a gradual increase was noted for the delayed group. At the age of 25-30,The pregnancy rate per cycle was similar in both groups (14.5% *vs.* 13.4%) ($P = 0.670$).When the woman was 30-35 years old, The delayed group had higher gravidity than the continuous group(19.4% *vs* 10.9%, difference 0.085, 95% CI 0.154-0.016, $P = 0.011$) (Figure 1.). The difference between the two groups was statistically significant. When the age was over 35 years old, the pregnancy rate in the delayed group decreased, and the pregnancy rate in the two groups tend to be the same. However, the pregnancy rate in the delayed group was still higher than that in the continuous group (16.2% *vs.* 13.8%) ($P = 0.725$).

Duration of infertility

In this study, we divided the patients into three groups according to the duration of infertility,≤ 2 years, 3-4 years, and ≥ 5 years.Stratified analysis results showed that when the duration of infertility was ≤ 2 years, The delayed group had a higher pregnancy rate than the continuous group(20.7% *vs.* 12.5%, difference 0.107, 95% CI 0.150-0.014, $P = 0.013$). There were statistically significant differences between the two groups. As the time extension of the duration of infertility, the pregnancy rate in the delayed group gradually decreased and eventually plateaued. The pregnancy rate in the continuous group first increased slightly, and then also decreased. Finally, the pregnancy rate of the two groups tend to the same, and the difference between the two groups was not statistically significant ($P > 0.05$). See Figure 2.

Number of cycles

In the same way, all cycles were divided into three groups according to the number of cycles, namely 2 cycles, 3 cycles, and ≥ 4 cycles respectively. Stratified analysis results showed that the pregnancy rate of the delayed group decreased gradually with the increase of the number of cycles, while, a scatter plot between the number of cycles and the pregnancy rate showed a U-shaped curve tendency in the continuous group. when the ≥ 4 cycles, The continuous group had higher the pregnancy rate than the delayed group(19.4% *vs.* 6.1%, difference 0.133, 95% CI 0.246-0.020, $P = 0.038$).The difference was statistically significant, illustrated in Figure 3.

Discussion

The primary purpose of this study was to answer two major questions, namely "this IUI failed. Do we need to rest and try again? Will this help our pregnancy?".We got some answers to these questions by studying specific problems: In general, prolonging the interval between two IUI did not significantly improve pregnancy outcomes. Yet, for different age stages, duration of infertility, and the number of treatment cycles, we suggest that more flexible treatment strategies can be tried to improve the clinical pregnancy rate.

The first report of human IUI came from Guttmacher [8] and Kohlberg [9, 10], which has a history of nearly 60 years. over half a century, people's awareness has gradually increased of IUI. Like other assisted

reproductive technologies, IUI is expected to achieve a higher pregnancy rate and reduce the risk as much as possible. But the IUI as compared to the IVF-ET, the pregnancy rate of IUI has remained stagnant [11]. Many previous studies have confirmed that the following factors may affect the pregnancy rate of IUI, such as female age, duration of infertility, history of pelvic diseases (such as pelvic inflammatory diseases, surgery, or endometriosis), and serious male factors. However, IUI is more effective in infertility with cervical causes, unexplained infertility, and ovulation disorders[12]. Many studies showed that symptoms of depression and anxiety were significantly more common in infertile women than infertile women [13]. The European Society for human reproduction and Embryology (ESHRE) reported that although IVF technology has changed with each passing day in recent years, without a significant increase in embryo transfer rate. This means that there may be other factors other than physiological factors influencing the pregnancy outcome of IVF. Indeed, plenty of evidence suggests that negative emotions such as stress, anxiety, and depression may have an impact on the clinical pregnancy rate and live birth rate of IVF-ET. the more painful women are before and during treatment, the lower their pregnancy rate [14–19]. In a study involving 501 American women, to explored associations between the salivary alpha-amylase (a stress-related biomarker) and the time required for pregnancy. Experimental results showed that: Nearly one-quarter of the patients with the highest amylase levels are twice as likely to develop infertility as those with normal levels [20].In another study of 135 in vitro fertilization patients, the researchers further evaluated the mental state of patients by collecting their hair and detecting the hair cortisol concentration. The measurement lasted from 3 months before treatment to 6 months after treatment. The results showed that there was a significant negative correlation between hair cortisol level and pregnancy rate ($P = 0.017$) [21].In fact, this finding is consistent with the personal experience of most infertile patients in the actual diagnosis and treatment process [22]. One recent meta-analysis showed that the positive effect of psychological intervention on alleviating patients' anxiety and improving the pregnancy rates. Anxiety has a significant negative correlation with the pregnancy rate. The higher the pregnancy rate, the lower the degree of anxiety[23, 24].

To our knowledge, no such studies have been reported on the relationship between the interval between two IUI and pregnancy outcome. The existing studies mainly focus on the IVF-ET cycle. Horowitz e et al. [25] discussed whether frozen embryo transfer should be performed again after the failure of fresh IVF cycle, or whether it can be performed in the next menstrual cycle without any waiting. The results showed that the pregnancy outcomes of immediate and delayed frozen embryo transfer in the natural cycle were similar. Delayed frozen embryo transfer did not improve reproductive outcomes after failure of the fresh cycle in vitro fertilization cycle. This result was consistent with two other studies[26, 27]. Reichman DE et al.[28] conducted a study to explore the therapeutic implication of interval treatment in IVF cycles of continuous GnRH-antagonist regimen. A total of 721 cycles were included in the experiment, of which 164 cycles started another cycle after only waiting for one menstrual cycle (35–55 days after the last egg retrieval), and 557 cycles started after waiting for two or more menstrual cycles (56–140 days) after the last egg retrieval. The results showed that the implantation rate (11.1% *vs.* 13.7%), clinical pregnancy rate (26.4% *vs.* 30.4%) and live birth rate (21.4% *vs.* 23.4%) in the delayed group were higher than those in the

continuous cycle group, but these differences were not statistically significant. It is concluded that delaying two or more menstrual cycles may not have any advantage over continuous cycles. The conclusions of this study were consistent with the above findings. Our study found that the clinical pregnancy rate (13.7% *vs.* 15.0%) and live birth rate (78.7% *vs.* 74.3%) in the delayed group were higher than those in the continuous cycle group, and the abortion rate was lower than that in the continuous cycle group (17.3% *vs.* 18.4%). Similarly, the above differences were not statistically significant. Clinically, the reason why patients or doctors choose to receive delayed treatment may be that they are worried that the ovulation induction scheme will have an adverse impact on the ovary, endometrium, or endocrine environment, which were not beneficial for fertilization and implantation. Nevertheless, the conclusions of relevant studies show that this concern is unnecessary[28, 29]. One endometrial regeneration cycle should be sufficient to allow embryo implantation[30].

For a long time, It is a long-held belied that female age is strictly related to fertility. Women's fertility also shows a gradual downward trend as age advances. An observational study shows that the monthly fertility rate of women gradually decreases after the age of 30, and worsens more rapidly after the age of 36[31]. The pregnancy rate of IUI in women over 41 years old is almost zero, which may be related to the deterioration of egg quality. It is reported that female age is the most paramount factor affecting the pregnancy rate of artificial insemination[31–33]. Our results show that when the woman is 30–35 years old, the pregnancy rate in the delayed group is significantly higher than that in the continuous group. When facing patients of different ages, different treatment strategies should be adopted. We can try to give the following suggestions carefully: for young women, continuous treatment should be adopted, while for older patients, delaying treatment may have more benefits. The reason for this situation may be that young patients recover faster after treatment failure. And in the face of failure, because young women occupy the advantage of time, their psychological pressure is much smaller than older women. Older patients tend to have greater expectations for each treatment. If they fail, they often need more time to adjust their physical and emotional effects.

At present, there has been disagreement on the impact of infertility duration on pregnancy outcomes. It is generally believed that a longer infertility duration hinders the therapeutic effect of IUI [34]. Our study found that when the duration of infertility was short, the pregnancy rate in the delayed group was significantly higher than that in the continuous group. With the extension of the duration of infertility, the pregnancy rate decreased and tended to be similar in both groups. The reason for this situation may be that the adjustment of psychological state has played a great role in improving pregnancy outcomes. In addition, when a failure occurs, we often analyze the causes of failure and adjust the treatment plan, which is also conducive to the improvement of pregnancy outcomes in the delayed group. However, with the increase of infertility duration, the psychological pressure of patients increases gradually. Psychological problems such as anxiety and depression may have adverse effects on pregnancy outcomes. At the same time, primary infertility patients who have been infertile for many years cannot rule out infertility factors that cannot be overcome by IUI, such as sperm-egg binding disorder. Secondary infertility did not get pregnant for many years after a previous pregnancy, suggesting that there may be

new infertility factors such as fallopian tube and pelvic cavity, which can not be overcome by IUI technology. This is why the longer the duration of infertility, the lower the clinical pregnancy rate.

For those who are not pregnant after one IUI treatment, several cycles of treatment are needed in the follow-up, and no consensus has been reached so far. It is reported that among many factors affecting the outcome of IUI, increasing the number of IUI cycles is also helpful to improve the pregnancy rate. Aboulghar et al.[35] conducted a prospective study to explore the impact of the number of treatment cycles on pregnancy outcomes. A total of 594 women treated with IUI for unexplained infertility were included in the study. All participants received 1–3 cycles of treatment. In addition, 91 participants failed to conceive in the first three cycles, so they continued IUI treatment for 1–3 cycles. The authors found that the clinical pregnancy rate in each of the first three cycles was significantly higher than that in the next three cycles. Therefore, it is recommended that the number of IUI cycles should be at least 3 times. A meta-analysis published in 2018 suggested that couples with infertility should have at least three consecutive IUI cycles[36]. Dinelli et al.[37] believe that women aged 36–38 can try IUI four times within one year. Those aged 39–40 with good ovarian reserve function and secondary infertility can be treated with IUI, but they should be controlled 2–3 times. Those aged > 40 are not recommended to be treated with IUI. However, it is worth noting that our study found that with the increase of the number of treatment cycles, the pregnancy rate decreased gradually. However, in patients with 4 cycles or more, the pregnancy rate in the continuous group was significantly higher than that in the delayed group. The possible explanation is that with the increase of the number of cycles, the age of patients is also gradually increasing. At the same time, as the number of treatment cycles increases, the accompanying negative emotions are gradually accumulating[38]. At this time, the influence of age and negative emotion on pregnancy outcome is more and more important. Early and continuous treatment can benefit patients. Therefore, the pregnancy rate in the continuous group is significantly higher than that in the delayed group.

For those patients who are suitable for IUI treatment, each additional treatment means the failure of the previous treatment, and each failure may have a great impact on the patient's body and spirit. These effects may come from the stress state caused by long-term infertility, the physical discomfort caused by the side effects of ovulation-inducing drugs, the pain caused by multiple injections and blood testing, the blow caused by the failure of IUI, the economic pressure caused by long-term treatment, and the pressure from family and society. Delaying treatment can provide a buffer time for patients, which may play a positive role in alleviating the accumulation of such adverse emotions. However, for patients with mild infertility, IUI has less trauma, a relatively small economic burden, and a short treatment cycle compared with IVF-ET. after failure, IVF and other alternatives can still be considered, which may reduce the psychological burden of patients to a certain extent. This may also be one reason why the pregnancy rate in the delayed group did not increase significantly compared with the continuous group.

Compared to other similar studies, the novelty of this study is to carry out a hierarchical design for the included factors and draw some suggestions for clinical reference. In addition, this study reviewed and analyzed the medical record data of the center in the past 8 years by consulting the medical record system, and the approach demonstrates high repeatability and reliability. However, this study also has

some drawbacks. Firstly, because our research design is a retrospective study, we give the above conclusions more conservatively. Our above conclusions still need to be verified by more centers, a larger sample size,s or prospective randomized controlled trials. In addition, there are few variables included in this study, and there may still be other factors causing bias. More research variables need to be included for analysis in the follow-up.

Overall, prolonging the interval between two IUI did not significantly improve pregnancy outcomes. Yet, for different age stages, duration of infertility, and the number of treatment cycles, we suggest that more flexible treatment strategies can be tried to improve the clinical pregnancy rate.

Declarations

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Authors' contributions

Shuai zhang and Minglian Zhou contributed to the conception and design of the study. Shuai zhang , Hanhan Tang,and Hui Juan were responsible for data collection and checking. Shuai zhang and Hanhan Tang performed the data analysis, interpretation and manuscript drafting.Minglian Zhou and Huaiyun Tang supervised the project administration. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.Ethics approval and consent to participate This study was approved by the Ethics Committee (Institutional Review Board) of Lianyungang Maternal and Child Health Hospital. Written informed consent was waived due to the retrospective nature, and patients' data were used anonymously.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Demographic characteristics of continuous group and delayed group

Variable	Continuous group n=990	Delay group n=501	*P* value
Male age (years)*	30.91±4.369	31.14±4.316	0.317
Female age(years)*	29.7±3.804	29.96±3.74	0.215
Type of infertility n(%)			
primary infertility	654（66.1）	340（67.9）	0.485
secondary infertility	336（33.9）	161（32.1）	
Number of treatment n(%)			
2 cycles	600（60.6）	297（59.3）	
3 cycles	318（32.1）	155（30.9）	
4 cycles and above	72（7.3）	49（9.8）	0.244
Treatment moden n(%)			
natural cycle	117（11.8）	67（13.4）	0.388
ovulation induction cycle	873（88.2）	434（86.6）	
Duration of infertility n(%)			
≤2 years	375（37.9）	179（35.7）	0.193
2-5 years	460（46.5）	225（44.9）	
（5 years	155（15.7）	97（19.4）	
Causes of infertility n(%)			
female factors	409（41.3）	236（47.1）	0.182
male factors	103（10.4）	46（9.2）	
unexplained infertility	380（38.4）	170（33.9）	
factors of husband and wife	98（9.9）	49（9.8）	

Note: * The numerical expressions of age are mean ± SD.

Table 2.Pregnancy outcomes in continuous and delayed groups

		Continuous group n=990	Delay group n=501	$\chi 2$ value	*P* value
Pregnancy outcomes	clinical pregnancy rates n(%)	136（13.7）	75（15.0）	0.416	0.519
	abortion rate n(%)	25（18.4）	13（17.3）	0.036	0.849
	live birth rate n(%)	101（74.3）	59（78.7）	0.511	0.475

Table 3.relationship between the interval between two IUI and clinical pregnancy after adjusting for confounding factors.

	Continuous group n=990	Delay group n=501	*OR*（95%CI）	Adjusted *OR*（95%CI）
clinical pregnancy rates n(%)	136（13.7）	75（15.0）	1.106 (0.815-1.5),*P*=0.519	1.101 (0.807-1.499),*P*=0.546

Note:adjustment factors include: age of the woman, the age of the man, the number of treatment cycles, the duration of infertility, the type of infertility, the mode of treatment, and the cause of infertility.

Figures

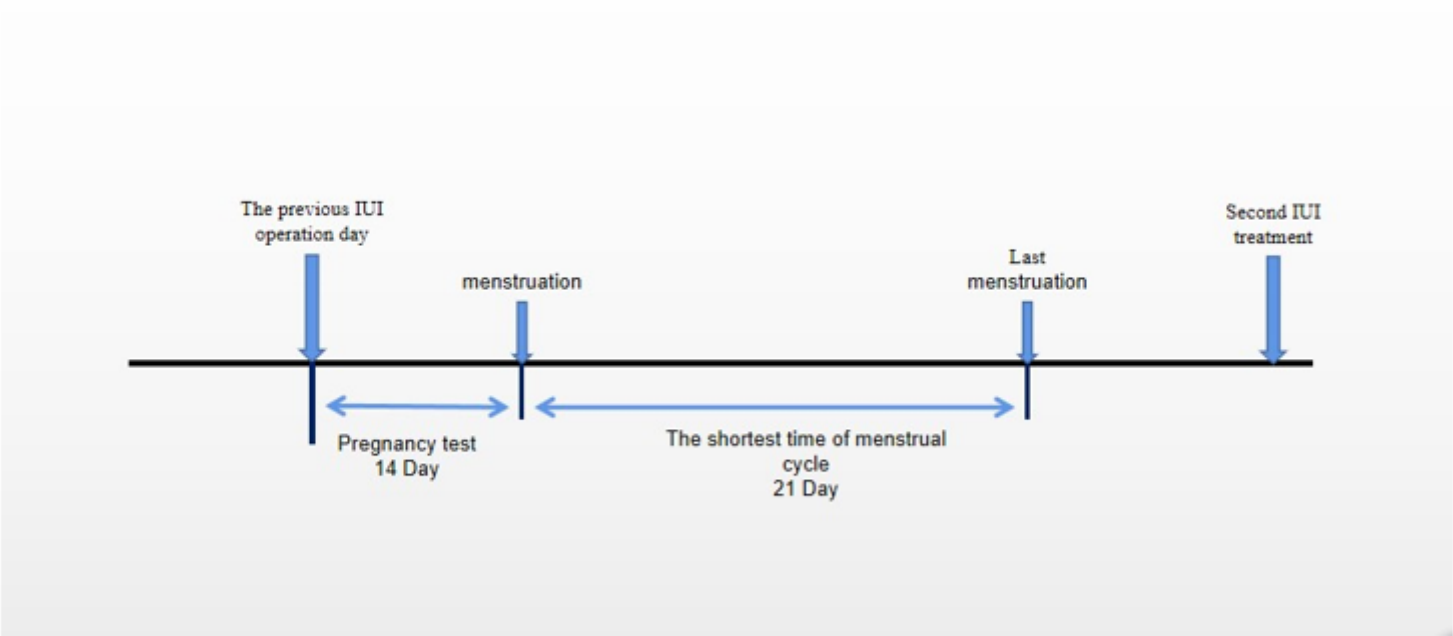

Figure 1

Continuous group (defined as the time from the last menstrual day(LMD) to the previous IUI operation day(POD)≤34 days) and delayed group (defined as the time from the last menstrual day (LMD)to the previous IUI operation day(POD)≥ 35 days).

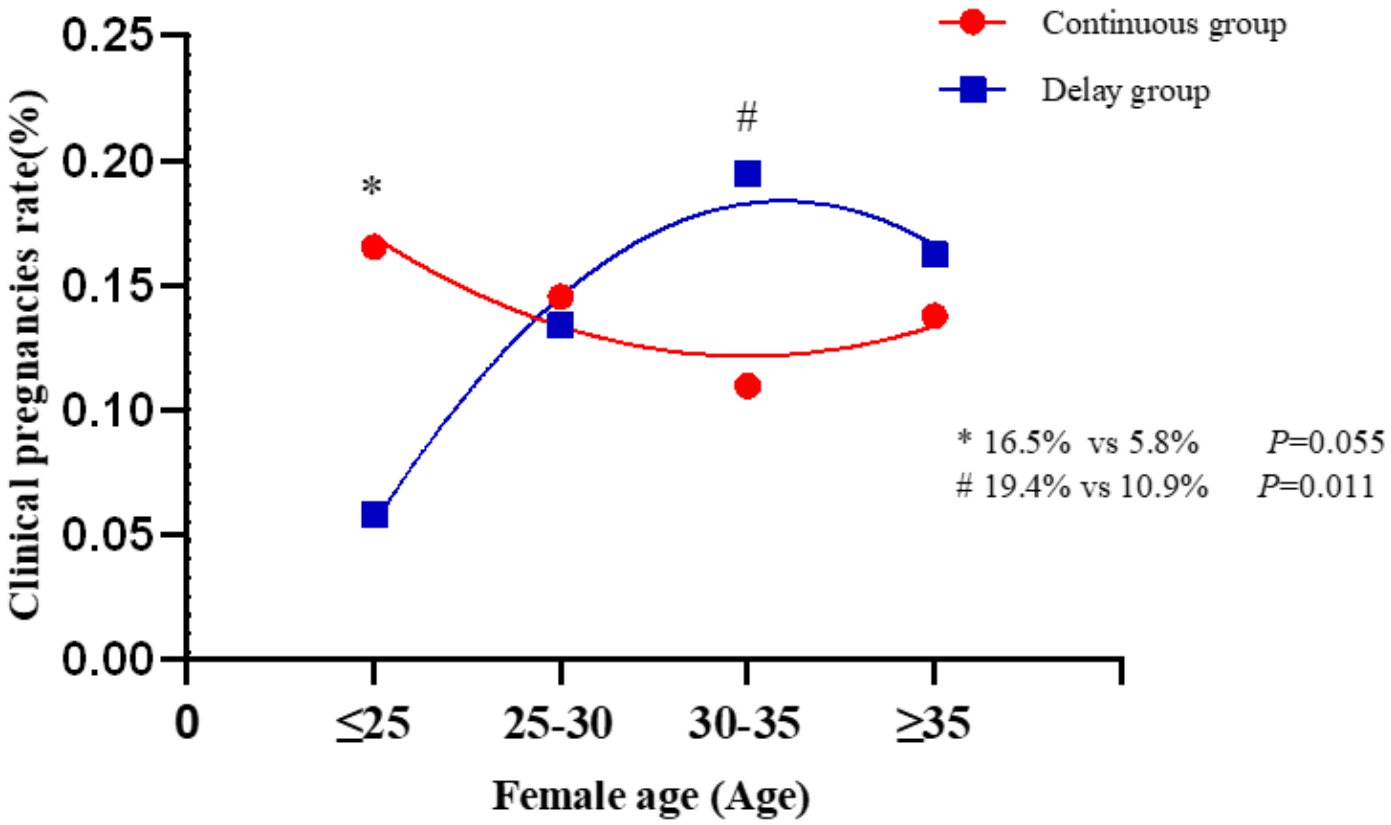

Figure 2

female age-stratified analysis showed that when the woman was 30-35 years old, The delayed group had higher gravidity than the continuous group(19.4% vs 10.9%, difference 0.085, 95% CI 0.154-0.016, P = 0.011). P=P value.

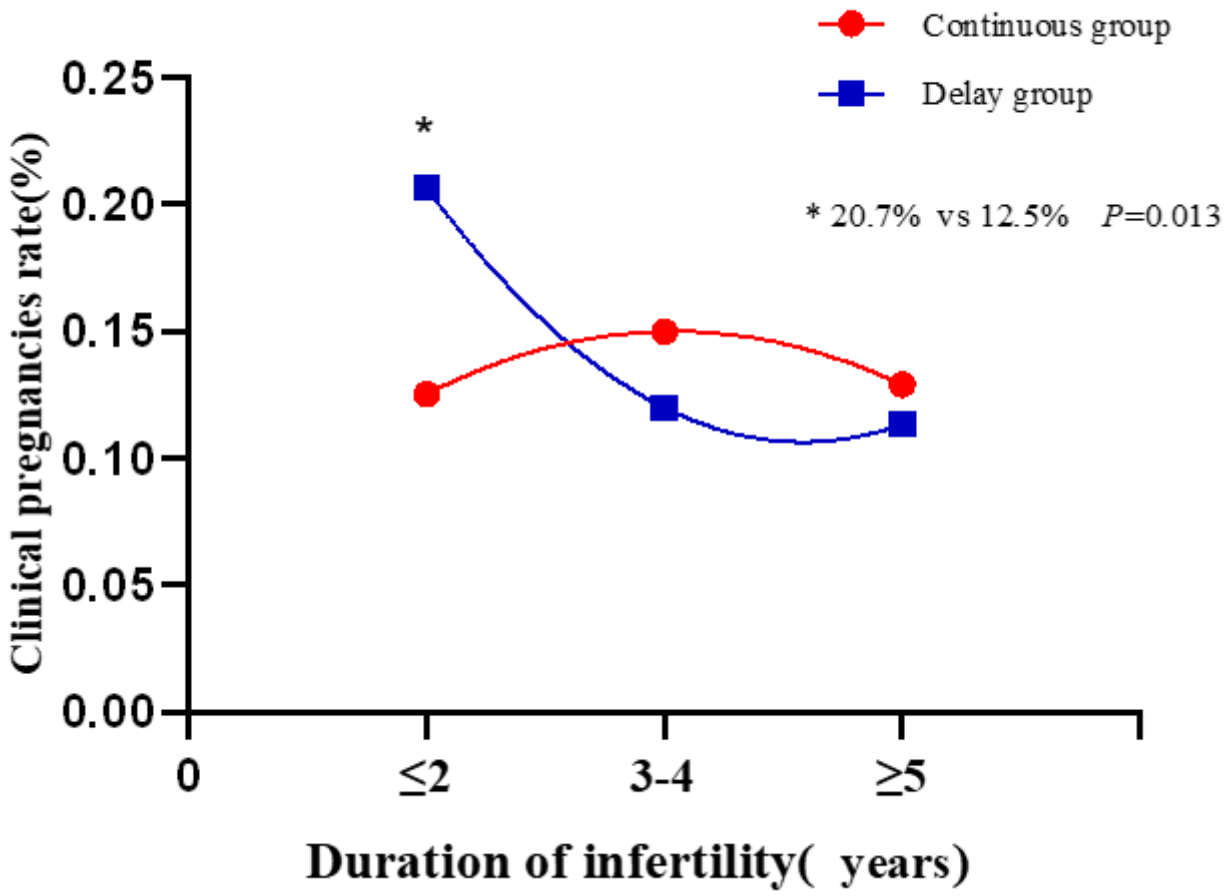

Figure 3

Duration of infertility stratified analysis showed that the duration of infertility was ≤ 2 years, The delayed group had a higher pregnancy rate than the continuous group(20.7% vs 12.5%, difference 0.107, 95% CI 0.150-0.014, P = 0.013). There were statistically significant differences between the two groups.P=P value

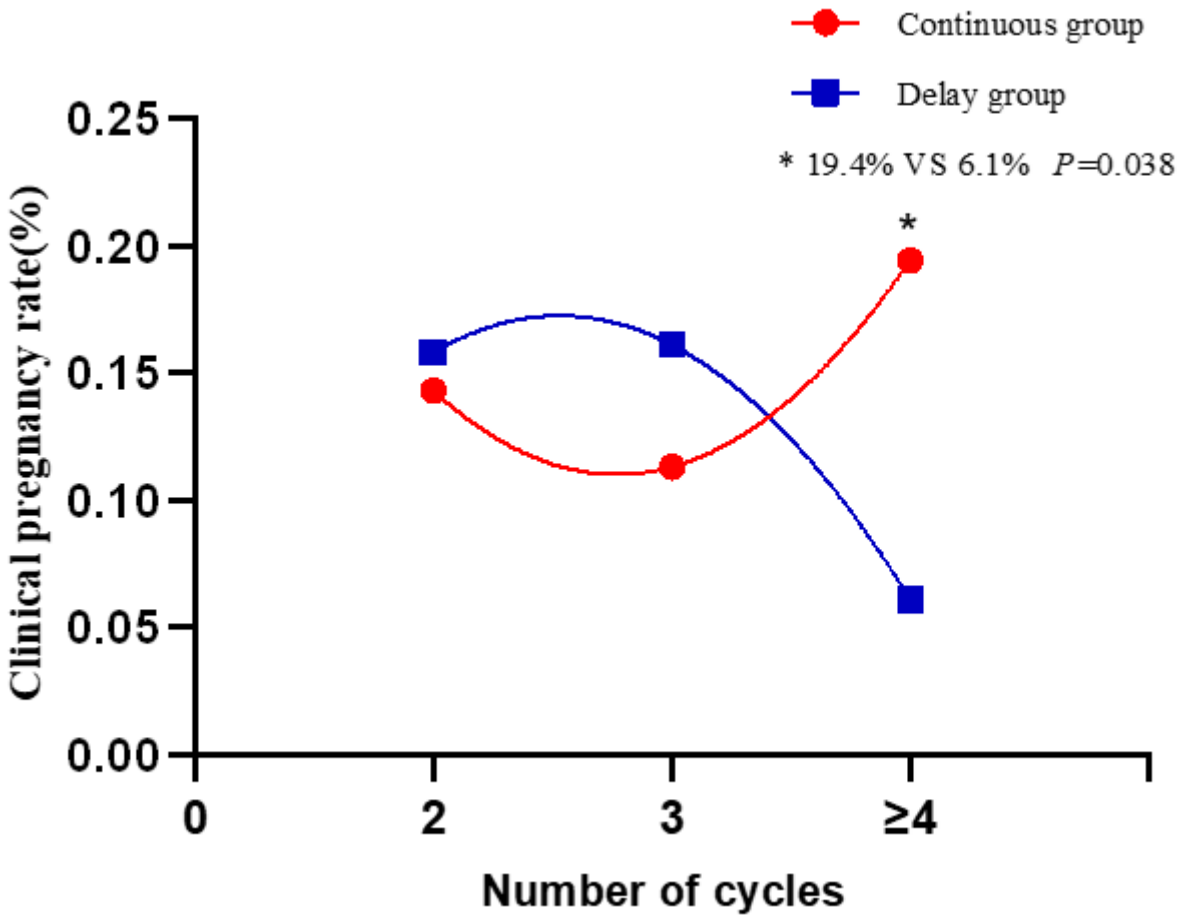

Figure 4

number of cycles-stratified analysis showed that when the ≥ 4 cycles,The continuous group had higher the pregnancy rate than the delayed group(19.4% vs 6.1%,difference 0.133, 95% CI 0.246-0.020, P = 0.038).P=P value