The Impact of the Time Interval Between Cycles on Pregnancy Outcome of Ovulation Induction Cycle Intrauterine Artificial Insemination

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Research

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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 in patients undergoing successive cycles of ovulation stimulation, 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 2017 to December 2019. 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). We excluded cycles with intervals of more than 180 days.In order to avoid the inclusion of multiple repeat cycles for the same couple, only the first two cycles of IUI treatment in the same couple were allowed to be included in this study. That is, when they failed the first IUI cycle, they were given a second IUI treatment.

Intervention(s)

No intervention.

Main Outcome Measure(s)

A total of 550 cycles met the inclusion criteria, and 374 (68.0%) cycles met the inclusion criteria for the continuous group,the remaining 176 (32.0%) cycles with at least one or more menstruations between two IUI cycles were included in the delayed group.The primary outcome measure was clinical pregnancy rate (CPR), with secondary outcomes including abortion rate. Differences in clinical pregnancy rate (CPR)、abortion rate were compared between the two groups.

Result

There was no significant difference between the continuous group and the delayed group in female age, male age, infertility duration, infertility type, female BMI, endometrial classification, endometrial thickness, semen volume before treatment, sperm density before treatment, percentage of forward motile sperm

before treatment, sperm density after treatment, and percentage of forward motile sperm after treatment. There were no statistical differences between the delayed group vs continuous group regarding the clinical pregnancy rate (20.5 % *vs* 21.9 %) and abortion rate (27.8% *vs* 22.0%)（*P*>0.05）. The above factors were included for binary logistic regression analysis. It was found that the increase of endometrial thickness promoted the clinical pregnancy rate, which was statistically significant (*OR*=1.205, 95% *CI* 1.05-1.384,*P*=0.008). Compared with primary infertility, secondary infertility can promote the improvement of clinical pregnancy rate, which is statistically significant (*OR*=2.637,95%*CI* 1.313-5.298,*P*=0.006). The effect of time interval between IUI on clinical pregnancy was not statistically significant (*OR*=1.007,95% *CI* 0.513-1.974,*P*=0.985).

Conclusions

Overall, prolonging the interval between two IUI did not significantly improve pregnancy outcomes. Unless there are clear clinical indications, it is not necessary to deliberately prolong the interval between two treatments.

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, 2017, and December 31, 2019. 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, and throughout the course of IUI

treatment, all cycles received by patients were ovarian stimulation 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. In order to avoid the inclusion of multiple repeat cycles for the same couple, only the first two cycles of IUI treatment in the same couple were allowed to be included in this study. That is, when they failed the first IUI cycle, they were given a second IUI treatment.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(LYG-MEP2021013).

IUI treatment procedure

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.

Endometrial thickness and type monitoring

On the day of IUI operation, the endometrial thickness was measured by transvaginal ultrasound. According to the characteristics of ultrasound and referring to the Gonen classification standard, the endometrium was divided into ABC three types. Endometrial thickness: the maximum thickness of the middle and upper endometrium measured perpendicular to the uterine cavity line in the longitudinal section of the uterus. Gonen classification: (i) type A: typical trilinear sign; (ii) Type B: isolated echo in the middle; (iii) Type C: homogeneous strong echo, no midline echo of uterine cavity.

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 this were 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,and the density, viability and volume of sperm before and after density gradient centrifugation were detected.

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: (i)Continuous group: the period of IUI treatment immediately; (ii) Delayed group: waiting for at least one menstrual cycle before receiving IUI treatment, This is illustrated in Figure 1.

Primary and secondary outcome measures

The primary outcome measure was the clinical pregnancy rate (CPR) in the second IUI cycle, with secondary outcomes including abortion rate. Clinical pregnancy will be defined as the observed of an intrauterine gestation sac at 7 weeks of gestation by transvaginal ultrasound.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.

Statistical analysis:

All statistical analyses were performed using SPSS Statistics 26.0 (IBM, Inc.). 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 female age, male age, infertility duration, infertility type, female BMI, endometrial classification, endometrial thickness, semen volume before treatment, sperm density before treatment, percentage of forward motile sperm before treatment, sperm density after treatment, percentage of forward motile sperm after treatment and the interval between two IUI cycles. $P<0.05$ was defined as the difference was statistically significant.

Results

Basic information

A total of 1358 cycles were conducted from January 2017 to December 2019. 722 cycles only received ovarian stimulation during the whole treatment process. Since we only allowed the first two cycles of the same couple who received the second IUI treatment after the failure of the first IUI cycle to be included in the study, we excluded a total of 160 redundant cycles. We calculated the interval (day) between two adjacent weeks, excluding 12 cycles with an interval of more than 180 days. Finally, 550 cycles of 275 couples met the criteria and were included in the study.Figure 2.

Among these cycles, A total of 374 (68.0%) cycles met the criteria for the continuous group, and 176 (32.0%)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 ($P > 0.05$).

Pregnancy outcome

By contrast, no significant differences were found between the continuous group and delayed group in the clinical pregnancy rate (21.9% *vs.*20.5%,P=0.782).The abortion rate(22.0% *vs.* 27.8%, respectively; P=0.628).Again, this difference was not statistically significant.Table 2.

Multivariate analysis.

Female age, male age, infertility duration, infertility type, female BMI, endometrial classification, endometrial thickness, semen volume before treatment, sperm density before treatment, percentage of forward motile sperm before treatment, sperm density after treatment, percentage of forward motile sperm after treatment and the interval between two IUI cycles were included for binary logistic regression analysis, the results showed that the increase of endometrial thickness promoted the clinical pregnancy rate, which was statistically significant (*OR*=1.205, 95% *CI* 1.05-1.384,P=0.008).Compared with primary infertility, secondary infertility can promote the improvement of clinical pregnancy rate, which is statistically significant (*OR*=2.637,95% *CI* 1.313-5.298,P=0.006).The effect of time interval between IUI on clinical pregnancy was not statistically significant (*OR*=1.007,95% *CI* 0.513-1.974,P=0.985).Table 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 results of a newly published randomized controlled trial showed that for women who received the first FET after the failure of the fresh embryo transfer (ET) cycle, although the fresh et failed, the immediate FET had no adverse effect on the final pregnancy outcome compared with the delayed FET [29]. 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[28,30]. One endometrial regeneration cycle should be sufficient to allow embryo implantation[31].

Through multivariate regression analysis, it was found that endometrial thickness and infertility type were two independent factors affecting the clinical pregnancy rate of IUI. It is generally believed that endometrial thickness can be used as an important index to evaluate endometrial receptivity. Studies have found that thin endometrium is associated with low pregnancy rate[32]. This result may be due to the difficulty of embryo implantation caused by too thin endometrium[33]. Liu et al.[34] studied the relationship between endometrial thickness and pregnancy outcome in 1065 IUI cycles. The results showed that too high or too low endometrial thickness would have a negative impact on the clinical pregnancy rate. The clinical pregnancy rate was the highest when the peak endometrial thickness was between 10.5-13.9 mm. However, studies by other scholars did not find a correlation between the two, and proposed that endometrial thickness is not a good prognostic factor for the success of IUI treatment[35]. Similarly, the correlation between infertility types and clinical pregnancy rate is also controversial[36]. It is generally believed that the prognosis of secondary infertility is better than that of primary infertility, because patients with primary infertility may have infertility factors that are not easy to check, such as sperm egg binding disorder and poor endometrial receptivity.

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.

This study reviewed and analyzed the medical record data of the center in the past 3 years by consulting the medical record system, and the data has high reliability. However, this study also has its shortcomings. Firstly, in order to avoid possible errors caused by repeated inclusion of multiple cycles of the same case, the information we included only includes the first two cycles accepted by patients. For patients with multiple IUI treatment cycles, whether they can benefit from delaying treatment at different stages of the treatment process is a question worthy of in-depth discussion. Secondly, because our research design is a retrospective study and the included time span is short, we give this conclusion more conservatively. Our above conclusions still need to be verified by more centers, larger sample size 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.

Conclusions

Overall, prolonging the interval between two IUI did not significantly improve pregnancy outcomes.Unless there are clear clinical indications, it is not necessary to deliberately prolong the interval between two treatments.

Declarations

Author contributions

Shuai Zhang and Ming-lian Zhou designed the research; Shuai Zhang, Han-han Tang and Hui-juan Guan collected the data and wrote the paper; Shuai Zhang and Hanhan Tang analysed the data; Shuai Zhang andHan-han Tang edited the manuscript. All authors have 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(no.LYG-MEP2021013). Written informed consent was waived due to the retrospective nature, and patients' data were used anonymously.

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=187	Delayed group n=88	*P* value
Male age (years)	30.44±3.93	30.70±3.88	0.600
Female age(years)	29.34±3.42	29.50±4.12	0.739
Type of infertility n(%)			
primary infertility	132（70.6）	56（63.6）	0.248
secondary infertility	55（29.4）	32（36.4）	
Female BMI	24.19±3.88	24.92±3.51	0.135
Endometrial thickness(mm)	11.37±2.40	11.04±2.45	0.287
Endometrial classification,n(%)			
A	111（59.4）	51（58.0）	0.461
B	71（38.0）	32（36.4）	
C	5（2.7）	5（5.7）	
Semen volume before treatment (mL)	3.10±1.34	3.19±1.29	0.592
Sperm density before treatment (*10^6/mL)	81.23±55.25	79.95±56.30	0.859
Percentage of forward motile sperm before treatment (%)	48.43±13.78	47.65±11.20	0.643
Sperm density after treatment (*10^6/mL)	86.98±55.96	83.72±53.40	0.648
Percentage of forward motile sperm after treatment (%)	97.70±3.54	97.66±3.82	0.939
Duration of infertility n(%)			
≤2 years	64（34.2）	29（33.0）	0.295
2-5 years	89（47.6）	36（40.9）	
（5 years	34（18.2）	23（26.1）	

Note: BMI:body mass index.

Table 2.Pregnancy outcomes in continuous and delayed groups

	Continuous group n=187	Delayed group n=88	$\chi 2$ value	*P* value
Clinical pregnancy rates n(%)	41（21.9）	18（20.5）	0.077	0.782
Abortion rate n(%)	9（22.0）	5（27.8）	0.235	0.628

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

Variable	Control group	*B* value	*OR* value	*OR* 95%CI	*P* value
The interval between two IUI cycles					
Delayed group	Continuous group	0.007	1.007	0.513-1.974	0.985
Type of infertility n					
secondary infertility	primary infertility	0.970	2.637	1.313-5.298	0.006
Endometrial thickness		0.187	1.205	1.050-1.384	0.008

Note:IUI:intrauterine insemination, OR:odds ratio, 95%CI:95%confidence interval.

Adjustment factors include: Female age, male age, infertility duration, infertility type, female BMI, endometrial classification, endometrial thickness, semen volume before treatment, sperm density before treatment, percentage of forward motile sperm before treatment, sperm density after treatment, percentage of forward motile sperm after treatment and the interval between two IUI cycles.

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). IUI:intrauterine insemination.

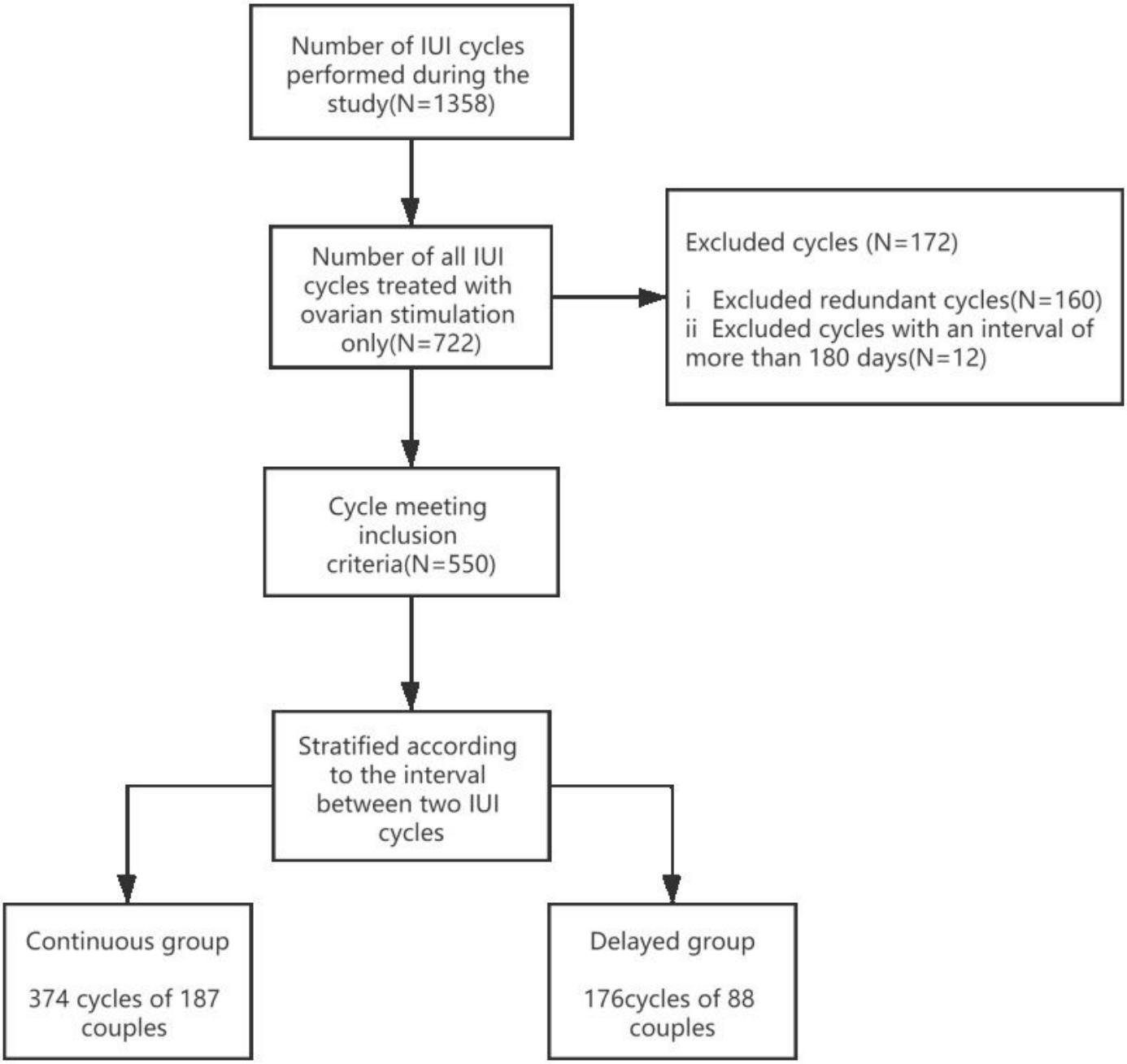

Figure 2

Flow chart of the study. IUI:intrauterine insemination.