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Impact of prolonged one or more natural menstrual cycles on the outcomes of ovulation induction intrauterine artificial insemination pregnancy: a single-centre, retrospective study in China

Shuai Zhang ,[1] Han-Han Tang,[2] Ming-Lian Zhou[1]

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SZ and H-HT contributed equally.

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[1]Clinical Center of Reproductive Medicine, Lianyungang Maternal and Child Health Hospital, Lianyungang, Jiangsu, China
[2]Graduate School of Xuzhou Medical University, Xuzhou Medical University, Xuzhou, Jiangsu, China

Correspondence to
Dr Shuai Zhang; senomega@hotmail.com

ABSTRACT

Objectives We determined if the time interval between two ovulation induction intrauterine artificial insemination (IUI) treatment cycles should be extended by one or more natural menstrual cycles in patients undergoing successive cycles of ovulation stimulation, and whether this affects clinical pregnancy rate (CPR).

Design This study was conducted on infertility patients treated under the ovulation induction programme IUI in a large reproductive centre in China. Study participants were assigned into continuous and discontinuous groups. Differences in baseline clinical pregnancy and abortion rates were compared between the groups. A multivariate logistic model was used to evaluate the effects of time interval on clinical pregnancy outcomes.

Setting Reproductive Centre of Maternal and Child Health Hospital of Lianyungang city.

Interventions None.

Primary and secondary outcome measures The primary outcome measure was CPR, the secondary outcome measure was the abortion rate.

Results A total of 550 IUI treatment cycles involving 275 couples were included in this study. Differences in CPR and abortion rate between the groups were not significant (20.5% vs 21.9% and 27.8% vs 22.0%, p≥0.05). Stratified analyses based on infertility factors did not reveal any significant differences in pregnancy and abortion rates between the groups (p≥0.05). Multivariate analysis showed that increased endometrial thickness correlates with CPR (OR 1.205, 95% CI 1.05 to 1.384, p=0.008). Compared with primary infertility, secondary infertility significantly correlated with improved CPR (OR 2.637, 95% CI 1.313 to 5.298, p=0.006). The effects of time interval between the first two ovulation induction IUI treatment cycles on clinical pregnancy were not significant (OR 1.007, 95% CI 0.513 to 1.974, p=0.985).

Conclusions Longer time intervals between the first two ovulation induction IUI treatment cycles did not significantly improve CPR. Therefore, in the absence of clear clinical indications, it may not be necessary to deliberately prolong the interval between two ovulation induction IUI treatment cycles.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to explore the effects of one or more prolonged natural menstrual cycles on pregnancy outcomes in intrauterine artificial insemination.
⇒ The number of cases included is large.
⇒ Data were obtained from a reliable clinical database of a large medical institution.
⇒ There were no subgroup analyses in the discontinuous group according to the delay time range, such as 1, 2, 3 or more natural cycles before the second treatment cycle.
⇒ This study was conducted in a single centre, therefore, the applicability of our conclusions to other populations maybe limited.

INTRODUCTION

Intrauterine insemination (IUI) is commonly used to enhance the success rate of pregnancy in fertility clinics. This technique is less likely to incur damage to the uterus as well as ovaries and is highly affordable.[1] IUI involves identifying excellent sperms after removal of seminal plasma and transcervically introducing the sperms into the uterine cavity. However, compared with in vitro fertilisation and embryo transfer (IVF-ET), the successful pregnancy rate of IUI is low. Therefore, for most patients, multiple attempts are necessary before successful pregnancy. This necessitates the need to develop novel strategies for improving the success rate of IUI treatments. The number of studies investigating if frozen ET should be delayed during IVF-ET treatment have gradually increased, but they have reported inconsistent conclusions. Some studies report that extending the interval between two IVF treatments does not significantly improve the pregnancy rate,[2–5] while other studies have come to the opposite conclusion, favouring a longer interval between IVF cycles as an effective way for increasing the clinical pregnancy rates (CPRs).[6 7] Currently, it has not been conclusively determined whether rest after IUI failure is beneficial. Thus, to inform clinical applications of IUI, we determined if the time interval between two ovulation induction IUI treatment cycles influences CPRs.

MATERIALS AND METHODS

Study population and design

We retrospectively reviewed all IUI cases at the Reproductive Medicine Centre of Lianyungang Maternal and Child Health Hospital from 1 January 2017 to 31 December 2019. Indications for IUI treatment included tubal problems, unexplained infertility, infertility due to cervical factors, ovulation disorders (refer to Rotterdam standard),[8] and infertility due to mild or moderately low male fertility (refer to WHO standard).[9] This study included patients who had received at least two ovulation induction cycle IUI treatments. To avoid including cases with multiple repeat cycles involving the same couple, only the first two ovulation induction IUI treatment cycles were included per couple. To minimise the impacts of confounding factors associated with long intervals and advancing age on pregnancy outcomes, the interval between the first two ovulation induction IUI treatment cycles was less than 180 days. Patient data were obtained from the clinical database and statistical analyses performed with reference to the above standards.

IUI treatment procedures

Ovulation induction therapy

For patients with sparse menstruation, natural cycle follicular dysplasia, ovulation disorders or previous natural cycle IUI treatment but not pregnant, ovulation induction treatment was performed. Prior to insemination operation, patients were given oralletrozole (LE) combined with human menopausal gonadotropin (HMG) for ovulation induction therapy. Namely, ovulation induction IUI treatment. After 48 hours, the number and diameter of follicles were measured by transvaginal ultrasonography, and the maturation degree of ovarian follicles evaluated by assessing luteinising hormone levels in blood and urine. Based on examination results, the dose of LE combined with HMG was timely adjusted to control the number of dominant follicles (diameter ≥14 mm) to within 3, checking every other day after that. When any follicle reached 18 mm in diameter, 5000 IU of human chorionic gonadotropin (hCG) was injected. After injection, b-mode ultrasound was performed to check ovulation and prepare for insemination. In cases of non-ovulation, subcutaneous injection of triprerelin hydrochloride 0.1 mg was performed to promote ovulation. If there is still no ovulation, artificial insemination was judged to have failed.

Endometrial thickness and type monitoring

On the insemination day, endometrial thickness was measured by vaginal ultrasound and classified according to ultrasonic characteristics. Endometrial thickness is the maximum thickness of the upper endometrium measured on the longitudinal section of the uterus perpendicular to the uterine cavity line. Gonen classification was used to classify the endometrium into three types. Type A: typical trilinear sign, type B: isolated echo in the middle, type C: homogeneous strong echo with no midline echo of the uterine cavity. This monitoring was repeated for each cycle of each patient.

Semen collection and treatment

Generally, patients were required to ejaculate once, 2–7 days before insemination and to avoid sex in this period. This was done to ensure semen quality on the insemination day. On the insemination day, male partners were asked to collect semen in a private room next to the laboratory to minimise the adverse effects of fluctuating ambient temperatures on sperm quality. Semen samples were collected by masturbation and purified by density gradient centrifugation after liquefaction for 30 min at 37°C. Sperm density, viability and volume were determined before and after density gradient centrifugation.

Timing of insemination

In ordinary circumstances, insemination was scheduled for 24–36 hours after hCG injection.

Luteal support and follow-up

Immediately after insemination, patients began oral progesterone for luteal support therapy. On day 14 after artificial insemination, serum β-HCG levels were used for pregnancy detection. For negative pregnancy tests, luteal support therapy was immediately stopped. For pregnancy positive patients (β-HCG levels >20 IU/L), luteal support therapy was continued until 10–12 weeks of gestation.

GROUPING METHOD

Systematic database searches were conducted to determine the date of first insemination operation, the date of last menstruation before the second ovulation induction IUI treatment cycle and the start date of second ovulation induction cycle IUI treatment cycle. First, the time interval between the first two ovulation induction IUI treatment cycles was ensured to be less than 180 days. Then, groups were divided according to time intervals between the date of first insemination operation and the date of last menstruation before the second ovulation induction IUI treatment. At 14 days after the first insemination operation, serum HCG levels were measured to determine pregnancy. None of the patients in this study were pregnant after the first IUI, therefore, luteal support therapy was immediately stopped. If the patient does not receive the next ovulation induction IUI treatment at this time, but performs the ovulation induction IUI treatment after one or more natural menstrual cycles, because the normal menstrual level of women was defined as a spontaneous cycle length of 21–35 days,[5] then the last menstrual date before the second ovulation induction IUI treatment is at least 35 days (14+21) from the date of

Figure 1 Grouping method. In the continuous treatment group the time interval between the date of first insemination operation and the last menstrual date before the second ovulation induction IUI treatment was ≤34 days. In the discontinuous treatment group the time interval between the date of first insemination operation and the last menstrual date before the second ovulation induction cycle IUI treatment was ≥35 days. IUI, intrauterine insemination.

first insemination operation. This case was defined as the discontinuous treatment group (≥35 days). If there was less than 35 days between the last menstrual date before the second ovulation induction IUI treatment and the date of first insemination operation, then, this indicated that the patient had immediately began the next ovulation induction IUI treatment without experiencing a natural menstrual cycle, which was defined as the continuous treatment group (≤34 days; figure 1).

Primary and secondary outcome measures

The primary outcome measure was CPR the second ovulation induction IUI treatment cycle. Secondary outcomes included abortion rates. Clinical pregnancy was indicated by the presence of an intrauterine gestation sac at 7 weeks of gestation, as revealed by transvaginal ultrasound. Pregnancy termination due to any cause after confirmed clinical pregnancy was considered as abortion. Abortion rate was determined as: number of abortion cycles/number of clinical pregnancy cycles.

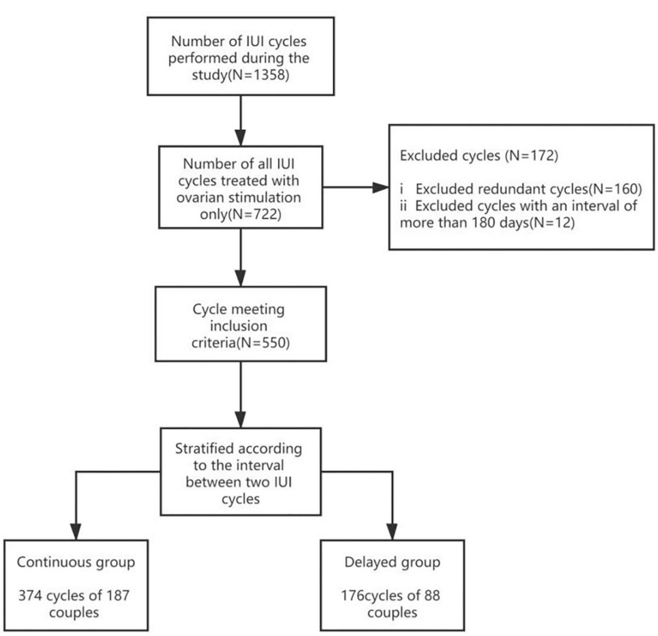

Figure 2 Flow chart of the study. Flow chart of the study. IUI, intrauterine insemination.

Patient and public involvement

No patient involved.

Statistical analysis

All statistical analyses were performed using SPSS V.26.0 (IBM). First, data were tested for normality using Shapiro-Wilk's statistics. Values are expressed as mean±SD Categorical variables are expressed as percentages (n%). Comparisons between groups were performed using the χ^2 or Fisher's exact tests. Given that this retrospective study may have included numerous unmeasured confounders, binary logistic regression analysis was used to evaluate the relationship between IUI interval and clinical pregnancy and to estimate the OR with a corresponding bilateral 95% CI. The confounding factors included age, infertility duration, infertility type, female body mass index (BMI), endometrial classification, endometrial thickness, semen volume before treatment, sperm density before treatment, percentage of forward motile sperms before treatment, sperm density after treatment, percentage of forward motile sperms after treatment and the interval between two IUI cycles. A p≤0.05 was considered statistically significant.

RESULTS

Basic information

A total of 1358 treatment cycles of IUI were conducted between January 2017 and December 2019. Among them, 722 ovulation induction IUI treatment cycles were included in this study. Since we only included the first two ovulation induction IUI treatment cycles, 160 redundant treatment cycles of IUI were excluded. Next, patients whose time interval between the first IUI and second IUI was more than 180 days were excluded. Finally, 550 ovulation induction IUI treatment cycles involving 275 couples were included in this study (figure 2). Among them, 374 (68.0%) ovulation induction IUI treatment cycles were classified in the continuous treatment group, while 176 (32.0%) were classified in the discontinuous treatment group. Baseline characteristics for patients in the two groups were comparable (p>0.05, table 1).

Pregnancy outcomes

Differences in clinical pregnancy and abortion rates between the continuous and discontinuous treatment groups were not significant (21.9% vs 20.5%; p=0.782% and 22.0% vs 27.8%; p=0.628, respectively, table 2).

The study population was also stratified according to infertility factors. With regards to infertility factors, differences between pregnancy outcomes under different infertility factors were insignificant (p≥0.05, tables 3 and 4).

Multivariate analysis

Age (male and female), infertility duration, infertility type, female BMI, endometrial classification, endometrial thickness, semen volume before treatment, sperm density before treatment, percentage of forward motile sperms before

Table 1 Demographic characteristics of continuous treatment group and discontinuous treatment group

Variable	Continuous treatment group n=187	Discontinuous treatment 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 ($\times 10^6$/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 ($\times 10^6$/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)	
Infertility factorsn, n (%)			
Ovulation disorders	92 (49.2)	42 (47.7)	0.830
Unexplained infertility	48 (25.7)	24 (27.3)	
Tubal problems	21 (11.2)	9 (10.2)	
Male factor	11 (5.9)	8 (9.1)	
Cervical factors	15 (8.0)	5 (5.7)	

BMI, body mass index.

treatment, sperm density after treatment, percentage of forward motile sperms after treatment, infertility factors and the interval between two IUI cycles were included in the binary logistic regression analysis. Increased endometrial thickness was significantly correlated with higher CPRs (OR 1.217, 95% CI 1.056 to 1.401, p=0.006). Compared with primary infertility, secondary infertility significantly correlated with better CPRs (OR 2.917, 95% CI 1.421 to 5.988, p=0.004). The impact of time interval between the first two ovulation induction IUI treatment cycles on clinical pregnancy was not significant (OR 0.984, 95% CI 0.495 to 1.957, p=0.964, table 5).

DISCUSSION

In this study, we found that spacing one or more natural menstrual cycles before the second ovulation induction IUI treatment did not significantly improve pregnancy outcomes.

Human IUI, which was first reported by Guttmacher[10] and Kohlberg,[11 12] has a history of nearly 60 years and its

Table 2 Pregnancy outcomes in continuous and discontinuous treatment groups

	Continuous treatment group n=187	Discontinuous treatment group n=88	χ^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 Comparison of clinical pregnancy rate between two groups under different infertility factors

Clinical pregnancy rates n (%)	Continuous treatment group n=41	Discontinuous treatment group n=18	χ^2 value	P value
Ovulation disorders	25 (27.2)	11 (26.2)	0.014	0.905
Unexplained infertility	9 (18.8)	1 (4.2)	1.756	0.185
Tubal problems	5 (23.8)	1 (11.1)	Fisher	0.637
Male factor	2 (18.2)	3 (37.5)	Fisher	0.603
Cervical factors	0 (0)	2 (40.0)	Fisher	0.053

Fisher: Fisher's exact probability test.

awareness has gradually increased. Like other assisted reproductive technologies, IUI is aimed at enhancing the pregnancy rates and minimising risks. However, relative to IVF-ET, pregnancy rates after IUI remain low.[13] The IUI pregnancy rate may be influenced by factors such as female age, duration of infertility, history of pelvic diseases (including pelvic inflammatory disease, surgery and endometriosis) and serious male factors (including severe oligospermia, severe asthenospermia and teratospermia). However, IUI is effective for infertility resulting from cervical causes, unexplained infertility and ovulation disorders.[14] Depression and anxiety are more common in infertile women than in fertile women.[15] The European society for human reproduction and embryology reported that despite advances in IVF technology, the increase in ET rates have not been significant, suggesting that in addition to physiological factors, other factors may influence pregnancy outcomes after IVF. Indeed, negative emotions like stress, anxiety, and depression affect clinical pregnancy and live birth rates after IVF-ET. The more distressed women are before and during treatment, the lower the pregnancy rate.[16–21]

However, to our knowledge, the relationship between the interval between two IUIs and pregnancy outcomes has not been evaluated, and past studies have mainly focused on IVF-ET. Horowitz *et al*[22] determined whether frozen ET should be performed again after failure of fresh IVF cycles and whether it can be performed immediately in the next menstrual cycle. They found that pregnancy outcomes of immediate and delayed frozen ETs in the natural cycle were comparable. Delayed frozen ETs did not improve reproductive outcomes after failure of fresh cycle IVF, consistent with findings by previous studies.[23 24] Reichman *et al*[25] evaluated the therapeutic implications of interval treatment in IVF cycles using a continuous GnRH-antagonist regimen. Among the the 721 ovulation induction IUI treatment cycles included in Reichman's study, 164 cases began another ovulation induction IUI treatment cycle after waiting for one natural menstrual cycle (35–55 days after the last egg retrieval), while 557 cases started after waiting for two or more natural menstrual cycles (56–140 days after the last egg retrieval). The implantation rate (11.1% vs 13.7%), CPR (26.4% vs 30.4%) and live birth rate (21.4% vs 23.4%) in the discontinuous treatment group were higher than in the continuous treatment cycle group, however, differences were not significant, indicating that delaying for two or more natural menstrual cycles may not have any advantage over continuous cycles. In a large retrospective study, 4404 patients were assessed on whether delayed frozen ETs improved CPRs and live birth rates. It was found that when participants were subjected to the same COS protocol, differences in CPRs, live birth rates, or early abortion rates between the immediate and delayed FET groups were insignificant. Moreover, differences in mean gestational age, mean birth weight, low birth weight and very low birth weight between the immediate and delayed FET groups were insignificant.[26] Clinically, the choice for using delayed treatment by doctors and patients may be due to concerns that the ovulation induction regimen may adversely impact the ovary, endometrium, or the endocrine system, which may negatively affect fertilisation and implantation. However, various studies suggest that these concerns may not be warranted[25 27] and that one endometrial regeneration cycle should be sufficient for embryonic implantation.[28]

Table 4 Comparison of abortion rate between two groups under different infertility factors

Abortion rate n (%)	Continuous treatment group n=9	Discontinuous treatment group n=5	χ^2 value	P value
Ovulation disorders	5 (20.0)	3 (27.3)	Fisher	0.678
Unexplained infertility	2 (22.2)	0 (0)	Fisher	1
Tubal problems	1 (20.0)	1 (100)	Fisher	0.333
Male factor	1 (50.0)	0 (0)	Fisher	0.400
Cervical factors	0 (0)	1 (100)		

Fisher: Fisher's exact probability test.

Table 5 Relationship between the time interval between two ovulation induction IUI trearment cycles and clinical pregnancy after adjusting for confounding factors

Variable	Control group	B value	OR value	OR 95% CI	P value
Time interval					
Discontinuous	Continuous	−0.016	0.984	0.495 to 1.957	0.964
Male age (years)		−0.026	0.974	0.849 to 1.117	0.708
Female age (years)		0.016	1.016	0.876 to 1.179	0.831
Type of infertility					
Secondary infertility	Primary infertility	1.07	2.917	1.421 to 5.988	0.004
Female BMI		0.059	1.061	0.972 to 1.159	0.186
Endometrial thickness (mm)		0.196	1.217	1.056 to 1.401	0.006
Semen volume before treatment (mL)		−0.224	0.799	0.615 to 1.039	0.095
Sperm density before treatment ($\times10^6$/mL)		−0.004	0.996	0.987 to 1.004	0.318
Percentage of forward motile sperm before treatment (%)		−0.005	0.995	0.97 to 1.021	0.73
Sperm density after treatment ($\times10^6$/mL)		0.004	1.004	0.995 to 1.013	0.419
Percentage of forward motile sperm after treatment (%)		0.041	1.042	0.937 to 1.157	0.448
Duration of infertility					
2–5 years	≤2 years	0.298	1.347	0.668 to 2.715	0.405
> 5 years	≤2 years	−0.836	0.433	0.159 to 1.185	0.103
Endometrial classification, n (%)					
B	A	−0.694	0.5	0.243 to 1.026	0.059
C	A	0.409	1.505	0.312 to 7.254	0.61
Infertility factors					
Ovulation disorders	Cervical factors	1.091	2.978	0.585 to 15.175	0.189
Unexplained infertility	Cervical factors	0.143	1.153	0.205 to 6.475	0.871
Tubal problems	Cervical factors	0.568	1.765	0.285 to 10.939	0.541
Male factor	Cervical factors	1.224	3.4	0.504 to 22.941	0.209

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, infertility factors and the time interval between two ovulation induction IUI trearment cycles.
BMI, body mass index; IUI, intrauterine insemination.

In this study, endometrial thickness and infertility type were identified to be independent factors affecting the CPR after IUI. It has been reported that endometrial thickness can be used as an indicator of endometrial receptivity. Studies have associated thin endometria with low pregnancy rates,[29] probably due to inefficient implantations.[30] A study of the relationship between endometrial thickness and pregnancy outcomes in 1065 IUI cycles found that abnormal (too high or too low) endometrial thickness negatively affects CPRs and that CPR was highest when peak endometrial thickness was between 10.5 and 13.9 mm.[31] However, other studies did not find any correlations between the two, suggesting that endometrial thickness is not a good prognostic factor for IUI success.[32] The correlation between infertility type and CPR is also controversial.[33] The prognosis of secondary infertility is better than that of primary infertility because patients with primary infertility may have infertility factors that are not easily identifiable, such as sperm egg binding disorders and poor endometrial receptivity.

In this study, we retrospectively reviewed all IUI cases at the Reproductive Medicine Centre of Lianyungang Maternal and Child Health Hospital from 1 January 2017 to 31 December 2019. These data are stored in the medical records system and have a high reliability. However, this study has some limitations. First, to avoid confounders that may be introduced by repeated inclusions of multiple cycles involving the same couple, only data on the first two ovulation induction IUI treatment cycles were included for each couple. Thus, we could not determine if patients who underwent more than two ovulation induction IUI treatment cycles can benefit from delaying treatment at different stages of the treatment process. Second, since our study is retrospective in nature and covered a short time span, our conclusions are conservative. Our findings should be validated via multicentre studies involving larger sample sizes or prospective randomised controlled trials. Additionally, although only a few variables were included in this study, additional factors may cause bias. Therefore, future studies should include more variables.

CONCLUSIONS

Prolonging the time interval between two ovulation induction IUI treatment cycles does not significantly improve pregnancy outcomes. In the absence of clear clinical indications, it may not be necessary to deliberately prolong time intervals between treatments.

Contributors SZ and M-LZ contributed to the conception and design of the study. SZ and H-HT were responsible for data collection and checking. SZ and H-HT performed the data analysis, interpretation and manuscript drafting. M-LZ supervised the project administration. All authors read and approved the final manuscript. SZ is responsible for the overall content as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval 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.

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Data availability statement Data are available on reasonable request.

ORCID iD

Shuai Zhang http://orcid.org/0000-0002-7099-1845

REFERENCES

1 Veltman-Verhulst SM, Hughes E, Ayeleke RO. Intra-Uterine insemination for unexplained subfertility. *Cochrane Database Syst Rev* 20162020;3:CD001838.
2 Horowitz E, Mizrachi Y, Farhi J, *et al*. Modified natural-cycle cryopreserved embryo transfer: is a washout period needed after a failed fresh cycle? *Reprod Biomed Online* 2019;39:439–45.
3 Lattes K, Checa MA, Vassena R, *et al*. There is no evidence that the time from egg retrieval to embryo transfer affects live birth rates in a freeze-all strategy. *Hum Reprod* 2017;32:368–74.
4 Ozgur K, Bulut H, Berkkanoglu M, *et al*. Frozen embryo transfer can be performed in the cycle immediately following the freeze-all cycle. *J Assist Reprod Genet* 2018;35:135–42.
5 Reichman DE, Chung P, Meyer L, *et al*. Consecutive gonadotropin-releasing hormone-antagonist in vitro fertilization cycles: does the elapsed time interval between successive treatments affect outcomes? *Fertil Steril* 2013;99:1277–82.
6 Kaye L, Marsidi A, Rai P, *et al*. Frozen blastocyst transfer outcomes in immediate versus delayed subsequent cycles following GnRH agonist or hCG triggers. *J Assist Reprod Genet* 2018;35:669–75.
7 Volodarsky-Perel A, Eldar-Geva T, Holzer HEG, *et al*. Cryopreserved embryo transfer: adjacent or non-adjacent to failed fresh long GnRH-agonist protocol IVF cycle. *Reprod Biomed Online* 2017;34:267–73.
8 Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004;81:19–25.
9 World Health Organization. *Laboratory manual for the examination and processing of human semen*. 5th edn. Geneva: WHO, 2010.
10 Guttmacher AF. The role of artificial insemination in the treatment of human sterility. *Bull N Y Acad Med* 1943;19:573–91.
11 Kohlberg K. Arzt und Samenübertragung. *Dtsch med Wochenschr* 1953a;78:855–6.
12 Kohlberg K. Die praxis Der Samenübertragung beim Menschen. *Dtsch med Wochenschr* 1953b;78:835–9.
13 Cohlen B, Bijkerk A, Van der Poel S, *et al*. IUI: review and systematic assessment of the evidence that supports global recommendations. *Hum Reprod Update* 2018;24:300–19.
14 Duran HE, Morshedi M, Kruger T, *et al*. Intrauterine insemination: a systematic review on determinants of success. *Hum Reprod Update* 2002;8:373–84.
15 Lakatos E, Szigeti JF, Ujma PP, *et al*. Anxiety and depression among infertile women: a cross-sectional survey from Hungary. *BMC Womens Health* 2017;17:48.
16 Rooney KL, Domar AD. The relationship between stress and infertility. *Dialogues Clin Neurosci* 2018;20:41–7.
17 Massey AJ, Campbell BK, Raine-Fenning N, *et al*. Relationship between hair and salivary cortisol and pregnancy in women undergoing IVF. *Psychoneuroendocrinology* 2016;74:397–405.
18 Klonoff-Cohen H, Chu E, Natarajan L, *et al*. A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. *Fertil Steril* 2001;76:675–87.
19 An Y, Sun Z, Li L, *et al*. Relationship between psychological stress and reproductive outcome in women undergoing in vitro fertilization treatment: psychological and neurohormonal assessment. *J Assist Reprod Genet* 2013;30:35–41.
20 Xu H, Ouyang N, Li R, *et al*. The effects of anxiety and depression on in vitro fertilisation outcomes of infertile Chinese women. *Psychol Health Med* 2017;22:37–43.
21 Palomba S, Daolio J, Romeo S, *et al*. Lifestyle and fertility: the influence of stress and quality of life on female fertility. *Reprod Biol Endocrinol* 2018;16:113.
22 Horowitz E, Mizrachi Y, Farhi J, *et al*. Modified natural-cycle cryopreserved embryo transfer: is a washout period needed after a failed fresh cycle? *Reprod Biomed Online* 2019;39:439–45.
23 Lattes K, Checa MA, Vassena R, *et al*. There is no evidence that the time from egg retrieval to embryo transfer affects live birth rates in a freeze-all strategy. *Hum Reprod* 2017;32:368–74.
24 Ozgur K, Bulut H, Berkkanoglu M, *et al*. Frozen embryo transfer can be performed in the cycle immediately following the freeze-all cycle. *J Assist Reprod Genet* 2018;35:135–42.
25 Reichman DE, Chung P, Meyer L, *et al*. Consecutive gonadotropin-releasing hormone-antagonist in vitro fertilization cycles: does the elapsed time interval between successive treatments affect outcomes? *Fertil Steril* 2013;99:1277–82.
26 He Y, Zheng H, Du H, *et al*. Delayed frozen embryo transfer failed to improve live birth rate and neonatal outcomes in patients requiring whole embryo freezing. *Reprod Biol Endocrinol* 2020;18:1.
27 Santos-Ribeiro S, Siffain J, Polyzos NP, *et al*. To delay or not to delay a frozen embryo transfer after a failed fresh embryo transfer attempt? *Fertil Steril* 2016;105:1202–7.
28 Al-Serehi A, Mhoyan A, Brown M, *et al*. Placenta accreta: an association with fibroids and Asherman syndrome. *J Ultrasound Med* 2008;27:1623–8.
29 De Geyter C, Schmitter M, De Geyter M, *et al*. Prospective evaluation of the ultrasound appearance of the endometrium in a cohort of 1,186 infertile women. *Fertil Steril* 2000;73:106–13.
30 Casper RF. It's time to pay attention to the endometrium. *Fertil Steril* 2011;96:519–21.
31 Liu Y, Ye XY, Chan C. The association between endometrial thickness and pregnancy outcome in gonadotropin-stimulated intrauterine insemination cycles. *Reprod Biol Endocrinol* 2019;17:14.
32 Weiss NS, van Vliet MN, Limpens J, *et al*. Endometrial thickness in women undergoing IUI with ovarian stimulation. How thick is too thin? A systematic review and meta-analysis. *Hum Reprod* 2017;32:1009–18.
33 Dinelli L, Courbière B, Achard V, *et al*. Prognosis factors of pregnancy after intrauterine insemination with the husband's sperm: conclusions of an analysis of 2,019 cycles. *Fertil Steril* 2014;101:994–1000.