The duration of estrogen treatment before progesterone application does not affect neonatal and perinatal outcomes in single frozen blastocyst transfer cycles

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Research

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Abstract

Background: The number of frozen embryo transfer (FET) cycles has substantially increased in the past decade. Preparing the endometrium in artificial cycles is widely used in clinical practice. Therefore, how to optimize this program, improve the clinical outcome and ensure the safety of the perinatal period is the focus of our attention. The purpose of this study was to explore whether the duration of estrogen treatment before progesterone application affects neonatal and perinatal outcomes in single frozen blastocyst transfer cycles.

Methods: It was a retrospective cohort study. Patients receiving single frozen blastocyst transfer and delivering a single live birth between January 2015 and December 2019 were included. Primary outcome was small for gestational age (SGA). Secondary outcomes were neonatal birthweight, gestational weeks at delivery, preterm birth, low birth weight (LBW), macrosomia, large for gestational age (LGA), neonatal malformation and rate of pregnancy-related complications.

Cycles were allocated to four groups according to the estrogen-treatment duration before single frozen blastocyst transfer ≤ 12 days (n=306), 13-15 days (n=620), 16-18 days (n=471), ≥ 19 days (n=275).

Results: In total, 1672 cycles were analyzed. Cycles were allocated to four groups according to the estrogen-treatment duration before single frozen blastocyst transfer ≤ 12 days (n=306), 13-15 days (n=620), 16-18 days (n=471), ≥ 19 days (n=275). The rates of SGA among the four groups were 7.8% (24/306), 4.8% (30/620), 5.7% (27/471), and 7.6% (21/275), with no statistical significance ($P=0.20$). Other neonatal outcomes, including mean neonatal birth weight, gestational weeks at delivery, preterm birth rate, LBW, macrosomia, LGA and neonatal malformation, were comparable among the groups ($P=0.38$, $P=0.16$, $P=0.20$, $P=0.58$, $P=0.20$, $P=0.34$, $P=0.96$). The rate of pregnancy-related complications was similar among the groups. Multiple logistics regression showed that the duration of estrogen treatment did not affect the rate of singleton SGA (13-15 days, AOR=1.37, 95% CI= 0.70-2.70, $P=0.36$; 16-18 days, AOR=0.74, 95% CI= 0.40-1.36, $P=0.34$; ≥ 19 days, AOR=0.81, 95% CI= 0.44-1.49, $P=0.50$).

Conclusion: The estrogen-treatment duration before progesterone application does not affect neonatal and perinatal outcomes in single frozen blastocyst transfer cycles.

Introduction

In the past decade, the number of frozen embryo transfer (FET) cycles has substantially increased. Currently, up to half of embryos are cryopreserved, and FET is performed[1]. This trend may be related to the improvement and development of vitrification technology and a rapid rise in single embryo transfer (ET), combined with the development of preimplantation genetic tests (PGTs) [2–4]. In addition, current studies have shown that FET can reduce in vitro fertilization (IVF) complications, such as ovarian hyperstimulation syndrome, increase the cumulative live birth rate, and improve perinatal and offspring outcomes[5–7]. How to improve the live birth rate of FET cycles and ensure the safety of mothers and offspring is the focus of our research and attention. Ensuring the synchronization of embryo and endometrial development is a key step in obtaining pregnancy. However, the optimal endometrial preparation protocols for FET are still a topic of constant debate[8–10]. The artificial cycle is mainly suitable for patients with abnormal ovulation or nonovulation. The application of exogenous estrogen and progesterone can promote the development of the endometrium and promote the synchronization of the development of the endometrium and the embryo. Preparing the endometrium in artificial cycles, which can flexibly arrange the transplantation time and reduce the number of monitoring procedures, is widely used in clinical practice[1]. Therefore, how to optimize this program, improve the clinical outcome and ensure the safety of the perinatal period is the focus of our attention. At present, there are studies exploring the optimal duration of estrogen treatment before progesterone application; however, most studies focus on the pregnancy rate or live birth rate [11–15]. To the best of our knowledge, only two studies have analyzed the relationship between the duration of estrogen treatment and offspring safety[13, 15]. However, the conclusions of the two studies are not consistent. Due to the differences in the included population and groupings, it is necessary to further analyze the effect of estrogen use time on neonatal and perinatal outcomes. Therefore, the purpose of this study was to analyze the effect of the duration of estrogen treatment before progesterone application on the safety of offspring and perinatal outcomes. To reduce the influence of confounding factors, this study only included the offspring of single blastocyst transfer and delivery of a single live birth.

Materials And Methods

Study design and population

This was a retrospective cohort study conducted in the reproductive center of the Third Affiliated Hospital of Zhengzhou University. Permission to conduct this study was obtained from the Ethics Committee of the Third Affiliated Hospital of Zhengzhou University. The outcomes of patients receiving single frozen blastocyst transfer and delivering a single live birth between January 2015 and December 2019 were included for potential analysis. All included patients had the endometrium prepared for ET through artificial cycles. Cycles with more than one blastocyst transfer were excluded from the analysis. We excluded cycles with oocyte donation, PGT and incomplete data. In addition, studies have shown that thin endometrium thickness (EMT) may have an impact on offspring weight and perinatal outcomes [16-19]. To reduce the influence of thin EMT, cycles with EMT ≤ 7 mm on the 10 days from the initiation of estrogen administration were excluded from analysis.

Endometrial preparation and ET

The controlled ovarian stimulation protocols and IVF/ICSI process have been described in our previous studies[5, 20, 21]. In the present study, all patients underwent artificial cycles for FET. Vaginal ultrasound examination was performed on the 2nd/3rd day of the menstrual cycle, 2-3 mg of estradiol valerate was taken orally three times daily (Bayer Co. Germany), and vaginal ultrasound examination was performed 7 days later. The drug dose was adjusted according to the thickness of the endometrium (up to 9 mg per day). The duration of estrogen treatment continued for at least 10 days. If conditions were appropriate (EMT > 7 mm, serum estrogen level ≥ 150 pg/ml and serum progesterone < 1.5 ng/ml) and the patient's schedule was feasible, the progesterone exposure day was formulated. Routine corpus luteum support, namely, oral dydrogesterone (2 times daily, 10 mg once) (Abbott Co. America) and intravaginal administration of 90 mg of a progesterone sustained-release vaginal gel (Merck Co. Germany), was given. Five days after endometrial development with corpus luteum support, single blastocyst transplantation was carried out by abdominal ultrasound. Corpus luteum support was performed at least until 55 days after transplantation if pregnancy occurred.

According to the duration of estrogen treatment before single frozen blastocyst transfer, we divided the cycles into four groups: ≤ 12 days, 13-15 days, 16-18 days, and ≥ 19 days. The ' ≤ 12 days group' was considered the reference group. The grouping was mainly based on the interquartile range of estrogen treatment.

Outcome measures and definition

The primary concern of this study was smallness for gestational age (SGA), which was defined as a birth weight less than the 10th centile for gestational age[22]. The weight criteria refer to the weight of Chinese newborns[23].

The secondary outcomes included neonatal birthweight, gestational weeks at delivery, preterm birth (defined as a birth that takes place after 28 weeks and before 37 completed weeks of gestational age), low birth weight (LBW, defined as a neonatal birth weight less than 2500 g)[22], macrosomia (defined as a neonatal birth weight more than 4000 g), largeness for gestational age (LGA, defined as a birth weight greater than the 90th centile of the sex-specific birth weight[22], with sex-specific birth weight referring to the weight of Chinese newborns[23]) and neonatal malformation. We also analyzed the rate of pregnancy-related complications among groups, including hypertensive states of pregnancy, gestational diabetes mellitus, placenta previa, placental abruption and premature rupture.

Statistical analysis

All the data in this article were obtained from the electronic medical record system of the reproductive center of the Third Affiliated Hospital of Zhengzhou University.

The one-sample Kolmogorov–Smirnov test was used to check for normality of continuous variables. Continuous variables with abnormal distributions are expressed as the median (P25, P75), and the between-group differences were assessed by the Wilcoxon rank sum test. Categorical variables are represented as the number of cases (n) and percentage (%). The means from chi-square analyses were used to assess the differences between groups with Fisher's exact test when necessary. For the main concern of this study, namely, SGA, multiple logistic regression were used to adjust for the baseline characteristics. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were calculated. $P < 0.05$ was considered to be statistically significant.

All statistical management and analyses were performed using SPSS software, version 22.0.

Results

Study population

The detailed inclusion and exclusion criteria are shown in Fig. 1. A total of 20,345 FET cycles were performed from January 2015 to December 2019. Cycles with cleavage ET (n = 9512), more than one blastocyst transfer (n = 365), oocyte donation (n = 139), PGT (n = 224) and incomplete important data (n = 79) were excluded. We excluded natural cycles (n = 3265), GnRH-agonist + artificial cycles (n = 762) and ovarian stimulation cycles (n = 1980). Cycles with EMT ≤ 7.5 mm were excluded (n = 162). A total of 1672 cycles with singleton live births from single blastocyst transfer were included for analysis.

Cycles were allocated to four groups according to the duration of estrogen treatment before single frozen blastocyst transfer ≤ 12 days (n = 306), 13–15 days (n = 620), 16–18 days (n = 471), ≥ 19 days (n = 275).

Baseline characteristics

The details of the baseline and cycle characteristics among the groups are described in Table 1. The endometrial thickness was different among groups on the first day of progesterone administration (≤ 12 days, 9.5 (8.7, 10.5); 13–15 days, 9.0 (8.3, 10.0); 16–18 days, 8.5 (8.0, 9.3); ≥ 19 days, 8.1 (7.5, 9.0), $P < 0.001$). Apart from this, there were no significant differences in other basic characteristics, including maternal age at oocyte retrieval, paternal age, body mass index (BMI), duration of infertility, type of infertility, gravidity, parity, causes of infertility, basal serum FSH level, AMH, basal antral follicle count, serum estradiol on the trigger day of the controlled ovarian hyperstimulation (COH) cycles, the rate of IVF and the rate of good-quality blastocyst transfer (a good-quality blastocyst is defined as a B3-B4 or B5 embryo $\geq$ BB(AA, AB, BA, BB)) according to the grading scale proposed by Gardner[24]).

Table 1
Baseline and cycle characteristics among groups.

Parameters	Duration of estrogen treatment before embryo transfer (days)				P-value
	≤ 12 (n = 306)	13–15 (n = 620)	16–18 (n = 471)	≥ 19 (n = 275)	
Maternal age at oocytes retrieved(year)	30.0(28.0,33.0)	30.0(27.0,33.0)	30.0(28.0,32.0)	29.0(27.0,32.0)	0.06
Paternal age(year)	31.0(28.0,34.0)	30.0(28.0,34.0)	30.0(28.0,33.0)	30.0(27.0,34.0)	0.17
BMI(kg/m ²)	24.1(21.7,26.2)	23.6(21.5,25.8)	24.1(22.0,26.1)	23.4(21.4,25.4)	0.07
Duration of infertility(year)	3.0(1.0,5.0)	3.0(1.0,5.0)	3.0(1.0,4.0)	3.0(1.0,4.0)	0.07
Type of infertility (%)					0.13
Primary infertility	52.0(159/306)	45.6(283/620)	46.5(219/471)	42.5(117/275)	
Secondary infertility	48.0(147/306)	54.4(337/620)	53.5(252/471)	57.5(158/275)	
Gravidity	0(0,1)	1(0,2)	1(0,2)	1(0,2)	0.19
Parity	0(0,1)	0(0,1)	0(0,1)0	0(0,1)	0.61
Causes of infertility (%)					0.06
Tubal factor	28.4(87/306)	28.5(177/620)	31.0(146/471)	37.5(103/275)	
Male factor	20.3(62/306)	26.0(161/620)	25.3(119/471)	20.4(56/275)	
Male + female factors	21.9(67/306)	16.9(105/620)	16.8(79/471)	18.9(52/275)	
Others	29.4(90/306)	28.5(177/620)	27.0(127/471)	23.3(64/275)	
Basal serum FSH level(IU/L)	6.2(4.9,7.4)	6.1(4.7,7.2)	6.0(4.7,7.4)	6.4(5.0,7.3)	0.31
AMH(ng/ml)	4.6(2.1,6.6)	4.8(2.9,6.2)	4.9(2.1,6.8)	5.0(2.4,6.3)	0.11
Basal antral follicle count	20.0(13.0,24.0)	20.0(15.0,24.0)	22.0(15.0,24.0)	22.0(17.0,24.0)	0.15
Serum estradiol on the trigger day of the COH cycles (pg/ml)	3033.0(1866.5,4532.5)	3077.9(2197.5,4607.5)	3191.5(2123.5,4637.3)	3090.2(2091.5,4167.5)	0.39
Fertilization method (%)					0.50
IVF	68.6(210/306)	65.0(403/620)	68.4(322/471)	69.1(190/275)	
ICSI	31.4(96/306)	35.0(217/620)	31.6(149/471)	30.9(85/275)	
Endometrial thickness on the first day of progesterone administration (mm)	9.5(8.7,10.5)	9.0(8.3,10.0)	8.5(8.0,9.3)	8.1(7.5,9.0)	< 0.001

Parameters	Duration of estrogen treatment before embryo transfer (days)				P-value
	≤ 12 (n = 306)	13–15 (n = 620)	16–18 (n = 471)	≥ 19 (n = 275)	
The rate of good-quality blastocyst transfer*	63.1(193/306)	63.9(396/620)	67.9(320/471)	61.5(169/275)	0.27
Note: Data are presented as median (P25,P75) for continuous variable and %(n/N) for categorical variable. *A good-quality blastocyst defined as B3-B4 or B5 embryo ≥ BB(AA, AB,BA,BB) according to the grading scale proposed by Gardner.					

Table 2
Comparison of neonatal and perinatal outcomes among groups.

	Duration of estrogen treatment before embryo transfer (days)				P-value
	≤ 12 (n = 306)	13–15 (n = 620)	16–18 (n = 471)	≥ 19 (n = 275)	
Neonatal outcomes					
Neonatal birth weight (g)	3500(3200,3850)	3500(3200,3895)	3400(3100,3800)	3500(3100,3800)	0.38
Neonatal sex (%)					0.45
Male	57.5(176/306)	55.6(345/620)	57.1(269/471)	51.6(142/275)	
Female	42.5(130/306)	44.4(275/620)	42.9(202/471)	48.4(133/275)	
Gestational weeks at delivery (week)	39(38,40)	39(38,40)	39(38,40)	39(38,40)	0.16
Preterm birth (%)	6.2(19/306)	6.3(39/620)	8.3(39/471)	4.4(12/275)	0.20
Low birth weight (%)	5.6(17/306)	4.8(30/620)	6.8(32/471)	5.5(15/275)	0.58
Small-for-gestational age (%)	7.8(24/306)	4.8(30/620)	5.7(27/471)	7.6(21/275)	0.20
Macrosomia (%)	14.4(44/306)	18.7(116/620)	16.6(78/471)	13.8(38/275)	0.20
Large-for-gestational age (%)	22.9(70/306)	26.3(163/620)	22.7(107/471)	21.5(59/275)	0.34
Neonatal malformation (%)	0.7(2/306)	0.5(3/620)	0.4(2/471)	0.4(1/275)	0.96
Pregnancy-related complications					
Hypertensive states of pregnancy (%)	5.6(17/306)	6.1(38/620)	8.7(41/471)	8.0(22/275)	0.24
Gestational diabetes mellitus (%)	3.9(12/306)	8.1(50/620)	7.0(33/471)	5.5(15/275)	0.09
Placenta previa (%)	1.3(4/306)	1.0(6/620)	0.4(2/471)	1.1(3/275)	0.54
Placental abruption (%)	0.7(2/306)	1.0(6/620)	0.2(1/471)	0.7(1/275)	0.49
Premature rupture (%)	2.9(9/306)	3.1(19/620)	2.5(12/471)	1.1(3/275)	0.37
Note: Data are presented as median (P25,P75) for continuous variable and %(n/N) for categorical variable .					

Neonatal And Perinatal Outcomes

The main outcome measure was the rate of SGA among the four groups, which was 7.8% (24/306), 4.8% (30/620), 5.7% (27/471), and 7.6% (21/275), with no statistical significance (P = 0.20). The mean neonatal birth weight was comparable among groups (≤ 12 days, 3500 (3200, 3850); 13–15 days, 3500 (3200, 3895); 16–18 days, 3400 (3100, 3800); ≥19 days, 3500 (3100, 3800), P = 0.38). The neonatal sex ratio (P = 0.45) and gestational weeks at delivery were similar between the groups (P = 0.16). The preterm birth rates among the four groups were 6.2% (19/306), 6.3% (39/620), 8.3% (39/471), and 4.4% (12/275), with no statistical significance (P = 0.20). The rates of LBW, macrosomia, LGA and neonatal malformation were comparable among the groups (P = 0.58, P = 0.20, P = 0.34, P = 0.96). Pregnancy-related complications, including hypertensive states of pregnancy, gestational diabetes mellitus,

placenta previa, placental abruption and premature rupture, were similar among the groups ($P = 0.24$, $P = 0.09$, $P = 0.54$, $P = 0.49$, $P = 0.37$).

Regarding SGA, to adjust for the influence of confounding factors, we conducted a multiple logistic regression analysis. The included factors were maternal age (continuous variable), body mass index (continuous variable), duration of infertility (continuous variable), type of infertility (primary/secondary infertility), infertility diagnosis (tubal/male/both/others), basal antral follicle count (continuous variable), basal serum FSH level (continuous variable), gravidity (continuous variable), parity (continuous variable), fertilization method (IVF/ICSI), endometrial thickness on the first day of progesterone administration (continuous variable) and blastocyst quality (good-quality/non-good-quality).

After adjustments for confounding factors, taking ' ≤ 12 days group' as the reference group, the duration of estrogen treatment did not affect the rate of singleton SGA (13–15 days, AOR = 1.37, 95% CI = 0.70–2.70, $P = 0.36$; 16–18 days, AOR = 0.74, 95% CI = 0.40–1.36, $P = 0.34$; ≥ 19 days, AOR = 0.81, 95% CI = 0.44–1.49, $P = 0.50$). The results of logistic regression analysis indicated that maternal BMI was a significant predictor for SGA (AOR = 0.93, 95% CI = 0.88–0.99, $P = 0.04$). The specific AOR values with their 95% CIs are presented in Table 3.

Table 3
Multivariable logistic regression analysis to account for confounding variables for SGA.

	Adjusted OR (95%CI)	Pvalue
Maternal age(year)	1.03(0.97–1.09)	0.36
Body mass index(kg/m ²)	0.93(0.88–0.99)	0.04
Duration of Infertility (year)	0.92(0.83–1.01)	0.09
Type of infertility(Primary/ Secondary infertility)	0.69(0.38–1.24)	0.21
Infertility diagnosis(Tubal/ Male/ both/Others)	1.05(0.88–1.26)	0.57
Basal antral follicle count	0.99(0.97–1.03)	0.93
Basal serum FSH level(IU/L)	1.03(0.95–1.11)	0.43
Gravidity	0.82(0.62–1.10)	0.18
Parity	1.32(0.90–1.96)	0.16
Fertilization method(IVF/ICSI)	1.03(0.94–1.12)	0.57
Endometrial thickness on the first day of progesterone administration (mm)	0.85(0.72–1.01)	0.07
Blastocyst quality(good-quality*/ Non-good-quality)	1.09(0.70–1.71)	0.70
Duration of estrogen treatment (days)		0.67
≤ 12 (reference)	1	
13–15	1.37(0.70–2.70)	0.36
16–18	0.74(0.40–1.36)	0.34
≥ 19	0.81(0.44–1.49)	0.50
Note: Variables entered in the logistics regression model listed. CI = confidence interval. *A good-quality blastocyst defined as B3-B4 or B5 embryo $\geq$ BB(AA, AB,BA,BB) according to the grading scale proposed by Gardner.		

Discussion

The purpose of this study was to analyze whether the duration of estrogen treatment before progesterone application affects neonatal and perinatal outcomes in single frozen blastocyst transfer cycles. Through our single-center retrospective cohort study, our results show that the duration of estrogen treatment does not affect offspring and perinatal outcomes.

Globally, the incidence of infertility is as high as 10%, and IVF is an important method of infertility treatment[25, 26]. However, adverse pregnancy and perinatal outcomes, such as SGA, LBW, preterm birth, pregnancy-induced hypertension and gestational diabetes, were increased in IVF/ICSI cycles, even for singleton births[27, 28]. However, the exact biological mechanism leading to adverse perinatal outcomes is unclear. Some studies have shown that infertility disease itself is the main reason for the poor perinatal outcome of assisted reproductive technology (ART) singleton offspring[29]. However, an increasing number of studies have shown that the process of ART, such as the exposure to superphysiological doses of estrogen, may have an adverse effect on perinatal outcomes[20, 30, 31]. The mechanism may be that superphysiological doses of estrogen may affect the development of the endometrium rather than the development and quality of the embryo[32, 33]. In the artificial cycle of FET, exogenous estrogen is supplemented to cause endometrial hyperplasia while inhibiting the development of dominant follicles. When the endometrium is suitable, exogenous progesterone is supplemented to promote the synchronous development of the endometrium and the embryo. It is not clear whether prolonging the use of estrogen would affect offspring and perinatal outcomes. To the best of our knowledge, only two studies have analyzed the relationship between the duration of estrogen treatment and neonatal and perinatal outcomes. Bourdon M *et al.*[13] reported that the mean birth weight and Z-scores were significantly lower for the '36–48 days' group than for the '≤21 days' group (3042 ± 801.2 g and -0.44 ± 1.50 vs. 3362 ± 602.9 g and 0.10 ± 0.94 , respectively). Another study included only single, vitrified-warmed, euploid blastocysts, and the results showed that variation in the duration of estradiol supplementation before progesterone initiation did not impact frozen, euploid blastocyst transfer outcomes. The duration of estrogen administration was inversely correlated with gestational age at delivery, but this did not translate into an increase in preterm delivery[15].

To date, our research is the largest retrospective cohort study to analyze the relationship between the duration of estrogen treatment before progesterone application and neonatal outcomes. This is the first study to analyze the relationship of this duration to pregnancy complications, including hypertensive states of pregnancy, gestational diabetes mellitus, placenta previa, placental abruption and premature rupture. Through analysis, different estrogen use times had no significant effect on offspring or perinatal outcomes. Moreover, because the neonatal and perinatal outcomes of embryo and blastocyst transfer may be different[34], this study included only single blastocyst transfer and delivery singleton birth, thereby reducing the influence of confounding factors. However, this study also has certain limitations. First, it suffers from the limitation of a retrospective cohort, although we used strict inclusion and exclusion criteria and multiple logistic regression to correct for the influence of confounding factors. Second, regarding the duration of estrogen use, the time range of hormone use at our center is 10–30 days, most of the treatment durations are 13–18 days (25%-75%), and only 275 cases have been treated more than 19 days; this estrogen use time is shorter than that in Bourdon M's[13] study, and his research shows that a duration of estrogen treatment greater than 35 days may have an impact on the outcome of offspring mean birth weight. However, in our center, there are almost no transplantation cycles with an estrogen application time greater than 35 days. According to our current data in our reproductive center, the duration of estrogen therapy does not affect offspring and perinatal outcomes, but it is uncertain whether extending the estrogen application time will affect the outcome. Consequently, further analysis of the safety of the estrogen-treatment duration before progesterone application is needed for a well-designed, prospective, and large-scale cohort study.

Conclusion

In conclusion, the duration of estrogen treatment before progesterone application does not affect neonatal and perinatal outcomes in single frozen blastocyst transfer cycles. For patients and clinicians, the transplant time can be flexibly arranged for FET in artificial cycles. However, further randomized controlled studies with large samples are needed.

Abbreviations

ART
assisted reproductive technology
BMI
body mass index
IVF
in vitro fertilization
ICSI
intracytoplasmic sperm injection

FSH
follicle-stimulating hormone
FET
frozen embryo transfer
hCG
human chorionic gonadotropin
GnRH
gonadotrophin-releasing hormone
SGA
small for gestational age
LGA
large for gestational age
LBW
low birth weight
OR
odds ratio
CI
confidence interval

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of The Third Affiliated Hospital of Zhengzhou University

Consent for publication

Not applicable.

Availability of data and material

All data are included in this article.

Competing interests

The authors declare that they have no competing interests.

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We did not receive any funding for this study.

Authors' contributions

GYC designed the study. DMZ and ZJW selected the population to be included and excluded. ZJW and LXM were involved in the data extraction and analysis. YXN and LJH reviewed the data. DMZ was involved in drafting this article. WXL reviewed and revised this manuscript. All authors have approved the final version of the manuscript.

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Figures

Figure 1

Flow chart of inclusion and exclusion criteria