Impact of maternal age on birthweight in frozen embryo transfer cycles: an analysis including 12565 singleton newborns

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Abstract

Background Previous studies have investigated the effect of maternal age on assisted reproductive technology (ART) success rates. However, little is known about the relationship between maternal age and neonatal birthweight in frozen embryo transfer (FET) cycles. Does maternal age have an impact on singleton birthweight in FET cycles?

Methods This retrospective study was conducted at a tertiary care centre, involving singleton live births born to women undergoing frozen-thawed embryo transfer during the period from January 2010 to December 2017. A total of 12565 women who fulfilled the inclusion criteria were enrolled and were grouped into four groups according to the maternal age: <30, 30–34, 35–39, and ≥ 40 years old. Maternal age between 30 and 34 years old was taken as a reference group. Singleton birthweight was the key outcome measure. A multivariable linear regression analysis was conducted to reveal the relationship between maternal age and neonatal birthweight with controlling for a number of potential confounders.

Results A modest decrease but no significant difference in birthweight and gestational age- and gender-adjusted birthweight (Z-scores) was observed in maternal age over 35 years old as compared with group with 30–34 years old. Further, multiple linear regression analyses indicated that maternal body mass index (BMI), embryo developmental stage at transfer, parity, number of embryos transferred, FET endometrial preparation, endometrial thickness, gestational age and newborn gender were all independent predictors of neonatal birthweight.

Conclusion Grouping with different maternal age was not associated with mean birthweight and Z-scores of singletons resulting from FET.

Background

In the past decades, many women delay childbearing until after the age of 40. The decline of fertility of elderly women forced them to seek the help of ART. According to statistics by European IVF-monitoring Consortium, the proportion of women over 40 years old pregnant through IVF/ICSI increased in Europe year by year. In the UK, for example, the proportion increased from 12.7–26% during 1997 to 2015, and the same trend was observed in other high-income countries [1, 2].

Having a healthy baby is the ultimate goal of ART treatment. Increased risk of adverse neonatal outcomes are believed to appear in *in vitro* fertilization or intracytoplasmic sperm injection (IVF/ICSI) - conceived babies, even singletons, such as preterm birth (PTB), low birthweight (LBW) and small for gestational age (SGA), when compared with peers conceived spontaneously [3]. Maternal age is a frequently-used predictor of PTB, LBW, and perinatal mortality in women who have conceived naturally [4–7], and a number of studies have well revealed the negative correlation between maternal age and neonatal outcomes [8, 9]. Women who have a baby through ART are, on average, older than women who conceive spontaneously, as these techniques are often applied in response to age-related infertility

problems [10]. However, little is known regarding the influence of maternal age on birthweight in vitrified-thawed blastocyst transfer cycles.

To our knowledge, only few studies have examined the effect of maternal age on birthweight with ART, containing different kinds of treatments without considering enough confounders [11–14]. Further, the published data, except for Lin's study [14], exclusively focused on fresh IVF cycles, without ruling out the possibility of adverse fetal growth caused by a hypoestrogenic milieu. Of note, supraphysiological estrogen levels during ovarian stimulation can create a suboptimal peri-implantation environment for implantation and placentation, thus causing abnormal fetal growth including LBW and SGA [15, 16]. Unlike fresh ovarian stimulation cycles, FET seems to provide a more physiological uterine environment for early fetal development [17]. Thus, the current study aims to explore the effect of maternal age on the birthweight of newborns conceived by blastocyst transfers during FET cycles.

Methods

Study design and patients

This retrospective study involved women who had undergone FET during the period from January 2010 to December 2017, which was performed at the Department of Assisted Reproduction of the Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine. Women who met the following inclusion criteria were involved in the study: BMI <30 kg/m², the transfer of blastocyst resulting in a live singleton birth.

The exclusion criteria were vanishing twin syndrome, congenital uterine malformations, and other diseases as determined by ultrasound or hysteroscopy. And exclude women with gestational diabetes, pregnancy-induced hypertension and preeclampsia, as these pregnancy-related factors may have bad effect on intrauterine fetal growth. Further, only the first pregnancy was retained for the women who had more than one delivery during the study period. This study was approved by the Institutional Review Board of the hospital.

Laboratory protocols

The procedures of ovarian stimulation, oocyte retrieval and IVF/ICSI have been described in previous studies [18, 19]. In brief, IVF or ICSI was conventionally carried out based on semen parameters and previous fertilization histories. For IVF, oocytes were inseminated in human tubal fluid (HTF; Irvine Scientific) with approximately 300 000 progressively motile spermatozoa, and was supplemented with 10%(v/v) serum substitute supplement (SSS; Irvine Scientific). For ICSI, oocytes were transferred into dishes immediately after microinjection with HTF+10% SSS. The assessment of fertilization was performed 16–18 h post insemination/injection. A dish containing preequilibrated culture medium was then prepared for the transfer of zygotes. In this study, blastocysts were cultured in early cleavage medium (Irvine Scientific) before Day 3 and then in multiblast medium (Irvine Scientific) before 2013. However, a continuous single culture medium (Irvine Scientific) was introduced after January 2013.

All embryos were cultured under mineral oil and grew in the incubator at 37 °C, under 5% O₂ and 6% CO₂ concentration (the balance gas was nitrogen). The assessment of embryo development was performed on Day 3, and only high-quality cleavage-stage embryos were selected for cryopreservation, which was at least six blastomeres with $\leq 20\%$ fragmentation. Except for the change of culture media types, no change was made for the other laboratory conditions and IVF protocols throughout the study period.

Endometrial preparation and vitrification

Protocols of endometrial priming for FET have been previously described [20]. Briefly, a natural cycle FET was suitable for women having regular menstrual cycles with the use of hCG for triggering ovulation. Artificial cycles were offered for women with irregular cycles according to the discretion of treating physicians. The procedure of vitrification and thawing were previously described [19]. In short, Cryotop carrier system with dimethylsulfoxide–ethylene glycol–sucrose was used as cryoprotectants for embryo vitrification. Dilution solution in a sequential manner (1 mol/L to 0.5 mol/L to 0 mol/L sucrose) was used for thawing of embryos. All embryos were thawed on the day of transfer.

Maternal age

Maternal age at the birth of the child was the key explanatory variable, which was divided into the following categories: <30, 30–34, 35–39, and ≥ 40 years old. The age group 30–34 years old was set as the reference category in our analyses, as most of the ART births were to women in this age group [13].

Outcome measures

The main neonatal outcomes was live singleton birthweight. The definition for live singleton birth was a delivery of a singleton viable infant after the 20th gestational week. Gestational age (GA) in FET cycles was calculated from the day of embryo transfer (Day 17 for cleavagestage embryo transfer) [21]. The definition for PTB and very PTB were delivery before 37 and 32 completed gestational weeks, respectively. Z-scores were calculated according to gestational age and newborn gender on birthweight based on the national birthweight reference as previously described [22,23]. Birthweight of infant was divided into the following categories: LBW (<2500 g), very LBW (<1500 g), high birthweight (HBW) (>4500 g) and normal birthweight. The neonatal parameters included birthweight percentiles also based on the national birthweight reference [23]: SGA defined as birthweight <10th percentile, very SGA defined as birthweight <3rd percentile, large for gestational age (LGA) defined as birthweight >90th percentile and very LGA defined as birthweight >97th percentile. The information of pregnancy and neonatal outcomes were obtained from electronic medical records. The missing data was perfected by contact with midwives or treating obstetricians.

Statistical analysis

One-way analysis of variance was performed for continuous data, while Pearson's chi-squared test or Fisher's exact test were applied for categorical data. A post hoc Bonferroni correction was performed for

multiple comparisons. The association between maternal age and neonatal outcomes was detected by multivariable logistic regression analysis, while the independent effect of maternal age on neonatal outcomes was analyzed by a multiple linear regression.

The multivariable analyses included the following confounders: maternal BMI, parity, infertility cause and duration, insemination method, the type of endometrial preparation, endometrial thickness, the year of treatment and newborn gender. In multivariable models, continuous covariates (maternal BMI, infertility duration, endometrial thickness and the year of treatment) and categorical covariates were indicated in Table 1. Maternal age with 30-34 years was taken as a reference group in multivariable analyses. For the development of IVF techniques over time [24], a sensitivity analysis was performed on treating the year of treatment as a categorical variable. All analyses were conducted with SPSS Statistics (version 21.0) and $P < 0.05$ was considered to be statistically significant.

Table 1 Patient treatment and demographic characteristics according to maternal age.

	<30 y n=3586	30-34 y n=5461	35-39 y n=2861	≥40 y n=657	P value
Age	27.29±1.63	31.93±1.40	36.47±1.34	41.31±1.53	<0.001 ^a
Maternal BMI (kg/m ²)	21.21±2.75	21.45±2.66	21.69±2.61	21.95±2.37	<0.001 ^a
Infertility cause					<0.001 ^b
Female	2508 (69.9)	3821 (70.0)	2001 (69.9)	449 (68.3)	
Male	504 (14.1)	653 (12.0)	284 (9.9)	64 (9.7)	
Mixed	510 (14.2)	828 (15.2)	494 (17.3)	127 (19.3)	
Unexplained	64 (1.8)	159 (2.9)	82 (2.9)	17 (2.6)	
Parity					<0.001 ^b
0	3489 (97.3)	5159 (94.5)	2478 (86.6)	471 (71.7)	
>0	97 (2.7)	302 (5.5)	383 (13.4)	186 (28.3)	
Infertility duration (years)	2.53±1.82	3.29±2.42	4.11±3.41	4.70±4.55	<0.001 ^a
FET cycle rank					<0.001 ^b
First	2332 (65.0)	3112 (57.0)	1444 (50.5)	298 (45.4)	
High order	1254 (35.0)	2349 (43.0)	1417 (49.5)	359 (54.6)	
Fertilization method					<0.001 ^b
IVF	2210 (61.6)	3425 (62.7)	1871 (65.4)	414 (63.0)	
ICSI	990 (27.6)	1407 (25.8)	762 (26.6)	225 (34.2)	
IVF+ICSI	386 (10.8)	629 (11.5)	228 (8.0)	18 (2.7)	
Number of embryos transferred					<0.001 ^b
1	555 (15.5)	985 (18.0)	569 (19.9)	145 (22.1)	
≥2	3031 (84.5)	4476 (82.0)	2292 (80.1)	512 (77.9)	
Embryo developmental stage at transfer					0.464 ^b
Day 3	3010 (83.9)	4573 (83.7)	2415 (84.4)	565 (86.0)	
Day 5/6	576 (16.1)	888 (16.3)	446 (15.6)	92 (14.0)	
FET endometrial preparation					<0.001 ^b
Natural cycle	737 (20.6)	1338 (24.5)	750 (26.2)	176 (26.8)	
Artificial cycle	2849 (79.4)	4123 (75.5)	2111 (73.8)	481 (73.2)	
Endometrial thickness (mm)					<0.001 ^b
<8	232 (6.5)	399 (7.3)	270 (9.4)	83 (12.6)	
8-11	1958 (54.6)	3067 (56.2)	1610 (56.3)	369 (56.2)	
>11	1396 (38.9)	1995 (36.5)	981 (34.3)	205 (31.2)	
Year of treatment					<0.001 ^b
2010-2012	276 (7.7)	465 (8.5)	218 (7.6)	33 (5.0)	
2013-2015	1693 (47.2)	2561 (46.9)	1219 (42.6)	250 (38.1)	
2016-2017	1617 (45.1)	2435 (44.6)	1424 (49.8)	375 (56.9)	

Data are mean $\pm$ SD or n (%).

aOne-way ANOVA.

bPearson chi-square test.

Results

The final dataset included 12565 women who fulfilled the inclusion criteria, with no loss to follow-up. Baseline demographic and cycle characteristics are presented in Table 1. Comparison between the four groups revealed significant difference for maternal BMI, infertility cause, parity, infertility duration, FET cycle rank, fertilization method, the number of embryo transferred, FET endometrial preparation, endometrial thickness and year of treatment. Embryo developmental stage at transfer did not differ significantly among maternal age categories.

Neonatal outcomes stratified by maternal age are listed in Table 2. There was no significant difference on mean birthweight and gestation-adjusted Z-scores varied significantly according to maternal age categories. The group with 30–34 years old had the highest birthweight and Z-scores (3355.8 ± 483.3 g, 0.38 ± 1.03). A modest decrease decline of birthweight was observed combined with the increased age when patients age over 30 years old, and group over 40 years old had the lowest birthweight values as 3321.6 ± 503.9 g. Additionally, no significant differences were found between any two groups by Post hoc analysis on birthweight and Z-scores. The highest proportions of LBW (4.1%) and HBW (1.2%) were found in group over 40 years old, but no difference was observed among four groups. In addition, this older group had the highest proportion on PTB (5.9%) and very PTB (0.9%), and Pearson chi-square test showed significant difference on very PTB among maternal age categories. Interestingly, the group with 35–39 years old had the highest very LBW (0.6%), while the group with 30–34 years old had the lowest SGA (2.7%). Furthermore, there was no difference in very LGA, LGA, very SGA, and newborn gender between groups.

Table 2
Neonatal outcomes of live born singletons by maternal age.

	< 30 y n = 3586	30–34 y n = 5461	35–39 y n = 2861	≥ 40 y n = 657	P value
Gestational age					
≥ 37 weeks	3367 (93.9)	5117 (93.7)	2694 (94.2)	612 (93.2)	0.254 ^b
preterm birth (< 37 weeks)	198 (5.5)	316 (5.8)	143 (5.0)	39 (5.9)	0.077 ^b
very preterm birth (< 32 weeks)	21 (0.6)	28 (0.5)	24 (0.8)	6 (0.9)	0.015 ^c
Birthweight (g)	3352.2 ± 485.7	3355.8 ± 483.3	3334.2 ± 493.6	3321.6 ± 503.9	0.711 ^a
Z-scores	0.36 ± 1.04	0.38 ± 1.03	0.35 ± 1.06	0.38 ± 1.10	0.253 ^a
Very low birthweight (< 1500 g)	12 (0.3)	19 (0.3)	17 (0.6)	2 (0.3)	0.030 ^c
Low birthweight (< 2500 g)	107 (3.0)	181 (3.3)	90 (3.1)	27 (4.1)	0.066 ^b
High birthweight (> 4500 g)	27 (0.8)	48 (0.9)	22 (0.8)	8 (1.2)	0.145 ^c
Very small for gestational age (< 3rd percentile)	48 (1.3)	83 (1.5)	35 (1.2)	9 (1.4)	0.488 ^c
Small for gestational age (< 10th percentile)	126 (3.5)	150 (2.7)	100 (3.5)	20 (3.0)	0.019 ^b
Large for gestational age (> 90th percentile)	369 (10.3)	583 (10.7)	326 (11.4)	74 (11.3)	0.203 ^b
Very large of gestational age (> 97th percentile)	258 (7.2)	354 (6.5)	183 (6.4)	46 (7.0)	0.337 ^b
Newborn gender	0.746 ^b				
Female	1881 (52.5)	2839 (52.0)	1522 (53.2)	349 (53.1)	
Male	1705 (47.5)	2622 (48.0)	1339 (46.8)	308 (46.9)	
Data are mean ± SD or n (%).					
aOne-way ANOVA.					
bPearson chi-square test.					
cFisher's exact test.					

In multivariate analyses (Table 3), the risk of PTB (< 37 weeks) was slightly increased in term singletons originating from the group with 35–39 years old as compared with those from the reference group (aOR 1.23, 95% CI: 1.00–1.51). The odds of LBW and HBW for term infants was lower in group over 40 years old as compared with the reference group, not reaching significant difference. Although the analysis of very PTB (< 32 weeks), very LBW(< 1500 g) were performed, the number of cases in the two categories was too small to make any meaningful comparisons. It was noteworthy that the risks of SGA and very LGA in term singletons of group under 30 years old was lower than the reference group (aOR 0.77, 95% CI: 0.60–0.99, aOR 0.84, 95% CI: 0.71–1.00).

Table 3
Odds Ratios for gestational age and birth weights by maternal age.

	< 30 y n = 3586	30–34 y n = 5461	35–39 y n = 2861	≥ 40 y n = 657
Gestational age between < 37 weeks				
Crude OR	1.05 (0.88–1.26)	Reference	1.16 (0.95–1.43)	0.97 (0.69–1.37)
Adjusted OR	1.01 (0.84–1.21)	Reference	1.23 (1.00–1.51)	1.07 (0.75–1.53)
Gestational age < 32 weeks				
Crude OR	0.88 (0.50–1.55)	Reference	0.61 (0.36–1.06)	0.56 (0.23–1.35)
Adjusted OR	0.88 (0.49–1.55)	Reference	0.60 (0.35–1.05)	0.52 (0.21–1.30)
Very low birthweight (< 1500 g)				
Crude OR	1.05 (0.51–2.16)	Reference	0.59 (0.30–1.13)	1.13 (0.26–4.86)
Adjusted OR	0.99 (0.48–2.06)	Reference	0.62 (0.32–1.21)	1.23 (0.28–5.48)
Low birthweight (< 2500 g)				
Crude OR	1.16 (0.88–1.42)	Reference	1.05 (0.82–1.36)	0.80 (0.53–1.21)
Adjusted OR	1.09 (0.85–1.40)	Reference	1.06 (0.82–1.38)	0.80 (0.52–1.23)
High birthweight (> 4500 g)				
Crude OR	1.17 (0.73–1.88)	Reference	1.14 (0.69–1.90)	0.71 (0.34–1.51)
Adjusted OR	1.12 (0.70–1.82)	Reference	1.21 (0.72–2.04)	0.81 (0.37–1.79)
Very small for gestational age (< 3rd percentile)				
Crude OR	1.10 (0.76–1.57)	Reference	1.20 (0.80–1.78)	1.07 (0.53–2.13)

Data are Odds Ratios (OR) with 95% confidence interval (CI). Analyses were adjusted for maternal BMI, infertility cause, parity, infertility duration, FET cycle rank, infertility cause, fertilization method, number of embryos transferred, embryo developmental stage at transfer, the type of endometrial preparation, endometrial thickness, year of treatment, and newborn sex.

	< 30 y n = 3586	30–34 y n = 5461	35–39 y n = 2861	≥ 40 y n = 657
Adjusted OR	1.11 (0.77–1.61)	Reference	1.12 (0.74–1.68)	0.91 (0.44–1.86)
Small for gestational age (< 10th percentile)				
Crude OR	0.78 (0.61–0.99)	Reference	0.78 (0.60–1.01)	0.89 (0.55–1.43)
Adjusted OR	0.77 (0.60–0.99)	Reference	0.79 (0.61–1.03)	0.92 (0.56–1.51)
Large for gestational age (> 90th percentile)				
Crude OR	1.02 (0.89–1.18)	Reference	0.92 (0.80–1.06)	0.93 (0.72–1.21)
Adjusted OR	1.00 (0.87–1.15)	Reference	0.94 (0.81–1.09)	0.96 (0.73–1.26)
Very large of gestational age (> 97th percentile)				
Crude OR	0.89 (0.76–1.06)	Reference	1.00 (0.83–1.20)	0.91 (0.66–1.26)
Adjusted OR	0.84 (0.71–1.00)	Reference	1.07 (0.88–1.29)	1.02 (0.73–1.42)
Data are Odds Ratios (OR) with 95% confidence interval (CI). Analyses were adjusted for maternal BMI, infertility cause, parity, infertility duration, FET cycle rank, infertility cause, fertilization method, number of embryos transferred, embryo developmental stage at transfer, the type of endometrial preparation, endometrial thickness, year of treatment, and newborn sex.				

Multiple linear regression analyses were conducted to assess the relationship between maternal age and birthweight (Table 4). Even after correction for a number of potential confounders, no significant correlation was found between maternal age and neonatal birthweight. Moreover, maternal BMI ($P < 0.001$), parity ($P < 0.001$), FET cycle rank ($P < 0.001$), number of embryos transferred ($P = 0.029$), embryo developmental stage at transfer ($P < 0.001$), FET endometrial preparation ($P = 0.045$), endometrial thickness (8–11 mm, $P = 0.025$; >11 mm, $P = 0.002$), year of treatment ($P < 0.001$), gestational age ($P < 0.001$) and newborn gender ($P < 0.001$) were all independent predictors for birthweight.

Table 4
Results of multiple regression analysis of singleton birthweight.

	Unstandardised coefficients		Standardised coefficients	t	P value
	B	Std. error	Beta		
(Constant)	-3887.276	100.441		-38.702	< 0.001
Maternal age					
< 30	-1.444	8.734	-0.001	-0.165	0.869
30–34 (Reference)					
35–39	-5.811	9.443	-0.005	-0.615	0.538
≥ 40	1.148	17.128	0.001	0.067	0.947
Maternal BMI (kg/m2)	25.116	1.358	0.137	18.498	< 0.001
Parity, high order (versus 0)	61.981	13.873	0.034	4.468	< 0.001
Infertility duration (years)	0.950	1.357	0.005	0.700	0.484
FET cycle rank, High order (versus First)	26.077	7.482	0.026	3.485	< 0.001
Infertility cause					
Female (reference)					
Male	-11.298	12.933	-0.008	-0.874	0.382
Mixed	-8.553	10.717	-0.006	-0.798	0.425
Unexplained	9.061	23.193	0.003	0.391	0.696
Fertilization method					
IVF (reference)					
ICSI	-16.795	9.827	-0.015	-1.709	0.087
VF + ICSI	1.821	12.534	0.001	.145	0.885
Number of embryos transferred, ≥ 2 (versus 1)	22.917	10.495	0.018	2.184	0.029
Embryo developmental stage at transfer, Day 5/6 (versus Day 3)	72.513	11.102	0.054	6.532	< 0.001

	Unstandardised coefficients		Standardised coefficients	t	P value
FET endometrial preparation, Artificial cycle (versus Natural cycle)	-17.009	8.471	-0.015	-2.008	0.045
Endometrial thickness (mm)					
< 8 (reference)					
8–11	30.651	13.712	0.031	2.235	0.025
> 11	44.592	14.187	0.044	3.143	0.002
Year of treatment					
2010–2012 (reference)					
2013–2015	-62.026	13.895	-0.063	-4.464	< 0.001
2016–2017	-78.956	14.033	-0.081	-5.626	< 0.001
Gestational age (week)	179.131	2.422	0.549	73.970	< 0.001
Newborn gender, female (versus male)	-137.087	7.179	-0.140	-19.097	< 0.001

Discussion

Recent years, much attention has been paid to the impact of maternal age on ART success rates, and several studies have revealed that a high maternal age (over 40 years old) has a negative effect on pregnancy outcomes [11, 13]. However, our study showed that no significant association existed between maternal age and neonatal birthweight. Furthermore, linear regression indicated that maternal age was not an independent predictor of birthweight.

Four studies, as we know, have been interested in the potential relationship between maternal age and neonatal birthweight. Wennberg *et al.* investigated maternal age influencing adverse maternal and neonatal outcomes following ART treatment, suggesting that the risk of LBW and very LBW was significantly higher in ART than in spontaneous conception (SC) singletons in all ages up to maternal age 40 years (LBW: aORs 1.44–2.35; VLBW: aORs 1.67–3.44). Additionally, when the analysis was restricted to maternal age > 35 years, an increased risk of LBW existed for SC pregnancies, but not for ART pregnancies [11]. Secondly, Moaddab *et al.* found that maternal age did not predict newborns' birthweight in pregnancies with maternal age grouping as < 40, 40–44, 45–49, ≥ 50 years old [12]. However, maternal age grouping < 40 years old per se have an inadequate analysis on birthweight and miss important information. Many studies have set up more detailed groups with maternal age under 40 years old to

assess the influence of maternal age on neonatal outcomes and gained the more credible results [13, 14]. Another study reported that the risk of LBW was increased only at maternal ages over 40 years old (6 percentage points, 95% CI: 0.2, 12) with medically assisted reproduction (MAR) [13]. However, a limited number of confounders were included in the study, and the effect of different kinds of MAR treatments could not be reliably distinguished, which included less invasive treatments that were less strongly associated with adverse birth outcomes [25]. A recent study based on 4,958 infertile women using a freeze-all strategy observed that maternal age grouping was not related with increased risks of LBW, very LBW, preterm LBW and macrosomia [14]. Yet it only focused on women undergoing their first embryo transfer cycle and ignored the differences in fetus number, and endometrial preparation methods between groups.

Our study aimed to improve on the flaws of abovementioned studies, and focused on the exact role of maternal age in the neonatal birthweight. The current study based on more than 12500 singleton newborns born after FET cycles, demonstrated that maternal age itself had no impact on singleton birthweight. The reason why no significant correlation existed between maternal age and birthweight in our study is likely complex. It is generally known that with aging comes a reduction in ovarian function, resulting in the decrease of ovarian response to ovulation promoting drugs and the low number of oocytes retrieved [26]. Additionally, the decreased quality of oocytes [27, 28], abnormal endometrial function and degeneration of multiple organs function will appear in women with advanced maternal age [22, 29]. All the above mentioned factors would affect the development of embryo and cause adverse effects on the newborn, leading to LBW. However, with the popularization of education, many women tend to choose late marriage and late childbearing and enjoy a simple single life before marriage. In this kind of life, they are less stressed and have more opportunities to get in touch with life freedom than the women who are married and have children. Meanwhile, these knowledge women have better living habits, physical quality and economic conditions, thus having a better choice on ART treatment [11]. Aging leads to an irreversible decline in fertility, forcing older women to pay more attention on pregnancy and to seek medical help more actively than the young. In addition, the spouse's income also increase with age to guarantee maternity. Most importantly, the development of ART has well fulfilled the reproductive needs of women with different ages to improve the quality of newborns.

In this study, results from multiple linear regression analysis indicated that maternal BMI, embryo developmental stage at transfer, parity, number of embryos transferred, FET endometrial preparation, endometrial thickness, gestational age and newborn gender, were the independent predictors for neonatal birthweight, which was consistent with previous results [22, 30, 31]. Z-scores were calculated and compared across the four groups in order to reduce bias caused by newborn gender and gestational age, and no significant difference on Z-scores was found among different maternal age groups. In addition, there were significant differences between the maternal age groups in baseline and cycle characteristics including infertility duration, infertility cause and fertilization method. However, these confounders had no impact on neonatal birthweight based on the linear regression model.

There are limitations in our study. The biggest one is its retrospective design, so we strictly checked the database with strict criteria. Secondly, due to personal privacy restrictions, we were unable to obtain the education and economic background of patients. However, The large number of singleton live births from a single centre can assure the practice consistency, which is the main strength of the current study. Additionally, aside from the change of culture medium types, all other laboratory conditions and protocols remained invariant throughout the study period. Further, maternal age was recorded according to the identification card, and endometrial thickness was measured by the same trained sonographers, reducing the recorder variability. Importantly, a number of potential confounders were included in our study, which may minimize their impact on the findings.

Conclusions

This study expands the current knowledge about association between maternal age and IVF/ICSI outcomes, especially indicated that maternal age was not associated with mean birthweight and Z-scores. This important finding should be adequately applied for women over 40 years old prior to FET and strengthen their confidence. A large prospective study, of course, are needed to verify our findings in future.

Abbreviations

ART assisted reproductive technology

FET frozen embryo transfer

BMI body mass index

IVF in vitro fertilization

ICSI intracytoplasmic sperm injection

PTB preterm birth

LBW low birthweight

SGA small for gestational age

GA gestational age

HBW high birthweight

LGA large for gestational age

OR odds ratios

CI confidence interval

SC spontaneous conception

MAR medically assisted reproduction

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine. Trial registration number was not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine, but restrictions apply to the availability of these data, which were used under guidelines for the current study, and so are not publicly available.

Competing Interest

The authors have no conflicts of interest to declare.

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Authors' contributions

C.Q.Y and Y.P.K. conceived and designed this study. Z.X.N. and S.S. contributed to data acquisition, analysis and interpretation and drafted the manuscript. W.C., J.Y., D.Z, D.Y.Z., and Z.L.C. were responsible for the collection of data. All authors interpreted the data.

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