RBMO

ARTICLE

A propensity-matched study of the association between pre-pregnancy maternal underweight and perinatal outcomes of singletons conceived through assisted reproductive technology

BIOGRAPHY

Dr Pengfei Qu is Assistant Researcher at Northwest Women's and Children's Hospital, Xi'an City, China. He received his PhD in epidemiology in 2017 from Xi'an Jiaotong University. His areas of research activity include growth and development of infants and children and public health for women and children.

Pengfei Qu[1,2], Fangfang Liu[3], Doudou Zhao[1,2], Yongbo Wang[1], Min Wang[1], Linyu Wang[1,2], Shaonong Dang[4], Duolao Wang[5], Juanzi Shi[1,2,*], Wenhao Shi[1,2,*]

KEY MESSAGE

A retrospective analysis of 6538 women undergoing assisted reproduction technology and their singleton live births. Propensity score matching analysis showed that pre-pregnancy maternal underweight was associated with lower birth weight and increased low birth weight and small for gestational age risks in singletons.

ABSTRACT

Research question: Is pre-pregnancy maternal underweight associated with perinatal outcomes of singletons who were conceived through assisted reproductive technology (ART)?

Design: A 10-year (2006–2015) Chinese sample of 6538 women and their singleton infants who were conceived through ART was used to examine the association between pre-pregnancy maternal underweight and perinatal outcomes. Propensity scores for underweight were calculated for each participant using multivariable logistic regression, which was used to match 740 (91.36% of 810) underweight women with 740 normal weight women; the effects of underweight on birth weight and gestational age were then assessed by generalized estimating equation model.

Results: After propensity score matching, the birth weight was lower (difference –136.83 g, 95% CI –184.11 to –89.55 g) in the underweight group than in the normal weight group. The risks of low birth weight (LBW) and small for gestational age (SGA) were increased in the underweight group compared with those in the normal weight group (LBW: RR 1.64, 95% CI 1.01 to 2.67; SGA: RR 1.46, 95% CI 1.06 to 2.02). The risks of fetal macrosomia and being large for gestational age (LGA) were decreased in the underweight group compared with those in the normal weight group (macrosomia: RR 0.39, 95% CI 0.26 to 0.61; LGA: RR 0.36, 95% CI 0.24 to 0.53). The associations between underweight, gestational age and preterm birth were not statistically significant.

Conclusions: Among women undergoing ART, pre-pregnancy maternal underweight was associated with lower birth weight, increased LBW and SGA risks, and decreased fetal macrosomia and LGA risks in singleton infants.

[1] Assisted Reproduction Center, Northwest Women's and Children's Hospital of Xi'an Jiaotong University Health Science Center, No.73 Houzaimen, Xi'an Shaanxi 710003, People's Republic of China
[2] Translational Medicine Center, Northwest Women's and Children's Hospital of Xi'an Jiaotong University Health Science Center, No.1616 Yanxiang Road, Xi'an Shaanxi 710061, People's Republic of China
[3] Department of stomatology, Xi'an Central Hospital, No.161 Xiwu Road, Xi'an Shaanxi 710003, People's Republic of China
[4] Department of Epidemiology and Health Statistics, School of Public Health, Xi'an Jiaotong University Health Science Center, No.76 Yanta West Road, Xi'an Shaanxi 710061, People's Republic of China
[5] Department of Clinical Sciences, Liverpool School of Tropical Medicine Pembroke Place, Liverpool, UK

KEYWORDS
Assisted reproductive technology
Low birth weight
Preterm birth
Propensity score matching
Underweight

*Corresponding authors. E-mail addresses: shijuanzi123@126.com (J Shi), swihao@126.com (W Shi). https://doi.org/10.1016/j.rbmo.2019.06.007 1472-6483/
Declaration: The authors report no financial or commercial conflicts of interest.

INTRODUCTION

Over the past 40 years, assisted reproductive technology (ART), such as IVF and intracytoplasmic sperm injection (ICSI), has become a widespread option for the treatment of infertile couples around the world. It is estimated that ART has contributed to the birth of over 5 million liveborn babies worldwide, and the proportion of infants who are born in China as a result of ART is greater than 1% (*Yang et al., 2014; Adamson et al., 2018*). Although ART helps millions of infertile couples to achieve pregnancy, it is associated with potential health risks for mothers and infants. Previous research has shown that infants who are conceived through ART have an increased risk of adverse pregnancy outcomes, such as low birth weight (LBW), preterm birth (PTB) and congenital malformations, compared with infants conceived spontaneously (*McDonald et al., 2009; Dunietz et al., 2015; Cavoretto et al., 2018; Jancar et al., 2018; Zheng et al., 2018*).

The nutritional status of a woman before and during pregnancy is important for a healthy pregnancy outcome (*Gondwe et al., 2018*). Maternal underweight in early pregnancy, which is common in China and even in Asia, is a leading risk factor for adverse birth outcomes, including LBW, PTB, small for gestational age (SGA) and stillbirth (*Siega-Riz et al., 1993; Abrams et al., 1995; Li et al., 2015*). *Liu et al. (2016)* systematically reviewed and collected 60 studies, of which 1,392,799 women were included and the proportion of underweight pregnant women was 8.18%; the investigators found that mothers who were underweight had a higher risk of PTB (OR 1.30, 95% CI 1.13 to 1.49) and delivering an infant that was SGA (OR 1.67, 95% CI 1.49 to 1.87) and LBW (OR 1.67, 95% CI 1.39 to 2.02). The studies of the relationship between maternal underweight before pregnancy and fetal growth with ART treatment, however, are limited (*Singh et al., 2012; Cai et al., 2017*). The aim of the present study was to reveal the effect of pre-pregnancy maternal underweight on birth weight and gestational age among infants who were conceived through ART. Data collected over a period of 10 years included ART treatments and perinatal outcomes. Birth weight and gestational age in the underweight group and normal weight group were compared in a single ART centre in Northwest China.

MATERIALS AND METHODS

Study design and population

This was a retrospective cohort study of all women who had a singleton birth resulting from an embryo transfer between January 2006 and March 2015 at the Assisted Reproduction Center of Northwest Women's and Children's Hospital, Xi'an, Northwestern China. Data were extracted from clinical records. In this time frame, a total of 12,572 infants were born as a result of IVF/ICSI treatment. The following were excluded from the study: multiple births (n = 3577), mothers with body mass index (BMI) of 24 kg/m^2 or over (1965), mothers with a missing BMI (n = 143) and mothers with missing covariates in singleton pregnancy (n = 349), leaving a total 6538 mothers who had undergone ART with their singleton infants in this study. Of these, 810 mothers were underweight and 5728 were normal weight (FIGURE 1).

In the Shaanxi province of China, it is a requirement that all ART birth outcomes, including birth weight and gestational age, are reported to the Shaanxi Assisted Reproduction Database. Demographic data that were collected from the Assisted Reproduction Center of Northwest Women's and Children's Hospital included year of transfer, maternal age, BMI, gravidity, parity, smoking history, cause of infertility, sperm donation, ovarian stimulation protocol, fertilization method, assisted hatching, basal serum FSH level, antral follicle count, endometrial thickness, fresh or frozen–thaw embryo transfer, blastocyst or cleavage-stage transfer, number of embryos transferred, number of gestational sacs by ultrasonographic visualization and infant's sex as assessed and collected by the patient's treating clinician.

Body mass index assessment

Nurses measured and recorded the weight and height of all women after the initial consultation. The BMI was calculated as kg/m^2. All 6538 women were separated into two groups based on the classification and evaluation criteria of weight for Chinese adults (*National Health and Family Planning Commission of the People's Republic of China, 2011*) as follows: underweight group (low BMI group): BMI <18.5 kg/m^2; and normal weight group (normal BMI group): 18.5 kg/m^2 ≤ BMI <24.00 kg/m^2.

Definitions of perinatal outcomes

The primary outcomes were birth weight and gestational age. Low birth weight is defined as birth weight less than 2500 g; fetal macrosomia is defined as birth weight 4000 g or over; The sex- and gestational age-adjusted birth weight Z score and birth weight centile was calculated according to international standards developed by the International Fetal and Newborn Growth Consortium for the 21st Century (*Villar et al., 2014*). Gestational age was calculated by the number of days from the day of transfer to birth plus the age of the embryo, and an additional 14 days according the formula suggested by American College of Obstetricians and Gynecologists (ACOG) (*ACOG, 2017*). Full term is defined as 37–42 complete weeks of gestational age; PTB is defined as born before 37 weeks of gestational age; SGA is defined as birth weight below the 10th percentile for gestational age; large for gestational age (LGA) is defined as birth weight above the 90th percentile for that gestational age; and appropriate for gestational age (AGA) is defined as a birth weight between the 10th and 90th percentile for that gestational age.

Confounding variables

Potential correlated factors of perinatal outcomes, such as patient baseline demographical characteristics, clinical characteristics and treatment procedure, were also collected for the study participants, including year of transfer, maternal age, gravidity, parity, maternal smoking history, cause of infertility, sperm donation, ovarian stimulation protocol, fertilization method, assisted hatching, basal serum FSH, antral follicle count, endometrial thickness, frozen or fresh embryo transfer, cleavage stage or blastocyst transfer, number of embryos transferred, and number of gestational sacs by ultrasonographic visualization and infant's sex.

Ethical approval

The Human Research Ethics Committee of the Northwest Women's

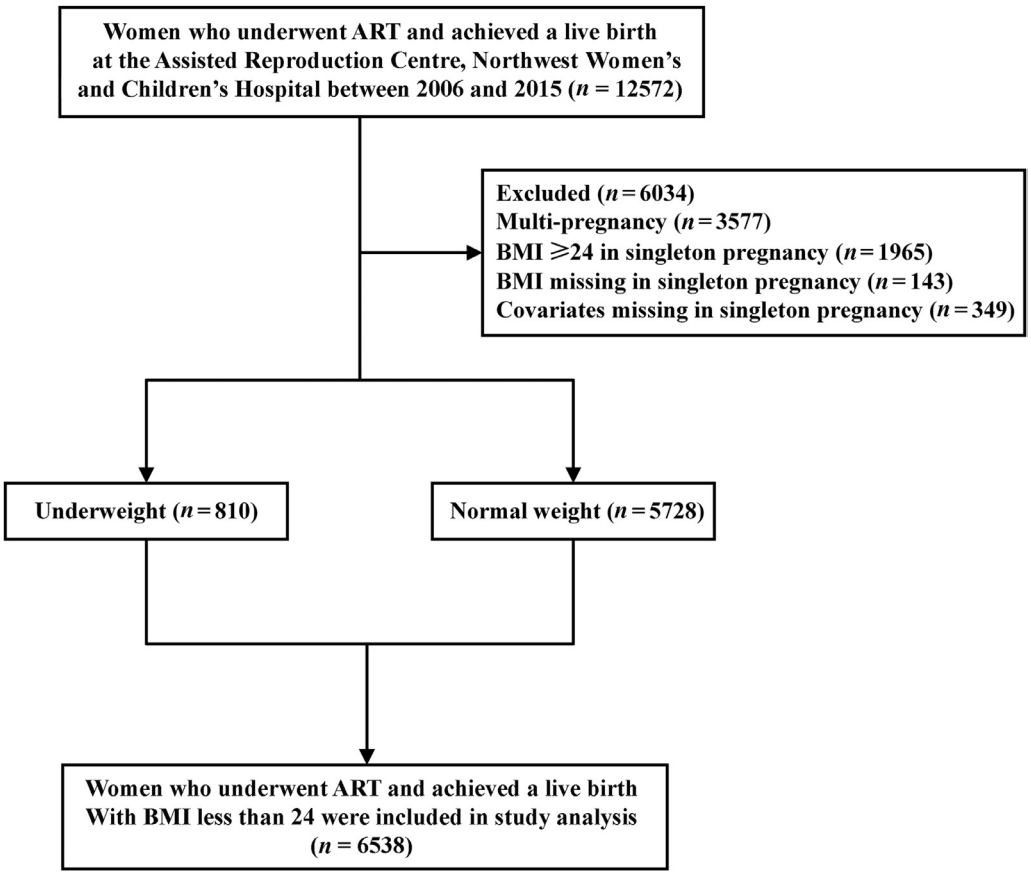

FIGURE 1 Sampling strategy with exclusion criteria. ART, assisted reproductive technology; BMI, body mass index.

and Children's Hospital approved this study in January 2018 (Grant number: 2018002). The ethics committee that approved this study waived the need to obtain informed consent. All research was conducted in accordance with the relevant guidelines and regulations.

Statistical analysis

A total of 6538 participants were categorized into either an underweight group or a normal weight group. Of the 6538 participants, 810 (12.39%) participants were underweight. Next, the propensity score of each participant was estimated using a multivariable logistic regression model, in which the BMI group was modelled using all of the baseline participant characteristics in TABLE 1. Then, the nearest neighbour within caliper was used to match each participant in the underweight with one in the normal weight group, thus matching 740 (12.92%) participants with low BMI to 740 participants with normal BMI with similar estimated propensity score (*Ahmed et al., 2006*). In our matching algorithm, each participant in the underweight group was matched with a participant in the normal weight group who had a propensity score that was similar to five decimal places. The nearest neighbour within caliper matching function is as follows:

$$C(P_i) = \min_j \left\| P_i - P_j \right\|, \quad j \in I_0$$
$$\left\| P_i - P_j \right\| < \varepsilon, \quad j \in I_o$$

P_i : propensity score of the underweight group; P_j : propensity score of the normal weight group; I_0: the set of normal weight group; $C(P_i)$: the matching normal weight participant for the underweight participant; ε: tolerance for matching (caliper).

The pre-match mean propensity score for each underweight and normal weight participant was 0.139607 and 0.121428, respectively (absolute standardized difference 55.41%; t-test $P < 0.001$). After matching, the mean propensity scores for the underweight and normal weight participants were 0.132429 and 0.132435, respectively (absolute standardized difference 0.02%; t-test $P = 0.998$). Pearson chi-squared and Student's test were used to compare the baseline characteristics of the underweight versus normal weight participants before and after matching. Wilcoxon rank test and Fisher's exact test were used if the assumptions for Student's test and Pearson chi-squared were violated. For a continuous covariate, the absolute standardized difference is defined as:

$$d = \frac{\left(\overline{x}_{treatment} - \overline{x}_{control}\right)}{\sqrt{\frac{s^2_{treatment} + s^2_{control}}{2}}}$$

where $\overline{x}_{treatment}$ and $\overline{x}_{control}$ denote the sample mean of the covariate in underweight and normal weight subjects, respectively, whereas $s^2_{treatment}$ and $s^2_{control}$ denote the sample variance of the covariates in underweight and normal weight

TABLE 1 BASELINE CHARACTERISTICS OF PARTICIPANTS BY BODY MASS INDEX BEFORE AND AFTER PROPENSITY SCORE MATCHING

	Before propensity score match			*After propensity score match*		
	Underweight group (n = 810)	***Normal weight group (n = 5728)***	***P-value***	***Underweight group (n = 740)***	***Normal weight group (n = 740)***	***P-value***
Year of transfer, *n* (%)						
2006–2009	86 (10.62)	455 (7.94)		79 (10.68)	76 (10.27)	
2010–2012	197 (24.32)	1527 (26.67)	0.022	185 (25.00)	215 (29.05)	NS
2013–2015	527 (65.06)	3746 (65.40)		476 (64.32)	449 (60.68)	
Maternal age (year), mean ± SD	28.61 ± 3.63	29.79 ± 4.00	<0.001[a]	28.91 ± 3.56	28.96 ± 3.60	NS
Gravidity, *n* (%)						
0	537 (66.30)	3290 (57.44)		478 (64.59)	490 (66.22)	
1–2	232 (28.64)	1991 (34.76)	<0.001	222 (30.00)	222 (30.00)	NS
≥3	41 (5.06)	447 (7.80)		40 (5.41)	28 (3.78)	
Parity						
0	770 (95.06)	5224 (91.20)	<0.001	700 (94.59)	710 (95.95)	NS
≥1	40 (4.94)	504 (8.80)		40 (5.41)	30 (4.05)	
Maternal smoking history, *n* (%)	2 (0.25)	18 (0.31)	NS	2 (0.27)	2 (0.27)	NS [b]
Male infertility, *n* (%)	328 (40.49)	1994 (34.81)	0.002	287 (38.78)	281 (37.97)	NS
Female infertility, *n* (%)						
No	318 (39.26)	1948 (34.01)	0.001	282 (38.11)	274 (37.03)	NS
Tubal factor	341 (42.10)	2781 (48.55)		325 (43.92)	325 (43.92)	
PCOS	22 (2.72)	209 (3.65)		21 (2.84)	21 (2.84)	
Other reasons	129 (15.93)	790 (13.79)		112 (15.14)	120 (16.22)	
Sperm donation, *n* (%)	87 (10.74)	391 (6.83)	<0.001	55 (7.43)	58 (7.84)	NS
Ovarian stimulation, *n* (%)	458 (56.54)	3353 (58.54)	NS	428 (57.84)	414 (55.95)	NS
Fertilization method, *n* (%)						
ICSI	248 (30.62)	1551 (27.08)		224 (30.27)	234 (31.62)	
IVF	549 (67.78)	4042 (70.57)	NS	504 (68.11)	485 (65.54)	NS
IVF + ICSI	13 (1.60)	135 (2.36)		12 (1.62)	21 (2.84)	
Assisted hatching	224 (27.65)	1580 (27.58)	NS	204 (27.57)	216 (29.19)	NS
Basal serum FSH level (U/l), mean ± SD	7.23 ± 2.12	6.86 ± 2.55	<0.001	7.12 ± 1.98	6.95 ± 2.15	NS
Antral follicle count, mean ± SD	12.82 ± 4.96	12.86 ± 5.29	NS [a]	12.89 ± 4.97	12.99 ± 5.35	NS
Endometrial thickness (mm), mean ± SD	10.69 ± 2.13	10.74 ± 2.04	NS	10.71 ± 2.14	10.62 ± 2.05	NS
Timing of embryo transfer, *n* (%)						
Fresh embryo transfer, *n* (%)	460 (56.79)	3359 (58.64)	NS	428 (57.84)	414 (55.95)	NS
Frozen embryo transfer, *n* (%)	350 (43.21)	2369 (41.36)		312 (42.16)	326 (44.05)	
Day 3 or 5, *n* (%)						
Cleavage stage transfer	515 (63.58)	3676 (64.18)	NS	476 (64.32)	479 (64.73)	NS
Blastocyst transfer	295 (36.42)	2052 (35.82)		264 (35.68)	261 (35.27)	
Embryos transferred, *n* (%)						
1	186 (22.96)	1209 (21.11)		167 (22.57)	149 (20.14)	
2	567 (70.00)	4105 (71.67)	NS	516 (69.73)	533 (72.03)	NS
≥3	57 (7.04)	414 (7.23)		57 (7.70)	58 (7.84)	
Gestational sacs by ultrasonographic visualization, *n* (%)						
1	722 (89.14)	5211 (90.97)		670 (90.54)	665 (89.86)	
2	85 (10.49)	505 (8.82)	NS [b]	68 (9.19)	70 (9.46)	NS [b]
≥3	3 (0.37)	12 (0.21)		2 (0.27)	5 (0.68)	
Male infant's sex, *n* (%)	421 (51.98)	2980 (52.03)	NS	389 (52.57)	404 (54.59)	NS

[a] Wilcoxon rank test.

[b] Fisher exact test.

ICSI, intracytoplasmic sperm injection; PCOS, polycystic ovary syndrome.

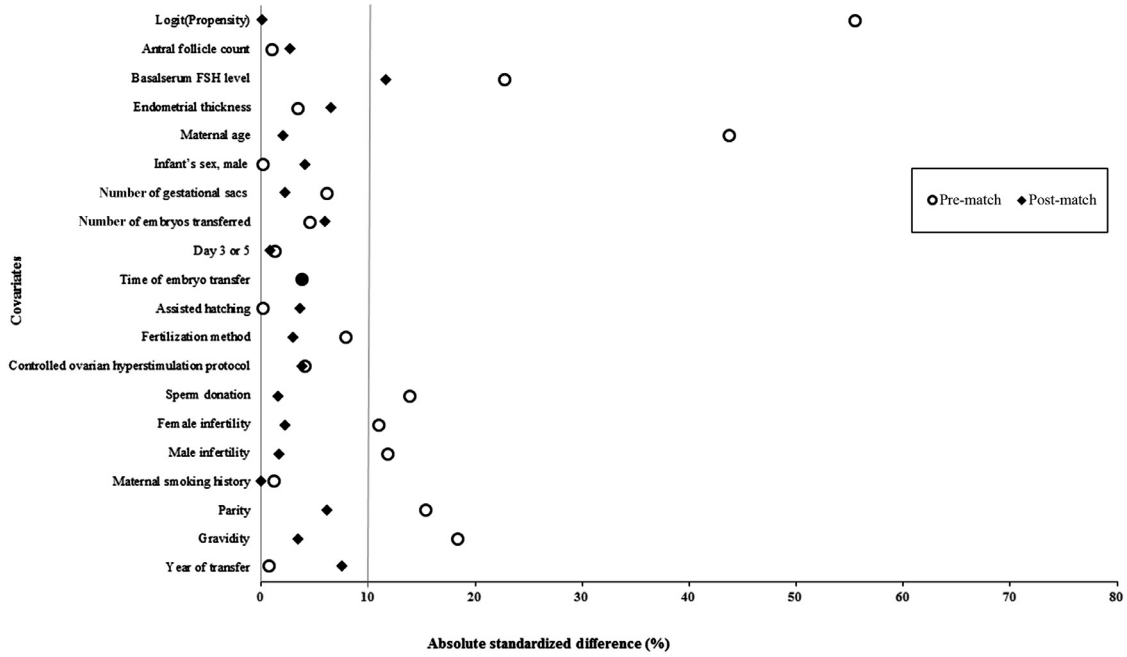

FIGURE 2 Absolute standardized differences before and after propensity score matching.

subjects, respectively. For dichotomous variables, the standardized difference is defined as:

$$d = \frac{\left(\hat{p}_{treatment} - \hat{p}_{control}\right)}{\sqrt{\frac{\hat{p}_{treatment}\left(1-\hat{p}_{treatment}\right) + \hat{p}_{control}\left(1-\hat{p}_{control}\right)}{2}}}$$

where $\hat{p}_{treatment}$ and $\hat{p}_{control}$ denote the prevalence or mean of the dichotomous variable in underweight and normal weight subjects, respectively (*Austin et al., 2011*).

Crude mean differences and 95% confidence intervals were estimated for birth weight and gestational age in a generalized estimating equation (GEE) model 1, with the BMI group as the only predictor, the matching number as the cluster effect, a normal distribution, and adjusted for the set of covariates in model 2. Relative risks and 95% confidence intervals were also estimated for LBW, PTB, SGA and LGA in model 1 and adjusted for the set of covariates in model 2 using GEE binomial regression models with log link.

A sensitivity analyses was conducted using two approaches to assess the robustness of our findings on the effects of underweight on birth outcomes to changes in the analytic approach. To address concerns about incomplete matching, data from all 6538 participants were analysed using generalized linear model adjustment for all baseline covariates, and subclassification based on tertiles of propensity score. To assess for potential heterogeneity of a BMI effect on birth weight, gestational age and SGA, the effects of underweight was estimated in several subgroups, using the pre-match cohort of 6538 patients. The effect of underweight in each of the subgroups was then estimated using generalized linear model adjustment for all baseline covariates. STATA version 12.0 software (STATA Corporation, College Station, TX, USA) was used for analyses. The level of significance was set at $P < 0.05$.

RESULTS

Participant characteristics

The mean (±SD) age of the 1480 women matched by propensity score was 28.90 (±3.58) years, 925 (62.50%) underwent embryo transfer between 2013 and 2015, and 989 (66.82%) received IVF treatment. The baseline characteristics of the participants by BMI before and after propensity score matching are presented in TABLE 1. Before matching, the underweight women were younger. They were more likely to have higher basal serum FSH level, sperm donation and male infertility. Underweight women were also more likely to have less gravidity, parity and female infertility.

After matching, underweight and normal weight women were similar in all of the 19 baseline covariates (TABLE 1 and FIGURE 2). Our propensity score matching reduced the standardized differences for all the observed covariates to below 10% in absolute value except basal serum FSH level, demonstrating a substantial improvement in the covariate balance across the BMI groups (FIGURE 2).

Underweight and birth weight

After propensity score matching, birth weight, birth weight Z score and birth weight centiles were lower in the underweight group compared with that of the normal weight group (birth weight mean difference –136.83 g, 95% CI –184.11 to –89.55 g, $P < 0.001$; birth weight Z score: mean difference –0.30, 95% CI –0.39 to –0.20, $P < 0.001$; birth weight centiles: mean difference –8.41, 95% CI –11.21 to – 5.62, $P < 0.001$) (TABLE 2). Higher risk of LBW (birth weight <2500 g) was observed in the underweight group compared with those of the normal weight group (LBW: RR 1.64, 95% CI 1.01 to 2.67, $P = 0.046$). Lower risk of fetal macrosomia (birth weight ≥4000 g) was observed in the underweight group compared with the normal weight group (fetal macrosomia: RR 0.39, 95% CI 0.26 to 0.61, $P < 0.001$). These associations remained essentially unchanged after adjustment for baseline covariates (TABLE 2).

TABLE 2 EFFECTS OF UNDERWEIGHT ON BIRTH OUTCOMES: RESULTS FROM GENERALIZED ESTIMATING EQUATION MODEL ANALYSIS

Birth outcomes	*Infants, n (%)*	*Mean ± SD*	*Model 1*[a]		*Model 2*[b]	
			Difference or relative risk (95% CI)	*P-value*	*Adjusted difference or relative risk (95% CI)*	*P-value*
Birth weight						
Birth weight (g)						
Normal weight	—	3317.24 ± 482.86	Ref		Ref	
Underweight	—	3180.64 ± 445.43	−136.83 (−184.11 to −89.55)	<0.001	−136.83 (−184.11 to −89.55)	<0.001
Birth weight Z scores						
Normal weight	—	0.28 ± 0.99	Ref		Ref	
Underweight	—	-0.01 ± 0.89	−0.30 (−0.39 to −0.20)	<0.001	−0.30 (−0.39 to −0.20)	<0.001
Birth weight centile						
Normal weight	—	58.15 ± 28.00	Ref		Ref	
Underweight	—	49.73 ± 26.90	−8.41 (−11.21 to −5.62)	<0.001	−8.41 (−11.20 to −5.62)	<0.001
Birth weight <2500 g						
Normal weight	25 (3.38)	—	Ref		Ref	
Underweight	41 (5.54)	—	1.64 (1.01 to 2.67)	0.046	1.64 (1.01 to 2.67)	0.047
Birth weight = 2500–3999 g						
Normal weight	647 (87.43)	—	Ref		Ref	
Underweight	672 (90.81)	—	1.04 (1.00 to 1.08)	0.037	1.04 (1.00 to 1.08)	0.037
Birth weight ≥4000 g						
Normal weight	68 (9.19)	—	Ref		Ref	
Underweight	27 (3.65)	—	0.39 (0.26 to 0.61)	<0.001	0.40 (0.26 to 0.61)	<0.001
Gestational age						
Gestational age (week)						
Normal weight	—	39.10 ± 1.42	Ref		Ref	
Underweight	—	39.08 ± 1.59	−0.02 (−0.18 to 0.13)	NS	−0.02 (−0.17 to 0.13)	NS
Gestational age <37 weeks						
Normal weight	48 (6.49)	—	Ref		Ref	
Underweight	49 (6.62)	—	1.02 (0.69 to 1.50)	NS	1.02 (0.70 to 1.50)	NS
Gestational age 37–42 weeks						
Normal weight	691 (93.38)	—	Ref		Ref	
Underweight	690 (93.24)	—	0.99 (0.97 to 1.03)	NS	0.99 (0.97 to 1.03)	NS
Gestational age >40 weeks						
Normal weight	165 (22.30)	—	Ref		Ref	
Underweight	158 (21.35)	—	0.96 (0.79 to 1.16)	NS	0.96 (0.79 to 1.16)	NS
Gestational age >41 weeks						
Normal weight	28 (3.79)	—	Ref		Ref	
Underweight	23 (3.11)	—	0.82 (0.48 to 1.42)	NS	0.82 (0.48 to 1.41)	NS
SGA, AGA and LGA						
SGA						
Normal weight	56 (7.57)	—	Ref		Ref	
Underweight	82 (11.08)	—	1.46 (1.06 to 2.02)	0.021	1.46 (1.06 to 2.02)	0.021
AGA						
Normal weight	597 (80.68)	—	Ref		Ref	
Underweight	627 (84.73)	—	1.05 (1.00 to 1.10)	0.040	1.05 (1.01 to 1.10)	0.040

(continued on next page)

Table 2 – (continued)

Birth outcomes	Infants, n (%)	Mean ± SD	Model 1[a]		Model 2[b]	
			Difference or relative risk (95% CI)	P-value	Adjusted difference or relative risk (95% CI)	P-value
LGA						
Normal weight	87 (11.76)	—	Ref		Ref	
Underweight	31 (4.19)	—	0.36 (0.24 to 0.53)	<0.001	0.36 (0.24 to 0.53)	<0.001

[a] Model 1 included only the study variable.

[b] Model 2 adjusted for all of the baseline covariates (year of transfer, maternal age, gravidity, parity, maternal smoking history, cause of infertility, sperm donation, ovarian stimulation protocol, fertilization method, assisted hatching, basal serum FSH, antral follicle count, endometrial thickness, frozen or fresh embryo transfer, cleavage stage or blastocyst transfer, number of embryos transferred, number of gestational sacs by ultrasonographic visualization and infant's sex).

AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

Underweight and gestational age

After propensity score matching, no significant difference was found in gestational age between the underweight group and the normal weight group (difference = –0.02 weeks, 95% CI –0.18 to 0.13 weeks) (TABLE 2). Compared with the normal weight group, the risk of PTB (<37 weeks) in the underweight group showed no significant increase (RR 1.02, 95% CI 0.69 to 1.50). Compared with the normal underweight group, the risks of gestational age between 37 weeks and 42 weeks, gestational age over 40 weeks and gestational age over 41 weeks also showed no significant increases in the underweight group. These associations remained essentially unchanged after adjustment for baseline covariates (TABLE 2).

Underweight and SGA, AGA and LGA

After propensity score matching, higher risks of SGA and AGA were observed in the underweight group compared with the normal weight group (SGA: RR 1.46, 95% CI 1.06 to 2.02, $P = 0.021$; AGA: RR 1.05, 95% CI 1.00 to 1.10, $P = 0.040$). In addition, a lower risk of LGA was observed in the underweight group compared with the normal weight group (RR 0.36, 95% CI 0.24 to 0.53, $P < 0.001$). These associations remained essentially unchanged after adjustment for baseline covariates (TABLE 2).

Sensitivity analyses

In the full (pre-matched) cohort ($n = 6538$), compared with the mean (3292.45 g) birth weight of the normal weight group, the mean birth weight was 3177.64 g in the underweight group, and this association was significant when adjusted for all baseline covariates (adjusted difference –114.28, 95% CI –151.26 to –77.30 g, $P < 0.001$). Compared with 7.86%, SGA in the normal weight group, 10.99% of infants were SGA in the underweight group, and this association was significant when adjusted for all baseline covariates (RR 1.43, 95% CI 1.15 to 1.78, $P = 0.001$). Compared with the mean gestational age (39.03 weeks) in the normal weight group, mean gestational age was 39.06 weeks in the underweight group, and this association was not significant when adjusted for all baseline covariates (adjusted difference –0.01 week, 95% CI –0.14 to 0.11 week).

Among the participants in propensity score tertiles two and three ($n = 4280$), similar associations were observed between being underweight and birth weight, gestational age and SGA when all baseline covariates were adjusted (birth weight: adjusted difference –115.59 g, 95% CI –74.68 to –156.49 g, $P < 0.001$; gestational age: adjusted difference –0.10 week, 95% CI –0.15 to 0.12 week; SGA: adjusted RR 1.52, 95% CI 1.20 to 1.93, $P = 0.001$).

Subgroup analyses

The association of being underweight with perinatal outcomes was observed across a wide spectrum of participants (TABLE 3). Maternal underweight was associated with lower birth weight in all subgroups. Maternal underweight was not associated with lower gestational age in all subgroups. Maternal underweight was associated with a higher risk of SGA in all subgroups, and this association was statistically significant for women aged between 28 and 30 years (adjusted RR 1.78, 95% CI 1.25 to 2.55, $P = 0.002$), first pregnancy (adjusted RR 1.49, 95% CI 1.16 to 1.93, $P = 0.002$), ICSI treatment (adjusted RR 1.65, 95% CI 1.13 to 2.41, $P = 0.010$), FSH less than or equal to 7.40 U/L (FSH <5.97 U/l: adjusted RR 1.57, 95% CI 1.02 to 2.45, $P = 0.041$; 5.98 ≤ FSH ≤7.40 U/l: adjusted RR 1.45, 95% CI 1.02 to 2.05, $P = 0.038$), fresh embryo transfer (adjusted RR 1.42, 95% CI 1.10 to 1.84, $P = 0.007$), cleavage stage or blastocyst transfer (cleavage stage: adjusted RR 1.36, 95% CI 1.04 to 1.78, $P = 0.027$; blastocyst: adjusted RR 1.46, 95% CI 1.02 to 2.09, $P = 0.040$), endometrial thickness less than 9.6 or greater than 11.4 mm (endometrial thickness <9.6 mm: adjusted RR 1.52, 95% CI 1.04 to 2.21, $P = 0.029$; endometrial thickness >11.4 mm: adjusted RR 1.51, 95% CI 1.06 to 2.16, $P = 0.022$), number of embryos transferred two or more (adjusted RR 1.42, 95% CI 1.11 to 1.83, $P = 0.005$), and girl or boy infants (boy: adjusted RR 1.39, 95% CI 1.03 to 1.88, $P = 0.031$; girl: adjusted RR 1.41, 95% CI 1.03 to 1.92, $P = 0.031$). No significant interactions were found between BMI and any of the covariates except for BMI and timing of embryo transfer for gestational age ($P = 0.038$).

DISCUSSION

In a large cohort of pregnant women undergoing ART treatment who received follow-up for their perinatal outcomes, we found that pre-pregnancy maternal underweight was significantly associated with lower birth weight and increased risks of LBW and SGA, and decreased risks of fetal macrosomia and LGA in singletons conceived through ART, whereas pre-pregnancy maternal underweight was not associated with gestational age and risk of PTB. These associations were consistent in the sensitivity analyses and subgroup analyses.

Because of the high prevalence of overweight and obesity in the USA and Europe (*Flegal et al., 2010; Blundell*

TABLE 3 EFFECTS OF UNDERWEIGHT ON BIRTH WEIGHT, GESTATIONAL AGE AND SMALL FOR GESTATIONAL AGE: RESULTS FROM THE GENERALIZED LINEAR MODEL ANALYSIS IN SUBGROUPS BEFORE PROPENSITY SCORE MATCHING

	Subgroup	n	*Adjusted difference or relative risk (95% CI)*	*P-value*
Birth weight (g)				
Maternal age (year)	Tertile 1 (20–27)	2104	–134.46 (–191.23 to –7.68)	<0.001
	Tertile 2 (28–30)	1974	–125.30 (–191.23 to –59.36)	<0.001
	Tertile 3 (>30)	2460	–74.19 (–144.46 to –3.92)	0.039
Gravidity	0	3827	–110.60 (–155.29 to –65.92)	<0.001
	≥1	2711	–113.72 (–178.25 to –49.18)	<0.001
Fertilization method	ICSI	1799	–147.50 (–213.02 to –81.97)	<0.001
	IVF	4591	–96.10 –141.40 to –50.79)	<0.001
FSH (U/l)	Tertile 1 (<5.97)	2182	–139.09 (–214.41 to –63.78)	<0.001
	Tertile 2 (5.98–7.40)	2177	–111.90 (–175.05 to –48.74)	<0.001
	Tertile 3 (>7.40)	2179	–90.73 (–148.16 to –33.34)	0.002
Timing of embryo transfer	Fresh embryo transfer	3819	–130.84 (–176.36 to –82.32)	<0.001
	Frozen embryo transfer	2719	–92.67 (–152.69 to –32.64)	0.003
Day 3 or 5	Cleavage stage transfer	4191	–130.89 (–176.41 to –85.37)	<0.001
	Blastocyst transfer	2347	–82.07 (–145.51 to –18.63)	0.011
Endometrial thickness (mm)	Tertile 1 (<9.6)	2217	–111.99 (-176.56 to –47.42)	<0.001
	Tertile 2 (9.7–11.4)	2164	–88.27 (–152.51 to –24.03)	0.007
	Tertile 3 (>11.4)	2157	–133.17 (–196.79 to –69.55)	<0.001
Number of embryos transferred	1	1395	92.57 (–169.40 to 15.77)	0.018
	≥2	5143	116.13 (–158.35 to –73.92)	<0.001
Infant's sex	Boy	3401	–135.08 (–187.66 to –82.83)	<0.001
	Girl	3137	–87.85 (–139.76 to –35.93)	<0.001
Gestational age (week)				
Maternal age (year)	Tertile 1 (20–27)	2104	–0.10 (–0.28 to 0.07)	NS
	Tertile 2 (28–30)	1974	1.17 (–0.07 to 0.41)	NS
	Tertile 3 (>30)	2460	–0.06 (–0.29 to 0.16)	NS
Gravidity	0	3827	0.01 (–0.13 to 0.16)	NS
	≥1	2711	0.00 (–0.21 to 0.21)	NS
Fertilization method	ICSI	1799	0.01 (–0.20 to 0.21)	NS
	IVF	4591	0.03 (–0.12 to 0.18)	NS
FSH (U/l)	Tertile 1 (<5.97)	2182	–0.01 (–0.26 to 0.23)	NS
	Tertile 2 (5.98–7.40)	2177	–0.01 (–0.22 to 0.19)	NS
	Tertile 3 (>7.40)	2179	0.04 (–0.16 to 0.24)	NS
Timing of embryo transfer	Fresh embryo transfer	3819	–0.07 (–0.22 to 0.09)	NS
	Frozen embryo transfer	2719	0.15 (–0.05 to 0.36)	NS
Day 3 or 5	Cleavage stage transfer	4191	–0.06 (–0.21 to 0.09)	NS
	Blastocyst transfer	2347	0.10 (–0.11 to 0.31)	NS
Endometrial thickness (mm)	Tertile 1 (<9.6)	2217	–0.07 (–0.28 to 0.14)	NS
	Tertile 2 (9.7–11.4)	2164	0.05 (–0.15 to 0.26)	NS
	Tertile 3 (>11.4)	2157	0.01 (–0.20 to 0.22)	NS
Number of embryos transferred	1	1395	–0.03 (–0.28 to 0.21)	NS
	≥2	5143	0.01 (–0.13 to 0.15)	NS
Infant's sex	Boy	3401	–0.02 (–0.19 to 0.15)	NS
	Girl	3137	0.01 (–0.16 to 0.19)	NS

(continued on next page)

Table 3 – (continued)

	Subgroup	n	Adjusted difference or relative risk (95% CI)	P-value
SGA				
Maternal age (year)	Tertile 1(20–27)	2104	1.36 (0.95 to 1.94)	NS
	Tertile 2 (28–30)	1974	1.78 (1.25 to 2.55)	0.002
	Tertile 3 (>30)	2460	1.08 (0.70 to 1.66)	NS
Gravidity	0	3827	1.49 (1.16 to 1.93)	0.002
	≥1	2711	1.17 (0.77 to 1.77)	NS
Fertilization method	ICSI	1799	1.65 (1.13 to 2.41)	0.010
	IVF	4591	1.27 (0.97 to 1.66)	NS
FSH (U/l)	Tertile 1 (<5.97)	2182	1.57 (1.02 to 2.45)	0.041
	Tertile 2 (5.98–7.40)	2177	1.45 (1.02 to 2.05)	0.038
	Tertile 3 (>7.40)	2179	1.29 (0.91 to 1.84)	NS
Timing of embryo transfer	Fresh embryo transfer	3819	1.42 (1.10 to1.84)	0.007
	Frozen embryo transfer	2719	1.34 (0.89 to 2.02)	NS
Day 3 or 5	Cleavage stage transfer	4191	1.36 (1.04 to 1.78)	0.027
	Blastocyst transfer	2347	1.46 (1.02 to 2.09)	0.040
Endometrial thickness (mm)	Tertile 1 (<9.6)	2217	1.52 (1.04 to 2.21)	0.029
	Tertile 2 (9.7–11.4)	2164	1.15 (0.77 to 1.71)	NS
	Tertile 3 (>11.4)	2157	1.51 (1.06 to 2.16)	0.022
Number of embryos transferred	1	1395	1.29 (0.83 to 2.00)	NS
	≥2	5143	1.42 (1.11 to 1.83)	0.005
Infant's sex	Boy	3401	1.39 (1.03 to 1.88)	0.031
	Girl	3137	1.41 (1.03 to 1.92)	0.031

Maternal age, FSH and endometrial thickness were classified by tertiles; all baseline covariates were adjusted in the model (year of transfer, maternal age, gravidity, parity, maternal smoking history, cause of infertility, sperm donation, ovarian stimulation protocol, fertilization method, assisted hatching, basal serum FSH, antral follicle count, endometrial thickness, frozen or fresh embryo transfer, cleavage stage or blastocyst transfer, number of embryos transferred, number of gestational sacs by ultrasonographic visualization and infant's sex); peak oestradiol level was also adjusted in the model in fresh embryo transfer group. An interaction was found between body mass index and timing of embryo transfer for gestational age (P = 0.038). SGA, small for gestational age.

et al., 2017), many studies have focused on the effect of obesity in pregnancies (*Maheshwari et al., 2007; Li et al., 2010*). Additionally, studies on the effect of BMI in pregnancies resulting from ART have principally been concerned with the number and quality of embryos, conception, miscarriage and live birth rates (*Bellver et al., 2010; Sermondade et al., 2019*). Furthermore, previous studies on the effects of underweight on ART outcomes were more focused on the rates of live birth and miscarriage than birth weight (*Wang et al., 2000; Wittemer et al., 2000; Veleva et al., 2008; Singh et al., 2012; Provost et al., 2016; Cai et al., 2017*; *Oliveira et al., 2018*). Therefore, few studies have examined the relationship of underweight mothers with perinatal outcomes in singleton infants conceived through ART.

In the present study, we found that singletons born to underweight women had lower birth weight, higher risks of LBW and SGA, and lower risk of fetal macrosomia and LGA than those born to women with normal weights after ART treatment. On the basis of 180,855 pregnancies conceived through IVF in the USA between 2008 and 2013, *Kawwass et al. (2016)* confirmed that being underweight was associated with an increased risk of LBW (RR 1.39, 95% CI 1.25 to 1.54). *Frankenthal et al. (2019)* also found that infants of pre-pregnancy underweight mothers treated with ART had higher SGA rates than those born to normal weight mothers (31.6% versus 26.6%). Those associations were similar in spontaneous pregnancies (*Belogolovkin et al., 2009; Salihu et al., 2009; Li et al., 2013; Pan et al., 2016; Du et al., 2017; Tamura et al., 2018*). *Han et al. (2011)* conducted a systematic review and meta-analyses that included 78 studies and 1,025,784 women. They and reported that, in both developed and developing countries, underweight women were at an increased risk of having an LBW infant (RR 1.48, 95% CI 1.29 to 1.68, and RR 1.52, 95% CI 1.25 to 1.85, respectively). In addition, *Rahman et al. (2015)* reported that maternal underweight was significantly associated with a higher risk of LBW (OR 1.66, 95% CI 1.50 to 1.84) and SGA (OR 1.85, 95% CI 1.69 to 2.02) in a systematic review and meta-analysis that included 42 studies. *Liu et al. (2016)* also found that pre-pregnancy maternal underweight was associated with lower risk of fetal macrosomia (OR 0.55, 95% CI 0.47 to 0.63) and LGA (OR 0.52, 95% CI 0.44 to 0.61) in a systematic review and meta-analyses (*Liu et al., 2016*).

A low pre-pregnancy BMI may be an indication of chronic nutritional deficiency of mothers, including macro- and micronutrients (folate and zinc), which may negatively affect the normal processes of fetal growth

and development, leading to adverse outcomes such as LBW and SGA. A poor maternal nutritional status has been associated with a reduction in placental weight and surface area, which may affect the ability of nutrients to transfer from the maternal circulation to the developing fetus. According to the theory of epigenetics during pregnancy, underweight mothers may not have sufficient nutritional ingredients required for optimal realization of epigenetic pathways that drive trophoblastic and fetal growth and development (*Belogolovkin et al., 2009*).

In the present study, pre-pregnancy maternal underweight was not associated with risk of PTB, full term, gestational age greater than 40 weeks and gestational age greater than 41 weeks, and the difference in gestational age was only –0.02 weeks between the underweight and normal weight groups. *Han et al. (2011)* reported that, in developed countries, underweight women had an increased risk of PTB (RR 1.22, 95% CI 1.15 to 1.30) but that this risk was not present in developing countries (RR 0.99, 95% CI 0.67 to 1.45). The results from *Han et al. (2011)* implied that socioeconomic status affects the relationship between maternal underweight and PTB. A prospective ART cohort study including socioeconomic status is needed to identify the relationship between maternal underweight and PTB.

Selection bias and an imbalance of important variables between the groups were major problems in previous observational studies (*Sturmer et al., 2006*), which usually used traditional regression methods to analyse the association between maternal underweight and perinatal outcomes (*Salihu et al., 2009; Dickey et al., 2012; Kawwass et al., 2016*). For an observational study, propensity score matching was effective in balancing the confounding factors for a similar randomized treatment and reduced the selection bias (*D'Agostino et al., 1998*; *Austin et al., 2011*) because propensity score is a function of multiple covariates and represents the combined action of multiple covariates. Propensity score matching provides an accurate estimated value compared with conventional multivariable methods (*Cepeda et al., 2003*). Therefore, the major strength of this study was the use of propensity score matching, which balanced underweight and normal weight groups on a large number of covariates by using a linear combination of covariates for a single score. To some extent, propensity score matching also reduced the confounding that may be present in our study.

The present study has some limitations. First, this was an observational study in which the causality of underweight and pregnancy outcomes could not be established. Additionally, although we used the propensity score matching technique to control for confounders between the two groups, the findings in our study might be potentially confounded by unmeasured or hidden covariates because the covariates that were used for propensity score matching were limited, resulting in incomplete or inexact matching. Lastly, because of the limitation of hospital information system and follow up system, some determinants (gestational weight gain, ethnic group, intrauterine growth retardation, preeclampsia, thyroid diseases and glucose intolerance, chronic hypertension, maternal diseases and other pregnancy complications) were not adjusted for in the model.

In conclusion, our findings indicate that underweight before ART was significantly associated with lower birth weight, increased risks of LBW and SGA and decreased risks of fetal macrosomia and LGA in singletons who are conceived by ART. These findings were important for the prevention of adverse birth outcomes in ART treatment. An additional large sample, multicentre, prospective cohort study is needed to confirm the risk of pre-pregnancy maternal underweight.

ACKNOWLEDGEMENTS

This work was supported by 'the Fundamental Research Funds for the Central Universities' (China) (Grant number: xzy012019116) and the National Natural Science Foundation of China (Grant number: 81771657). We thank the staff from Northwest Women's and Children's Hospital for their assistance with the data collection. We thank all participants in this study.

REFERENCES

Abrams, B., Carmichael, S., Selvin, S. **Factors associated with the pattern of maternal weight gain during pregnancy.** Obstet. Gynecol. 1995; 86: 170–176

Adamson, G.D., de Mouzon, J., Chambers, G.M., Zegers-Hochschild, F., Mansour, R., Ishihara, O., Banker, M., Dyer, S. **International Committee for Monitoring Assisted Reproductive Technology: world report on assisted reproductive technology, 2011.** Fertil. Steril. 2018; 110: 1067–1080

Ahmed, A., Husain, A., Love, T.E., Gambassi, G., Dell'Italia, L.J., Francis, G.S., Gheorghiade, M., Allman, R.M., Meleth, S., Bourge, R.C. **Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods.** Eur. Heart. J. 2006; 27: 1431–1439

American College of Obstetricians and Gynecologists. Method for estimating due date. Obstet. Gynecol. 2017; 129: 967–968

Austin, P.C. **An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies.** Multivariate. Behav. Res. 2011; 46: 399–424

Bellver, J., Ayllon, Y., Ferrando, M., Melo, M., Goyri, E., Pellicer, A., Remohi, J., Meseguer, M. **Female obesity impairs in vitro fertilization outcome without affecting embryo quality.** Fertil. Steril. 2010; 93: 447–454

Belogolovkin, V., Alio, A.P., Mbah, A.K., Clayton, H.B., Wathington, D., Salihu, H.M. **Patterns and success of fetal programming among women with low and extremely low pre-pregnancy BMI.** Arch. Gynecol. Obstet. 2009; 280: 579–584

Blundell, J.E., Baker, J.L., Boyland, E., Blaak, E., Charzewska, J., de Henauw, S., Fruhbeck, G., Gonzalez-Gross, M., Hebebrand, J., Holm, L., Kriaucioniene, V., Lissner, L., Oppert, J.M., Schindler, K., Silva, A.L., Woodward, E. **Variations in the Prevalence of Obesity Among European Countries, and a Consideration of Possible Causes.** Obes. Facts. 2017; 10: 25–37

Cai, J., Liu, L., Zhang, J., Qiu, H., Jiang, X., Li, P., Sha, A., Ren, J. **Low body mass index compromises live birth rate in fresh transfer in vitro fertilization cycles: a retrospective study in a Chinese population.** Fertil. Steril. 2017; 107: 422–429

Cavoretto, P., Candiani, M., Giorgione, V., Inversetti, A., Abu-Saba, M.M., Tiberio, F., Sigismondi, C., Farina, A. **Risk of spontaneous preterm birth in singleton pregnancies conceived after IVF/ICSI treatment: meta-analysis of cohort studies.** Ultrasound. Obstet. Gynecol. 2018; 51: 43–53

Cepeda, M.S., Boston, R., Farrar, J.T., Strom, B.L. **Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders.** Am. J. Epidemiol. 2003; 158: 280–287

D'Agostino, R.B.Jr. **Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group.** Stat. Med. 1998; 17: 2265–2281

Dickey, R.P., Xiong, X., Gee, R.E., Pridjian, G. **Effect of maternal height and weight on risk of preterm birth in singleton and twin births resulting from in vitro fertilization: a retrospective cohort study using the Society**

for Assisted Reproductive Technology Clinic Outcome Reporting System. Fertil. Steril. 2012; 97: 349–354

Du, M.K., Ge, L.Y., Zhou, M.L., Ying, J., Qu, F., Dong, M.Y., Chen, D.Q. **Effects of pre-pregnancy body mass index and gestational weight gain on neonatal birth weight.** J. Zhejiang. Univ. Sci. B. 2017; 18: 263–271

Dunietz, G.L., Holzman, C., McKane, P., Li, C., Boulet, S.L., Todem, D., Kissin, D.M., Copeland, G., Bernson, D., Sappenfield, W.M., Diamond, M.P. **Assisted reproductive technology and the risk of preterm birth among primiparas.** Fertil. Steril. 2015; 103: 974–979

Flegal, K.M., Carroll, M.D., Ogden, C.L., Curtin, L.R. **Prevalence and trends in obesity among US adults, 1999-2008.** JAMA 2010; 303: 235–241

Frankenthal, D., Hirsh-Yechezkel, G., Boyko, V., Orvieto, R., Ron-El, R., Lerner-Geva, L., Farhi, A. **The effect of body mass index (BMI) and gestational weight gain on adverse obstetrical outcomes in pregnancies following assisted reproductive technology as compared to spontaneously conceived pregnancies.** Obes. Res. Clin. Pract. 2019; 13: 150–155

Gondwe, A., Ashorn, P., Ashorn, U., Dewey, K.G., Maleta, K., Nkhoma, M., Mbotwa, J., Jorgensen, J.M. **Pre-pregnancy body mass index (BMI) and maternal gestational weight gain are positively associated with birth outcomes in rural Malawi.** PLoS. One. 2018; 13e0206035

Han, Z., Mulla, S., Beyene, J., Liao, G., McDonald, S.D., Knowledge Synthesis, G. **Maternal underweight and the risk of preterm birth and low birth weight: a systematic review and meta-analyses.** Int. J. Epidemiol. 2011; 40: 65–101

Jancar, N., Mihevc Ponikvar, B., Tomsic, S., Vrtacnik Bokal, E., Korosec, S. **Is IVF/ISCI an Independent Risk Factor for Spontaneous Preterm Birth in Singletons? A Population-Based Cohort Study.** Biomed. Res. Int 20187124362

Kawwass, J.F., Kulkarni, A.D., Hipp, H.S., Crawford, S., Kissin, D.M., Jamieson, D.J. **Extremities of body mass index and their association with pregnancy outcomes in women undergoing in vitro fertilization in the United States.** Fertil. Steril. 2016; 106: 1742–1750

Li, C., Liu, Y., Zhang, W. **Joint and Independent Associations of Gestational Weight Gain and Pre-Pregnancy Body Mass Index with Outcomes of Pregnancy in Chinese Women: A Retrospective Cohort Study.** PLoS. One. 2015; 10e0136850

Li, C.M., Li, G.H., Chen, Y., Ruan, Y., Wang, X., Zhang, W.Y. **Effects of pre-pregnancy body mass index on pregnancy outcomes.** Chin. Med. J. (Engl) 2013; 126: 4585–4587

Li, Y., Yang, D., Zhang, Q. **Impact of overweight and underweight on IVF treatment in Chinese women.** Gynecol. Endocrinol. 2010; 26: 416–422

Liu, P., Xu, L., Wang, Y., Zhang, Y., Du, Y., Sun, Y., Wang, Z. **Association between perinatal outcomes and maternal pre-pregnancy body mass index.** Obes. Rev. 2016; 17: 1091–1102

Maheshwari, A., Stofberg, L., Bhattacharya, S. **Effect of overweight and obesity on assisted reproductive technology–a systematic review.** Hum. Reprod. Update. 2007; 13: 433–444

McDonald, S.D., Han, Z., Mulla, S., Murphy, K.E., Beyene, J., Ohlsson, A. **Preterm birth and low birth weight among in vitro fertilization singletons: a systematic review and meta-analyses.** Eur. J. Obstet. Gynecol. Reprod. Biol. 2009; 146: 138–148

National Health and Family Planning Commission of the People's Republic of China. **Management and Specification in Maternal Health Care (in Chinese).** In, 2011.

Oliveira, J.B.A. **Does low BMI affect ART outcomes?** JBRA. Assist. Reprod 2018; 22: 1

Pan, Y., Zhang, S., Wang, Q., Shen, H., Zhang, Y., Li, Y., Yan, D., Sun, L. **Investigating the association between prepregnancy body mass index and adverse pregnancy outcomes: a large cohort study of 536 098 Chinese pregnant women in rural China.** BMJ. Open. 2016; 6e011227

Provost, M.P., Acharya, K.S., Acharya, C.R., Yeh, J.S., Steward, R.G., Eaton, J.L., Goldfarb, J.M., Muasher, S.J. **Pregnancy outcomes decline with increasing body mass index: analysis of 239,127 fresh autologous in vitro fertilization cycles from the 2008-2010 Society for Assisted Reproductive Technology registry.** Fertil. Steril. 2016; 105: 663–669

Rahman, M.M., Abe, S.K., Kanda, M., Narita, S., Rahman, M.S., Bilano, V., Ota, E., Gilmour, S., Shibuya, K. **Maternal body mass index and risk of birth and maternal health outcomes in low- and middle-income countries: a systematic review and meta-analysis.** Obes. Rev. 2015; 16: 758–770

Salihu, H.M., Mbah, A.K., Alio, A.P., Clayton, H.B., Lynch, O. **Low pre-pregnancy body mass index and risk of medically indicated versus spontaneous preterm singleton birth.** Eur. J. Obstet. Gynecol. Reprod. Biol. 2009; 144: 119–123

Sermondade, N., Huberlant, S., Bourhis-Lefebvre, V., Arbo, E., Gallot, V., Colombani, M., Freour, T. **Female obesity is negatively associated with live birth rate following IVF: a systematic review and meta-analysis.** Hum. Reprod. Update. 2019

Siega-Riz, A.M., Adair, L.S. **Biological determinants of pregnancy weight gain in a Filipino population.** Ann. N. Y. Acad. Sci. 1993; 678: 364–365

Singh, N., Gupta, P., Mittal, S., Malhotra, N. **Correlation of body mass index with outcome of in vitro fertilization in a developing country.** Arch. Gynecol. Obstet. 2012; 285: 259–263

Sturmer, T., Joshi, M., Glynn, R.J., Avorn, J., Rothman, K.J., Schneeweiss, S. **A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods.** J. Clin. Epidemiol. 2006; 59: 437–447

Tamura, N., Hanaoka, T., Ito, K., Araki, A., Miyashita, C., Ito, S., Minakami, H., Cho, K., Endo, T., Sengoku, K., Ogasawara, K., Kishi, R. **Different Risk Factors for Very Low Birth Weight, Term-Small-for-Gestational-Age, or Preterm Birth in Japan.** Int. J. Environ. Res. Public. Health. 2018; 15

Veleva, Z., Tiitinen, A., Vilska, S., Hyden-Granskog, C., Tomas, C., Martikainen, H., Tapanainen, J.S. **High and low BMI increase the risk of miscarriage after IVF/ICSI and FET.** Hum. Reprod. 2008; 23: 878–884

Villar, J., Cheikh Ismail, L., Victora, C.G., Ohuma, E.O., Bertino, E., Altman, D.G., Lambert, A., Papageorghiou, A.T., Carvalho, M., Jaffer, Y.A., Gravett, M.G., Purwar, M., Frederick, I.O., Noble, A.J., Pang, R., Barros, F.C., Chumlea, C., Bhutta, Z.A., Kennedy, S.H. **International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project.** Lancet 2014; 384: 857–868

Wang, J.X., Davies, M., Norman, R.J. **Body mass and probability of pregnancy during assisted reproduction treatment: retrospective study.** BMJ 2000; 321: 1320–1321

Wittemer, C., Ohl, J., Bailly, M., Bettahar-Lebugle, K., Nisand, I. **Does body mass index of infertile women have an impact on IVF procedure and outcome?** J. Assist. Reprod. Genet 2000; 17: 547–552

Yang, X., Li, Y., Li, C., Zhang, W. **Current overview of pregnancy complications and live-birth outcome of assisted reproductive technology in mainland China.** Fertil. Steril. 2014; 101: 385–391

Zheng, Z., Chen, L., Yang, T., Yu, H., Wang, H., Qin, J. **Multiple pregnancies achieved with IVF/ICSI and risk of specific congenital malformations: a meta-analysis of cohort studies.** Reprod. Biomed. Online. 2018; 36: 472–482

Received 7 May 2019; received in revised form 1 June 2019; accepted 18 June 2019.