Accepted Manuscript

A propensity-matched study of the association between prepregnancy maternal underweight and perinatal outcomes among singletons based on an ART cohort

Pengfei Qu , Fangfang Liu , Doudou Zhao , Yongbo Wang , Min Wang , Linyu Wang , Shaonong Dang , Duolao Wang , Juanzi Shi , Wenhao Shi

PII: S1472-6483(19)30594-2
DOI: https://doi.org/10.1016/j.rbmo.2019.06.007
Reference: RBMO 2223

To appear in: *Reproductive BioMedicine Online*

Received date: 7 May 2019
Revised date: 1 June 2019
Accepted date: 18 June 2019

Please cite this article as: Pengfei Qu , Fangfang Liu , Doudou Zhao , Yongbo Wang , Min Wang , Linyu Wang , Shaonong Dang , Duolao Wang , Juanzi Shi , Wenhao Shi , A propensity-matched study of the association between prepregnancy maternal underweight and perinatal outcomes among singletons based on an ART cohort, *Reproductive BioMedicine Online* (2019), doi: https://doi.org/10.1016/j.rbmo.2019.06.007

Title: A propensity-matched study of the association between prepregnancy maternal underweight and perinatal outcomes among singletons based on an ART cohort

Running title: underweight and ART perinatal outcomes

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]*

[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, United Kingdom.

Corresponding author:

Wenhao Shi, swihao@126.com; (handling correspondence at all stages of refereeing and publication, also post-publication.)

Juanzi Shi, shijuanzi123@126.com

Abstract:

Research question: Is prepregnancy maternal underweight associated with perinatal outcomes of singletons who were conceived by assisted reproductive technology (ART)?

Design: A 10-year (2006-2015) Chinese sample of 6538 women and their singletons who were conceived by ART was used to examine the association between prepregnancy maternal underweight and perinatal outcomes. Propensity scores(PS) for underweight were calculated for each participant using multivariable logistic regression, which was used to match 740 (91.35% of 810) underweight women with 740 normal weight women and then the effects of underweight on birth weight (BW) and gestational age (GA) were assessed by the generalized estimating equation (GEE) model.

Results: After PS matching, the BW 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 and GA and preterm birth (PTB) were not statistically significant.

Conclusions: Among women undergoing ART, prepregnancy maternal underweight was associated with lower BW, increased LBW and SGA risks and decreased fetal macrosomia and LGA risks in singletons.

Key words: underweight; assisted reproductive technology; preterm birth; low birth weight; propensity score matching

Introduction

In the past 40 years, assisted reproductive technology (ART), such as in vitro fertilization (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 live-born babies worldwide, and the proportion of infants who are born in China as a result of ART is greater than 1% (Adamson et al., 2018; Yang et al., 2014). Although ART helps millions of infertile couples to achieve pregnancy, ART is associated with potential health risks for both mothers and infants. Previous research has shown that infants who are conceived by ART have an increased risk of adverse pregnancy outcomes, such as low birth weight (LBW), preterm birth (PTB) and congenital malformations compared with those who are conceived spontaneously (McDonald et al., 2009; Cavoretto et al., 2018; Dunietz et al., 2015; 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 systematically reviewed and collected 60 studies, of which 1,392,799 women were included and the proportion of underweight pregnant women was 8.18%, and 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) (Liu et al., 2016). However, the studies of the relationship between maternal underweight before pregnancy and fetal growth with ART treatment are limited (Cai et al., 2017; Singh et al., 2012). The goal of our study was to reveal the impact of prepregnancy maternal underweight on birth weight (BW) and gestational age (GA) among infants who were conceived by ART. We collected 10 years of data, including ART treatments and the perinatal outcomes to compare the

BW and GA between the underweight group and normal weight group in a single ART center in Northwest China.

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 the clinical records. In this time frame, a total of 12,572 infants were born with IVF/ICSI treatment. We excluded 3,577 multiple births, 1,965 mothers with BMI ≥ 24 kg/m^2, 143 mothers with missing BMI and 349 mothers with missing covariates in singleton pregnancy, leaving a total 6,538 ART mothers with their singleton infants in this study. Of these, 810 mothers were underweight and 5,728 were normal weight (Fig. 1).

In the Shaanxi province of China, it is a requirement that all ART birth outcomes, including BW and GA, 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, etiology of infertility, sperm donation, controlled ovarian hyperstimulation protocol, fertilization method, assisted hatching, basal serum follicle stimulating hormone (FSH) level, antral follicle count, endometrial thickness, fresh/frozen-thaw embryo transfer, blastocyst/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.

BMI 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 6,538 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; normal weight group (normal BMI group): 18.5 kg/m^2 ≤ BMI <24.00 kg/m^2.

The definitions of perinatal outcomes

The primary outcomes were BW and GA. LBW is defined as BW <2500 g; fetal macrosomia is defined as BW ≥ 4000 g; 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). GA was calculated by the number of days from the day of transfer to birth plus the age of the embryo and plus 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 GA; PTB is defined as born before 37 weeks of GA; SGA is defined as a BW below the 10th percentile for the gestational age; large for gestational age (LGA) is defined as a BW above the 90th percentile for that gestational age; appropriate for gestational age (AGA) is defined as a BW between the 10th and 90th percentile for that GA.

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 subjects, including: year of transfer, maternal age, gravidity, parity, maternal smoking history, etiology of infertility, sperm donation, controlled ovarian hyperstimulation protocol, fertilization method, assisted hatching, basal serum FSH, antral follicle count, endometrial thickness, frozen or fresh embryo transfer, cleavage stage or blastocyst transfer, no. of embryos transferred, no. of gestational sacs by ultrasonographic visualization and infant's sex.

Ethical approval

The Human Research Ethics Committee of the Northwest Women's and Children's Hospital approved this study. The ethics committee that approved this study waived the need to obtain informed consent. All of the research was performed in accordance with the relevant guidelines and regulations.

Statistical analysis

We categorized 6,538 participants into the underweight group and normal weight group. Of the 6,538 participants, 810 (12.39% of 6,538) participants were

underweight. Next, we estimated the propensity score (PS) of each participant using a multivariable logistic regression model, in which the BMI group was modeled using all of the baseline participant characteristics in Table 1. Then, we used the nearest neighbor within caliper to match each participant in the underweight with one in the normal weight group, thus matching 740 (12.92% of 5,728) participants with low BMI to 740 participants with normal BMI with similar estimated PS (Ahmed et al., 2006). In our matching algorithm, we matched each participant in the underweight group with a participant in the normal weight group who had a PS that was similar to five decimal places. The nearest neighbor within caliper matching function is as follows:

$$\mathrm{C}(P_i) = \min_j ||P_i - P_j|| \ , \ j \in I_0$$

$$||P_i - P_j|| < \varepsilon \ , \ j \in I_0$$

P_i : PS of the underweight group; P_j : PS 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 prematch mean PS 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 PS 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-square 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 exact test were used if the assumptions for Student's test and Pearson chi-square were violated. For a continuous covariate, the absolute standardized difference is defined as:

$$\mathrm{d} = \frac{(\bar{x}_{treatment} - \bar{x}_{control})}{\sqrt{\frac{s^2_{treatment} + s^2_{control}}{2}}}$$

where $\bar{x}_{treatment}$ and $\bar{x}_{control}$ 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 subjects, respectively. For dichotomous variables, the standardized difference is defined as:

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

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).

We estimated the crude mean differences and 95% confidence intervals for BW and GA 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. We also estimated the relative risks (RR) and 95% confidence intervals 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.

We conducted sensitivity analyses using two approaches to assess the robustness of our findings regarding the effects of underweight on birth outcomes to changes in the analytic approach. To address concerns about incomplete matching, we analysed data from all 6,538 participants, using generalized linear model adjustment for all baseline covariates, and subclassification based on tertiles of PS. To examine for the potential heterogeneity of a BMI effect on BW, GA and SGA, we estimated the effects of underweight in several subgroups, using the prematch cohort of 6,538 patients. We then estimated the effect of underweight in each of the subgroups using generalized linear model adjustment for all baseline covariates. All of the analyses were performed with STATA version 12.0 software (STATA Corporation, College Station, TX, USA). The level of significance was set at $p<0.05$.

Results

Participants' characteristics

The mean (±SD) age of the 1,480 PS-matched women was 28.90 (±3.58) years, 925 (62.50%) embryos were transferred between 2013 to 2015 and 989 (66.82%) received IVF treatment. Table 1 compares the baseline characteristics of the participants by BMI before and after PS matching. Before matching, the underweight women were younger. They were more likely to have higher basal serum FSH level, sperm donation and male infertility. However, the underweight women were also

more likely to have less gravidity, parity and female infertility.

After matching, underweight and normal weight women were similar with regards to all of the 19 baseline covariates (Table 1 and Fig. 2). Our PS matching reduced the standardized differences for all of 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 (Fig. 2).

Underweight and BW

After PS matching, BW, BW Z score, and BW centiles were lower in the underweight group compared with that of the normal weight group (BW: mean difference= -136.83 g, 95% CI=-184.11 to -89.55 g, P<0.001; BW Z score: mean difference=-0.30, 95% CI=-0.39 to -0.20, P<0.001; BW centiles: mean difference=-8.41, 95% CI=-11.21 to -5.62, P<0.001) (Table 2). Higher risk of LBW (BW <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 (BW ≥ 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).

Underweight and GA

After PS matching, there was no significant difference in GA between the underweight group and the normal weight group (difference=-0.02 week, 95% CI=-0.18 to 0.13 week, P=0.782) (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, P=0.916). Compared with the normal underweight group, the risks of GA between 37 weeks and 42 weeks, GA >40 weeks and GA >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 PS 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 (prematched) cohort (n=6,538), compared with the mean (3292.45 g) BW of the normal weight group, the mean BW 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 GA (39.03 weeks) in the normal weight group, the mean GA 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, *P*=0.829).

Among the participants in PS tertiles two and three (n=4,280), we observed similar associations between being underweight and BW, GA and SGA when all baseline covariates were adjusted (BW: adjusted difference=-115.59 g, 95% CI=-74.68 to -156.49 g, *P*<0.001; GA: adjusted difference=-0.10 week, 95% CI=-0.15 to 0.12 week, *P*=0.849; 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 noted across a wide spectrum of participants (Table 3). Maternal underweight was associated with lower BW in all subgroups. Maternal underweight was not associated with lower GA in all subgroups. Maternal underweight was associated with a higher risk of SGA in all subgroups, and this association was statistically significant for ages between 28-30 years, first pregnancy, ICSI treatment, FSH <0.74 U/L, fresh embryo transfer,

cleavage stage or blastocyst transfer, endometrial thickness <9.6 or >11.4 mm, no. of embryos transferred ≥ 2, and girl or boy infants. There were no significant interactions between BMI and any of the covariates.

Discussion

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

Due to the high prevalence of overweight and obesity in the United States and Europe (Flegal et al., 2010; Blundell et al., 2017), a large number of 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 been principally concerned with the number and quality of embryos, conception, miscarriage and live birth rates (Bellver et al., 2010; Sermondade et al., 2019). Furthermore, the previous studies on the effects of underweight on ART outcomes were more focused on the rates of live birth and miscarriage than birth weight (Singh et al., 2012; Provost et al., 2016; Wang et al., 2000; Wittemer et al., 2000; Oliveira et al., 2018; Cai et al., 2017; Veleva et al., 2008). Therefore, very few studies have examined the relationship of underweight mothers with perinatal outcomes in singleton infants who are conceived with ART.

In our study, we found that singletons who were 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. Using 180,855 pregnancies with in vitro fertilization (IVF) in the United States from 2008 to 2013, Kawwass confirmed that being underweight was associated with an increased risk of LBW (RR=1.39, 95% CI=1.25 to 1.54) (Kawwass et al., 2016). Frankenthal also found that infants of underweight mothers with ART

treatment in prepregnancy had higher SGA rates than those born to normal weight mothers (31.6% vs 26.6%) (Frankenthal et al., 2019). Those associations were similarly existed in spontaneous pregnancies (Tamura et al., 2018; Du et al., 2017; Li et al., 2013; Pan et al., 2016; Salihu et al., 2009; Belogolovkin et al., 2009). Han preformed a systematic review and meta-analyses that included 78 studies and 1,025,784 women 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) (Han et al., 2011). In addition, Rahman reports 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 (Rahman et al., 2015). And Liu also found that prepregnancy 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 prepregnancy BMI may be an indication of chronic nutritional deficiency of mothers, including macro- and micronutrients (folate and zinc), which may negatively impact 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 impact the ability of nutrients to transfer from the maternal circulation to the developing fetus. Based the theory of epigenetics during pregnancy, underweight mothers may not have the sufficient nutritional ingredients that are required for the optimal realization of epigenetic pathways that drive trophoblastic and fetal growth and development (Belogolovkin et al., 2009).

In our study, prepregnancy maternal underweight was not associated with risk of PTB, full term, GA >40 weeks and GA >41 weeks, and the difference in GA was only -0.02 week between the underweight and normal weight groups. Han 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) (Han et al., 2011). Han's results implied that socioeconomic status affects the relationship between maternal underweight and PTB. A prospective ART cohort study including socioeconomic status was need 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; Kawwass et al., 2016; Dickey et al., 2012). For an observational study, PS matching was effective in balancing the confounding factors for a similar randomized treatment and reduced the selection bias (Austin et al., 2011; D'Agostino et al., 1998) because PS is a function of multiple covariates and represents the combined action of multiple covariates. PS matching provides an accurate estimated value compared with conventional multivariable methods (Cepeda et al., 2003). Thus, the major strength of this study was the use of PS 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, PS matching also reduced the confounding that may be present in our study.

This study had 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 PS 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 the PS 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 glucose intolerance, chronic hypertension, maternal diseases and other pregnancy complications) were not adjusted for in the model.

Conclusion

In conclusion, our findings indicate that underweight before ART was significantly associated with lower BW, 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 multicenter prospective cohort study is needed to confirm the risk of prepregnancy maternal underweight.

Author Contributions

The authors' contributions are as follows: P. Q., S. D., W. S, and J. S. conceived and designed the study; P. Q., F. L., D. Z., S. D., D. W., W. S. and J. S. drafted and revised the manuscript; P. Q., F. L., D. Z. and L. W. analysed and interpreted the data; P. Q., F. L., Y. W., L. W. and M. W. collected and cleared the data. All authors have read and approved the final version of the manuscript.

Funding

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).

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgements

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.

Reference

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

Adamson GD, de Mouzon J, Chambers GM, 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 TE, Gambassi G, Dell'Italia LJ, Francis GS, Gheorghiade M, Allman RM, Meleth S, Bourge RC. 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 PC. 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 AP, Mbah AK, Clayton HB, Wathington D, Salihu HM. Patterns and success of fetal programming among women with low and extremely low pre-pregnancy BMI. Arch. Gynecol. Obstet. 2009; 280: 579-584.

Blundell JE, Baker JL, Boyland E, Blaak E, Charzewska J, de Henauw S, Fruhbeck G, Gonzalez-Gross M, Hebebrand J, Holm L, Kriaucioniene V, Lissner L, Oppert JM, Schindler K, Silva AL, 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 MM, 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 MS, Boston R, Farrar JT, Strom BL. 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 RB, 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 RP, Xiong X, Gee RE, 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 MK, Ge LY, Zhou ML, Ying J, Qu F, Dong MY, Chen DQ. 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 GL, Holzman C, McKane P, Li C, Boulet SL, Todem D, Kissin DM, Copeland G, Bernson D, Sappenfield WM, Diamond MP. Assisted reproductive technology and the risk of preterm birth among primiparas. Fertil. Steril. 2015; 103: 974-979.

Flegal KM, Carroll MD, Ogden CL, Curtin LR. 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 KG, Maleta K, Nkhoma M, Mbotwa J, Jorgensen JM. Pre-pregnancy body mass index (BMI) and maternal gestational weight gain are positively associated with birth outcomes in rural Malawi. PLoS. One. 2018; 13: e0206035.

Han Z, Mulla S, Beyene J, Liao G, McDonald SD, 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. 2018: 7124362.

Kawwass JF, Kulkarni AD, Hipp HS, Crawford S, Kissin DM, Jamieson DJ. 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; 10: e0136850.

Li CM, Li GH, Chen Y, Ruan Y, Wang X, Zhang WY. Effects of pre-pregnancy body mass index on pregnancy outcomes. Chin. Med. J. (Engl) 2013; 126: 4585-7.

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 SD, Han Z, Mulla S, Murphy KE, 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 JBA. 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; 6: e011227.

Provost MP, Acharya KS, Acharya CR, Yeh JS, Steward RG, Eaton JL, Goldfarb JM, Muasher SJ. 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 MM, Abe SK, Kanda M, Narita S, Rahman MS, 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 HM, Mbah AK, Alio AP, Clayton HB, 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.(Epub ahead of print)

Siega-Riz AM, Adair LS. 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 RJ, Avorn J, Rothman KJ, 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, JS. 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 CG, Ohuma EO, Bertino E, Altman DG, Lambert A, Papageorghiou AT, Carvalho M, Jaffer YA, Gravett MG, Purwar M, Frederick IO, Noble AJ, Pang R, Barros FC, Chumlea C, Bhutta ZA, Kennedy SH, 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 JX, Davies M, Norman RJ. 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.

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

KEY MESSAGE

Based on a retrospective cohort with 6,538 women undergoing ART and their singletons live births and the propensity score (PS) matching analysis, prepregnancy maternal underweight was associated with lower birth weight and increased low birth weight (LBW) and small for gestational age (SGA) risks in singletons.

Table 1 Baseline characteristics of participants by BMI before and after PS matching (n (%)/(mean ± SD))

	Before PS match			After PS 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						
2006-2009	86 (10.62)	455 (7.94)		79 (10.68)	76 (10.27)	
2010-2012	197 (24.32)	1527 (26.66)	0.022	185 (25.00)	215 (29.05)	0.213
2013-2015	527 (65.06)	3746 (65.40)		476 (64.32)	449 (60.68)	
Maternal age (year)	28.61 ± 3.63	29.79 ± 4.00	<0.001[a]	28.91 ± 3.56	28.96 ± 3.60	0.783
Gravidity						
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)	0.322
≥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)	0.221
≥1	40 (4.94)	504 (8.80)		40 (5.41)	30 (4.05)	
Maternal smoking history	2 (0.25)	18 (0.31)	1.000	2 (0.27)	2 (0.27)	1.000[b]
Male infertility	328 (40.49)	1994 (34.81)	0.002	287 (38.78)	281 (37.97)	0.748
Female infertility						
No	318 (39.26)	1948 (34.01)		282 (38.11)	274 (37.03)	
Tubal factor	341 (42.10)	2781 (48.55)	0.001	325 (43.92)	325 (43.92)	0.942
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	87 (10.74)	391 (6.83)	<0.001	55 (7.43)	58 (7.84)	0.769
Controlled ovarian	458 (56.54)	3353 (58.54)	0.281	428 (57.84)	414 (55.95)	0.462

hyperstimulation protocol						
Fertilization method						
ICSI	238 (30.62)	1551 (27.08)		224 (30.27)	234 (31.62)	
IVF	549 (67.78)	4042 (70.57)	0.055	504 (68.11)	485 (65.54)	0.219
IVF+ICSI	13 (1.60)	135 (2.36)		12 (1.62)	21 (2.84)	
Assisted hatching	224 (27.65)	1580 (27.58)	0.966	204 (27.57)	216 (29.19)	0.489
Basal serum FSH level (U/L)	7.23 ± 2.12	6.86 ± 2.55	<0.001	7.12 ± 1.98	6.95 ± 2.15	0.105
Antral follicle count	12.82 ± 4.96	12.86 ± 5.29	0.991[a]	12.89 ± 4.97	12.99 ± 5.35	0.713
Endometrial thickness (mm)	10.69 ± 2.13	10.74 ± 2.04	0.513	10.71 ± 2.14	10.62 ± 2.05	0.377
Timing of embryo transfer						
Fresh embryo transfer	460 (56.79)	3359 (58.64)	0.317	428 (57.84)	414 (55.95)	0.462
Frozen embryo transfer	350 (43.21)	2369 (41.36)		312 (42.16)	326 (44.05)	
Day 3 or 5						
Cleavage stage transfer	515 (63.58)	3676 (64.18)	0.741	476 (64.32)	479 (64.73)	0.871
Blastocyst transfer	295 (63.58)	2052 (35.82)		264 (35.68)	261 (35.27)	
No. of embryos transferred						
1	186 (22.96)	1209 (21.11)		167 (22.57)	149 (20.14)	
2	567 (70.00)	4105 (71.67)	0.483	516 (69.73)	533 (72.03)	0.520
≥3	57 (7.04)	414 (7.23)		57 (7.70)	58 (7.84)	
No. of gestational sacs by ultrasonographic visualization						
1	722 (89.14)	5211 (90.97)		670 (90.54)	665 (89.86)	
2	85 (10.49)	505 (8.82)	0.134[b]	68 (9.19)	70 (9.46)	0.584[b]
≥3	3 (0.37)	12 (0.21)		2 (0.27)	5 (0.68)	
Infant's sex=male	421 (51.98)	2980 (52.03)	0.979	389 (52.57)	404 (54.59)	0.434

[a]Wilcoxon rank test; [b]Fisher exact test.

Table 2 Effects of underweight on birth outcomes: Results from the GEE model analysis

Birth outcomes	No. (%) of infants	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
BW						
BW (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**
BW 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**
BW 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**
BW <2500 g						
Normal weight	25 (3.92)	—	Ref		Ref	
Underweight	41 (5.54)	—	**1.64 (1.01-2.67)**	**0.046**	**1.64 (1.01-2.67)**	**0.047**
BW=2500-3999 g						
Normal weight	643 (86.89)	—	Ref		Ref	
Underweight	672 (90.81)	—	**1.04 (1.00-1.08)**	**0.037**	**1.04 (1.00-1.08)**	**0.037**
BW ≥ 4000 g						
Normal weight	68 (9.19)	—	Ref		Ref	
Underweight	27 (3.65)	—	**0.39 (0.26-0.61)**	**<0.001**	**0.40 (0.26-0.61)**	**<0.001**
GA						

GA (week)						
Normal weight	—	39.10 ± 1.42	Ref		Ref	
Underweight	—	39.08 ± 1.59	-0.02 (-0.18 to 0.13)	0.782	-0.02 (-0.17 to 0.13)	0.782
GA <37 weeks						
Normal weight	48 (6.49)	—	Ref		Ref	
Underweight	49 (6.62)	—	1.02 (0.69-1.50)	0.916	1.02 (0.70-1.50)	0.907
GA=37-42 weeks						
Normal weight	691 (93.38)	—	Ref		Ref	
Underweight	690 (93.24)	—	0.99 (0.97-1.03)	0.917	0.99 (0.97-1.03)	0.944
GA >40 weeks						
Normal weight	165 (21.35)	—	Ref		Ref	
Underweight	158 (22.30)	—	0.96 (0.79-1.16)	0.660	0.96 (0.79-1.16)	0.647
GA >41 weeks						
Normal weight	28 (3.78)	—	Ref		Ref	
Underweight	23 (3.11)	—	0.82 (0.48-1.42)	0.477	0.82 (0.48-1.41)	0.473
SGA, AGA and LGA						
SGA						
Normal weight	56 (7.57)	—	Ref		Ref	
Underweight	82 (11.08)	—	**1.46 (1.06-2.02)**	**0.021**	**1.46 (1.06-2.02)**	**0.021**
AGA						
Normal weight	597 (80.68)	—	Ref		Ref	
Underweight	627 (84.73)	—	**1.05 (1.00-1.10)**	**0.040**	**1.05 (1.01-1.10)**	**0.040**
LGA						
Normal weight	87 (11.76)	—	Ref		Ref	
Underweight	31 (4.19)	—	**0.36 (0.24-0.53)**	**<0.001**	**0.36 (0.24-0.53)**	**<0.001**

[a] Model 1 included only the study variable. [b] Model 2 adjusted for all of the baseline covariates.

Table 3 Effects of underweight on BW, GA and SGA: Results from the generalized linear model analysis in subgroups before PS matching

	Subgroup	N	Adjusted difference or relative risk (95% CI)	*P* value	*P* for interaction
BW (g)					
Maternal age (year)	Tertile 1 (20-27)	2104	**-134.46 (-191.23 to -77.68)**	**<0.001**	0.423
	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**	0.890
	≥ 1	2711	**-113.72 (-178.25 to -49.18)**	**<0.001**	
Fertilization method	ICSI	1799	**-147.50 (-213.02 to -81.97)**	**<0.001**	0.240
	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**	0.643
	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**	0.402
	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**	0.193
	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**	0.644
	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**	
No. of embryos transferred	1	1395	**-92.57 (-169.40 to -15.77)**	**0.018**	0.619
	≥ 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**	0.258
	Girl	3137	**-87.85 (-139.76 to -35.93)**	**<0.001**	
GA (week)					
Maternal age (year)	Tertile 1 (20-27)	2104	-0.10 (-0.28 to 0.07)	0.237	0.141

	Tertile 2 (28-30)	1974	1.17 (-0.07 to 0.41)	0.159	
	Tertile 3 (>30)	2460	-0.06 (-0.29 to 0.16)	0.587	
Gravidity	0	3827	0.01 (-0.13 to 0.16)	0.847	0.852
	≥ 1	2711	0.00 (-0.21 to 0.21)	0.999	
Fertilization method	ICSI	1799	0.01 (-0.20 to 0.21)	0.958	0.106
	IVF	4591	0.03 (-0.12 to 0.18)	0.736	
FSH (U/L)	Tertile 1 (<5.97)	2182	-0.01 (-0.26 to 0.23)	0.915	0.890
	Tertile 2 (5.98-7.40)	2177	-0.01 (-0.22 to 0.19)	0.906	
	Tertile 3 (>7.40)	2179	0.04 (-0.16 to 0.24)	0.696	
Timing of embryo transfer	Fresh embryo transfer	3819	-0.07 (-0.22 to 0.09)	0.397	0.038
	Frozen embryo transfer	2719	0.15 (-0.05 to 0.36)	0.132	
Day 3 or 5	Cleavage stage transfer	4191	-0.06 (-0.21 to 0.09)	0.399	0.200
	Blastocyst transfer	2347	0.10 (-0.11 to 0.31)	0.341	
Endometrial thickness (mm)	Tertile 1 (<9.6)	2217	-0.07 (-0.28 to 0.14)	0.504	0.588
	Tertile 2 (9.7-11.4)	2164	0.05 (-0.15 to 0.26)	0.611	
	Tertile 3 (>11.4)	2157	0.01 (-0.20 to 0.22)	0.920	
No. of embryos transferred	1	1395	-0.03 (-0.28 to 0.21)	0.780	0.712
	≥ 2	5143	0.01 (-0.13 to 0.15)	0.885	
Infant's sex	Boy	3401	-0.02 (-0.19 to 0.15)	0.846	0.852
	Girl	3137	0.01 (-0.16 to 0.19)	0.883	
SGA					
Maternal age (year)	Tertile 1(20-27)	2104	1.36 (0.95-1.94)	0.093	0.186
	Tertile 2 (28-30)	1974	**1.78 (1.25-2.55)**	**0.002**	
	Tertile 3 (>30)	2460	1.08 (0.70-1.66)	0.734	
Gravidity	0	3827	**1.49 (1.16-1.93)**	**0.002**	0.279
	≥ 1	2711	1.17 (0.77-1.77)	0.471	
Fertilization method	ICSI	1799	**1.65 (1.13-2.41)**	**0.010**	0.463
	IVF	4591	1.27 (0.97-1.66)	0.086	
FSH (U/L)	Tertile 1 (<5.97)	2182	**1.57 (1.02-2.45)**	**0.041**	0.875
	Tertile 2 (5.98-7.40)	2177	**1.45 (1.02-2.05)**	**0.038**	

	Tertile 3 (>7.40)	2179	1.29 (0.91-1.84)	0.157	
Timing of embryo transfer	Fresh embryo transfer	3819	**1.42 (1.10-1.84)**	**0.007**	0.780
	Frozen embryo transfer	2719	1.34 (0.89-2.02)	0.158	
Day 3 or 5	Cleavage stage transfer	4191	**1.36 (1.04-1.78)**	**0.027**	0.851
	Blastocyst transfer	2347	**1.46 (1.02-2.09)**	**0.040**	
Endometrial thickness (mm)	Tertile 1 (<9.6)	2217	**1.52 (1.04-2.21)**	**0.029**	0.581
	Tertile 2 (9.7-11.4)	2164	1.15 (0.77-1.71)	0.494	
	Tertile 3 (>11.4)	2157	**1.51 (1.06-2.16)**	**0.022**	
No. of embryos transferred	1	1395	1.29 (0.83-2.00)	0.257	0.692
	≥ 2	5143	**1.42 (1.11-1.83)**	**0.005**	
Infant's sex	Boy	3401	**1.39 (1.03-1.88)**	**0.031**	0.768
	Girl	3137	**1.41 (1.03-1.92)**	**0.031**	

Maternal age, FSH, and endometrial thickness were classified by tertiles. All of the baseline covariates were adjusted in the Model. Peak estradiol level was also adjusted in the Model in fresh embryo transfer group.

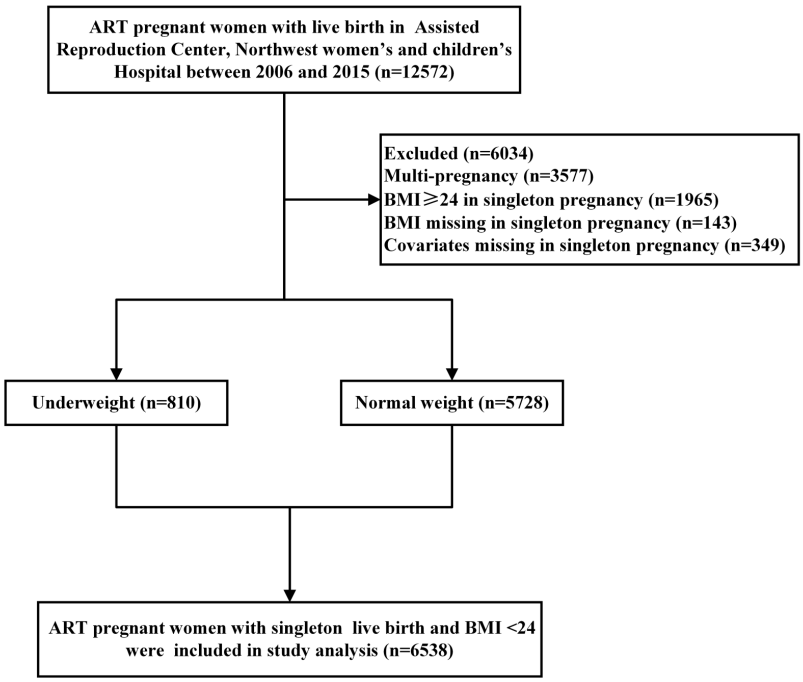

Figure 1. Flow diagram of sampling strategy with exclusion criteria.

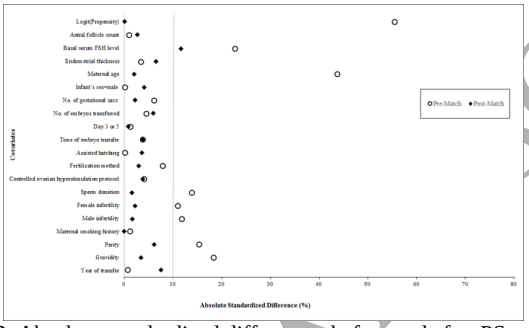

Figure 2. Absolute standardized differences before and after PS matching.