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The interaction effect of pre-pregnancy body mass index and maternal age on the risk of pregnancy complications in twin pregnancies after assisted reproductive technology

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ABSTRACT

Objective: The widespread use of assisted reproductive technology (ART) has led to an increased twin pregnancy rate and increased risk of pregnancy complications. Pre-pregnancy body mass index (BMI) and maternal age are both risk factors for pregnancy complications. This study aimed to explore whether there is an interaction effect between pre-pregnancy BMI and maternal age on pregnancy complications in women with twin pregnancies after ART.

Methods: Data of 445,750 women with twin pregnancies after ART were extracted from the National Vital Statistics System (NVSS) database in 2016-2021 in this retrospective cohort study. Univariate and multivariate logistic regression analyses were used to explore (1) the associations between pre-pregnancy BMI, maternal age, and total pregnancy complications; (2) interaction effect between pre-pregnancy BMI and maternal age on total pregnancy complications; and (3) this interaction effect in parity, race, gestational weight gain (GWG), and preterm birth subgroups. The evaluation indexes were odds ratios (ORs), relative excess risk of interaction (RERI), attributable proportions of interaction (AP), and synergy index (S) with 95% confidence intervals (CIs).

Results: A total of 6,827 women had pregnancy complications. After adjusting for the covariates, compared with women had non-AMA and pre-pregnancy BMI $<25\ kg/m^2$, higher maternal age combined with higher pre-pregnancy BMI was associated with higher odds of total pregnancy complications [OR = 2.16, 95%CI: (1.98-2.36)]. The RERI (95% CI) was 0.22 (0.04-0.41), AP (95% CI) was 0.10 (0.02-0.19), and S (95% CI) was 1.24 (1.03-1.49). Subgroup analysis results indicated that the potential additive effect between pre-pregnancy BMI and maternal age on total pregnancy complications was also found in women with different race, multipara/unipara, GWG levels, or preterm births/non-preterm births (all $p < 0.05$).

Conclusion: Pre-pregnancy BMI and maternal age may have an additive effect on the odds of pregnancy-related complications in women with twin pregnancy after ART.

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Pre-pregnancy BMI; maternal age; interaction effect; ART; twin pregnancy; NVSS

Introduction

With the increasing prevalence of infertility and delay of childbearing worldwide, the use of assisted reproductive technology (ART) is expanding rapidly [1]. More than seven million babies are born worldwide each year in virtue of ART [2]. Twin pregnancies caused by ART have increased globally in recent years due to the transfer of two or three embryos during ART to achieve a higher pregnancy rate [3]. Approximately 21.8% of all deliveries after ART occurred in pregnancies with more than one fetus [3]. ART improved clinical pregnancy rates and cumulative live birth rates [4], and however, had some adverse effects on the mother and newborn, especially non-physiological interventions during ART, such as the use of extra-physiological doses of hormonal drugs [5], which may influence the overall environment of pregnancy and interfere with gametogenesis or embryonic development [6]. Studies have reported that women who conceived by ART had an increased risk of maternal complications, including pregnancy-induced

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hypertension (PIH), gestational diabetes (GDM), bleeding, and postpartum depression [7,8]. Therefore, the prevention of pregnancy complications has important clinical significance in reducing the adverse outcomes of twin pregnancies after ART.

In recent years, women with delayed childbearing and advanced maternal age (AMA) had an increased need for ART as well as a higher risk of pregnancy complications [9]. Moaddab et al. [10] found that among women who were pregnant through ART, those with AMA (≥40 years old) had a significantly increased risk of pregnancy complications. Zhang et al. [11] also indicated that the incidence of gestational complications may increase in AMA singleton pregnant women aged ≥45 years old. Obesity during pregnancy is a major public health concern [12]. About 40% of pregnant women are overweight or obese, which is considered a major risk factor for maternal and perinatal morbidity and mortality in the United States [13]. Accordingly, body mass index (BMI) may be an important controllable influencing factor in reducing the risk of gestational complications. A meta-analysis confirmed the association between elevated pre-pregnancy BMI and higher odds of adverse maternal and fetal/neonatal outcomes [14]. A population-based study found that the association between pre-pregnancy BMI and the risk of adverse neonatal outcomes in singleton pregnancies varied according to the age of pregnancy, and the risk of adverse outcomes due to overweight and obesity increased with increasing maternal age [15]. AMA and obesity were both risk factors for needing of ART use and higher pregnancy complications, and however, the interaction effect between pre-pregnancy BMI and maternal age are not clear.

Herein, this study aims to explore the interaction effect between pre-pregnancy BMI and maternal age on the risk of pregnancy complications in women with twin pregnancies after ART to provide some references for the prevention of adverse pregnancy outcomes among women receiving ART.

Methods

Study design and population

The demographic and clinical data of women with twin pregnancies after ART in this retrospective cohort study were extracted from the National Vital Statistics System (NVSS) database from 2016 to 2021. NVSS is an official program that provides an extensive and longitudinal vital statistics database that includes natality data of all births registered within the United States in 50 states and the District of Columbia (https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm). The mother's worksheet and facility worksheet were used to collect data, and the medical and health information of the mother and infant was extracted from the worksheet completed by hospital staff [16].

A total of 445,750 women with twin pregnancies were included in the current study. We excluded women who failed the twin matching, or have not received ART, or have pre-pregnancy diabetes mellitus (DM) or hypertension, or without information of BMI or GWG. Ultimately, 21,770 of them were eligible. Since the NVSS database is publicly available and the data are de-identified, no approval from our Institutional Review Board (IRB) is required for this study.

Measurement of pre-pregnancy BMI

Pre-pregnancy BMI (kg/m^2) values were calculated using NVSS officially providing the following computational formula: mother's pre-pregnancy weight (lb)/[mother's height (in)]^2 × 703. BMI values before pregnancy were classified into two groups (BMI <25 and BMI ≥25) according to the World Health Organization (WHO) weight classification criteria [17].

Definition of maternal age

Maternal age was calculated using the following computational formula: maternal age = delivery age - gestational age/52.13 (weeks). We then divided the participants into non-AMA group (aged <35 years old) and AMA group (aged ≥35 years old) [9].

Study outcome

The study outcome was the occurrence of total pregnancy complications. Total pregnancy complications including PIH (including pre-eclampsia), eclampsia, and GDM, while non-pregnancy complications were considered only if none of the above diseases during the course of pregnancy.

Variables collection

We collected variables including maternal age (years), mother's race, mother's education level, marital status, father's age, father's race, father's education level, smoking status (before pregnancy and during pregnancy), timing of prenatal care initiation (months), pre-pregnancy BMI, gestational age (weeks), previous

preterm births, previous cesarean delivery, parity, GWG (kg), and neonatal sex.

GWG was calculated according to the NVSS variable "WTGAIN': GWG = delivery weight - pre-pregnancy weight. The classification of GWG was based on the 2009 Institute of Medicine (IOM) guidelines (excessive, normal, and insufficient GWG) [18]. The recording periods of smoking status were divided into three periods (first three months, 4-6 months, 7-10 months and unknown). Smoking before pregnancy was classified by the number of cigarettes smoked (0 represents nonsmoking, 1-98 represents smoking, and ≥99 represents unknown), while smoking during pregnancy was classified according to the number of cigarettes smoked during three periods of pregnancy (cigarette smoking in all three periods of pregnancy was 0 representing nonsmoking). Neonatal sex was classified as male-male, male-female, and female-female.

The variables for developing the algorithm to achieve twin pairs matching included dob_yy, mager, mbstate_rec, restatus, mrace31, mrace6, mrace15, mbrace, mhisp_r, mracehisp, dmar, meduc, fagecomb, frace31, frace6, frace15, fbrace, fhisp_r, fracehisp, feduc, precare, previs, cig_0, cig_1, cig_2, cig_3, m_ht_in, bmi, pwgt_r, dwgt_r, wtgain, rf_pdiab, rf_gdiab, rf_phype, rf_ghype, rf_ehype, rf_inftr, rf_fedrg, rf_artec, ip_gon, ip_syph, ip_chlam, ip_hepatb, ip_hepatc, mm_mtr, mm_plac, mm_rupt, mm_uhyst, mm_aicu, pay, dlmp_mm, dlmp_yy and oegest_comb.

Statistical analysis

Normal distributed data were described using the mean ± standard deviation (mean ± SD), and t-test was used for comparison between the two groups. Non-normal distributed data were described by median and quartiles [M (Q1, Q3)], and the Mann-Whitney U rank test was used for comparison. Categorical data were expressed as frequency and constituent ratio [N (%)], and chi-square test (χ^2) or Fisher's exact test was used for comparison.

Univariate logistic regression analysis was used to screen for covariates. Univariate and multivariate logistic regression analyses were used to explore (1) the association between maternal age and total pregnancy complications; (2) the association between pre-pregnancy BMI and total pregnancy complications; and (3) the interaction effect between pre-pregnancy BMI and maternal age on total pregnancy complications. Subgroup analyses of parity, race, GWG, and preterm birth were also performed. The multivariate model adjusted for mother's race, mother's education level, timing of initiation of prenatal care, smoke during pregnancy, previous cesarean, gestational age, parity and GWG. The evaluation indexes were odds ratios (ORs), relative excess risk of interaction (RERI), attributable proportions of interaction (AP), and synergy index (S) with 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$.

Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA) and R version 4.2.2 (2022-10-31 ucrt) (Institute for Statistics and Mathematics, Vienna, Austria). Heatmap was drawn using GraphPad 8.0.1 (GraphPad Software, La Jolla, CA). Missing data (including mother's education level, timing of prenatal care initiation, father's age, father's race, and father's education level) were recognized as "unknown" categories.

Results

Characteristics of study population

Figure 1 shows the flowchart of participants screening. We initially included 445,750 women with twin pregnancies in the NVSS from 2016 to 2021. Those who failed twin matching ($n = 162544$), or have not receive ART ($n = 259822$), or diagnosed with pre-pregnancy DM ($n = 241$) or pre-pregnancy hypertension ($n = 824$), or without the information of BMI ($n = 423$) or GWG ($n = 126$) were excluded. Finally, 21,770 of them were eligible.

The characteristics of participants were showed in Table 1. Among the eligible women, 6,827 (31.36%) had total pregnancy complications. In the non-pregnancy complications group, 6,437 (43.08%) women had AMA, while the number in the pregnancy complications group was 3,312 (48.51%). There were respectively

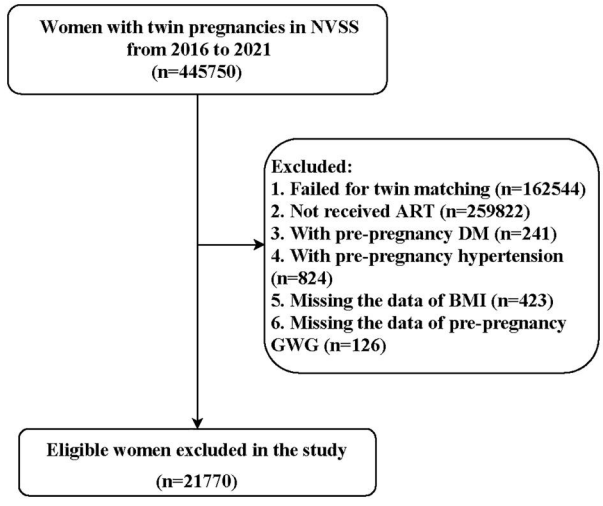

Figure 1. Flow chart of the study population screening.

Table 1. Characteristics of women with/without pregnancy complications.

Variables	Total ($n = 21770$)	Non-pregnancy complications ($n = 14943$)	Pregnancy complications ($n = 6827$)	*P*
Maternal age, years, n (%)				<0.001
<35	12021 (55.22)	8506 (56.92)	3515 (51.49)	
≥35	9749 (44.78)	6437 (43.08)	3312 (48.51)	
Mother's race, n (%)				<0.001
White	17114 (78.61)	11862 (79.38)	5252 (76.93)	
Black	1347 (6.19)	921 (6.16)	426 (6.24)	
Other	3309 (15.20)	2160 (14.45)	1149 (16.83)	
Mother's education level, n (%)				<0.001
12th grade with no diploma or less	283 (1.30)	162 (1.08)	121 (1.77)	
High school graduate or GED completed	1570 (7.21)	1074 (7.19)	496 (7.27)	
Associate degree or some college credit	4411 (20.26)	3008 (20.13)	1403 (20.55)	
Bachelor's degree and above	14662 (67.35)	10067 (67.37)	4595 (67.31)	
Unknown	844 (3.88)	632 (4.23)	212 (3.11)	
Marital status, n (%)				0.189
Married	17493 (92.21)	12005 (92.04)	5488 (92.59)	
Unmarried	1477 (7.79)	1038 (7.96)	439 (7.41)	
Father's age, years, M (Q_1, Q_3)				<0.001
<40	14125 (64.88)	9824 (65.74)	4301 (63.00)	
≥40	6661 (30.60)	4434 (29.67)	2227 (32.62)	
Unknown	984 (4.52)	685 (4.58)	299 (4.38)	
Father's race, n (%)				0.744
White	15771 (72.44)	10845 (72.58)	4926 (72.15)	
Black	1231 (5.65)	847 (5.67)	384 (5.62)	
Other	4768 (21.90)	3251 (21.76)	1517 (22.22)	
Father's education level, n (%)				<0.001
12th grade with no diploma or less	401 (1.84)	249 (1.67)	152 (2.23)	
High school graduate or GED completed	2365 (10.86)	1618 (10.83)	747 (10.94)	
Associate degree or some college credit	4736 (21.75)	3125 (20.91)	1611 (23.60)	
Bachelor's degree and above	12546 (57.63)	8711 (58.29)	3835 (56.17)	
Unknown	1722 (7.91)	1240 (8.30)	482 (7.06)	
Smoke before pregnancy, n (%)				0.442
No	21503 (98.77)	14756 (98.75)	6747 (98.83)	
Yes	230 (1.06)	158 (1.06)	72 (1.05)	
Unknown	37 (0.17)	29 (0.19)	8 (0.12)	
Smoke during pregnancy, n (%)				<0.001
No	21314 (97.91)	14565 (97.47)	6749 (98.86)	
Yes	82 (0.38)	56 (0.37)	26 (0.38)	
Unknown	374 (1.72)	322 (2.15)	52 (0.76)	
Timing of initiation of prenatal care, n (%)				0.038
1st trimester during pregnancy	9150 (42.03)	6203 (41.51)	2947 (43.17)	
2nd trimester during pregnancy	11671 (53.61)	8088 (54.13)	3583 (52.48)	
3rd trimester during pregnancy	563 (2.59)	399 (2.67)	164 (2.40)	
Unknown	386 (1.77)	253 (1.69)	133 (1.95)	
Pre-pregnancy BMI, kg/m^2, n (%)				<0.001
<25	10690 (49.10)	7916 (52.97)	2774 (40.63)	
≥25	11080 (50.90)	7027 (47.03)	4053 (59.37)	
Gestational age, weeks, Mean ± SD	35.57 ± 3.45	35.66 ± 3.65	35.39 ± 2.97	<0.001
Previous preterm births, n (%)				0.259
No	21024 (96.57)	14445 (96.67)	6579 (96.37)	
Yes	746 (3.43)	498 (3.33)	248 (3.63)	
Previous cesarean, n (%)				0.021
No	18755 (86.15)	12819 (85.79)	5936 (86.95)	
Yes	3015 (13.85)	2124 (14.21)	891 (13.05)	
Parity, n (%)				<0.001
Unipara	13350 (61.32)	8749 (58.55)	4601 (67.39)	
Multipara	8420 (38.68)	6194 (41.45)	2226 (32.61)	
GWG, n (%)				<0.001
Inadequate	8879 (40.79)	6337 (42.41)	2542 (37.23)	
Normal	8969 (41.20)	6210 (41.56)	2759 (40.41)	
Excessive	3922 (18.02)	2396 (16.03)	1526 (22.35)	
Neonatal sex, n (%)				0.541
F-F	5706 (26.21)	3908 (26.15)	1798 (26.34)	
F-M	9974 (45.82)	6821 (45.65)	3153 (46.18)	
M-M	6090 (27.97)	4214 (28.20)	1876 (27.48)	

Statistics: t test and chi-square test.
M: median, Q1:1st quartile, Q3:3st quartile, BMI: body mass index, SD: standard deviation, GWG: gestational weight gain, F: female, M: male.

7,027 (47.03%) and 4,053 (59.37%) women with pre-pregnancy BMI <25 kg/m^2 in non-pregnancy complications group and pregnancy complications group. The number of women who had excessive GWG in these two groups were respectively 2,396 and 1,526. In addition, mother's race, mother's education level,

father's age, father's education level, smoking during pregnancy, timing of prenatal care initiation, gestational age, previous cesarean section, and parity were all significantly different between women with and without total pregnancy complications (all $p < 0.05$).

Associations between pre-pregnancy BMI, maternal age, and total pregnancy complications

We first screened for the covariates associated with total pregnancy complications (Table S1). Then we explored the associations between pre-pregnancy BMI, maternal age, and total pregnancy complications (Table 2). After adjusting for covariates, we found that compared with women not have AMA, higher maternal age was associated with high odds of total pregnancy complications [OR = 1.31, 95%CI: (1.23-1.40)]. Similarly, compared with women had a pregnancy BMI $<25\ kg/m^2$, those who with a pregnancy BMI $\geq 25\ kg/m^2$ seemed to have high odds of total pregnancy complications [OR = 1.68, 95%CI: (1.58-1.78)].

Interaction effect between pre-pregnancy BMI and maternal age on total pregnancy complications

Figure 2 showed the population distribution of different interaction effects between pre-pregnancy BMI and maternal age in the total study populations. Also, the interaction effect between pre-pregnancy BMI and maternal age on total pregnancy complications was

Table 2. Associations between pre-pregnancy BMI, maternal age, and total pregnancy complications.

	Univariate model		Multivariate model	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*
Maternal age				
<35 years old	Ref		Ref	
≥35 years old	1.25 (1.18-1.32)	<0.001	1.31 (1.23-1.40)	<0.001
Pre-pregnancy BMI				
$<25\ kg/m^2$	Ref		Ref	
$\geq 25\ kg/m^2$	1.65 (1.55-1.74)	<0.001	1.68 (1.58-1.78)	<0.001

BMI: body mass index, OR: odds ratio, CI: confidence interval, Ref: reference.
Univariate model: the crude model, Multivariate model: adjusted for mother's race, mother's education level, timing of initiation of prenatal care, smoke during pregnancy, previous cesarean, gestational age, parity and GWG.

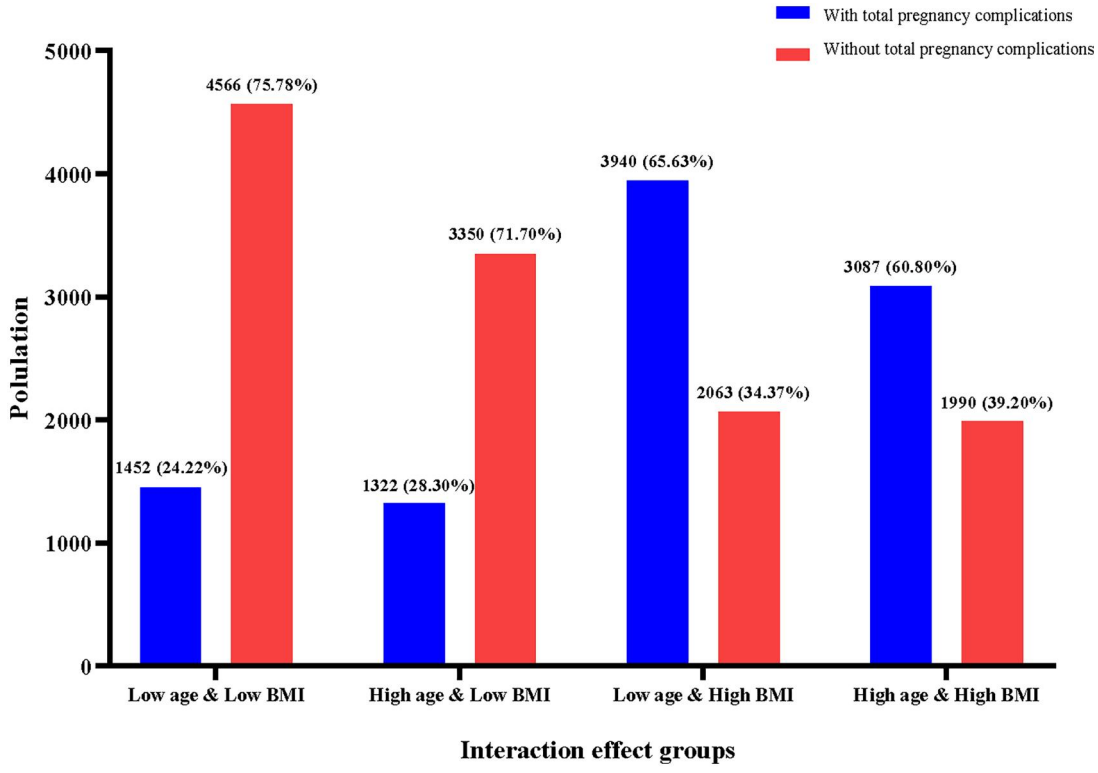

Figure 2. The population distribution of interaction between pre-pregnancy BMI and maternal age in total study population.

showed in Table 3. After adjusting for covariates, compared with women not have AMA and had pre-pregnancy BMI $<25\ kg/m^2$, higher maternal age combined with higher pre-pregnancy BMI was associated with higher odds of total pregnancy complications [OR = 2.16, 95%CI: (1.98-2.36)], with the RERI of 0.22, AP of 0.10, and S of 1.24. Moreover, Figure 3 was a heatmap of the interaction effect between pre-pregnancy BMI and maternal age on total pregnancy complications, indicating that pre-pregnancy BMI and maternal age may have an additive effect on the odds of total pregnancy complications.

Interaction effect between pre-pregnancy BMI and maternal age on total pregnancy complications in parity, race, GWG and preterm births subgroups

We further explored the interaction effect between pre-pregnancy BMI and maternal age in the parity, race, GWG, and preterm birth subgroups (Table 4). The results showed that higher pre-pregnancy BMI combined with higher maternal age was associated with higher odds of total pregnancy complications in women had different races, multipara/unipara, GWG levels, and preterm births/non-preterm births (all $p < 0.05$).

Table 3. The interaction of pre-pregnancy BMI and maternal age on the risk of pregnancy complications.

		Univariate model		Multivariate model	
Maternal age	Pre-pregnancy BMI	OR (95% CI)	*P*	OR (95% CI)	*P*
<35	<25	Ref		Ref	
≥35	<25	1.24 (1.14-1.35)	<0.001	1.28 (1.17-1.41)	<0.001
<35	≥25	1.65 (1.52-1.78)	<0.001	1.66 (1.53-1.80)	<0.001
≥35	≥25	2.03 (1.87-2.20)	<0.001	2.16 (1.98-2.36)	<0.001
RERI (95% CI)		0.14 (-0.03-0.31)		0.22 (0.04-0.41)	
AP (95% CI)		0.07 (-0.02-0.15)		0.10 (0.02-0.19)	
S (95% CI)		1.16 (0.96-1.40)		1.24 (1.03-1.49)	

BMI: body mass index, OR: odds ratio, CI: confidence interval, Ref: reference, RERI: relative excess risk of interaction, AP: attributable proportions of interaction, S: synergy index.
Univariate model: the crude model, Multivariate model: adjusted for mother's race, mother's education level, timing of initiation of prenatal care, smoke during pregnancy, previous cesarean, gestational age, parity and GWG.

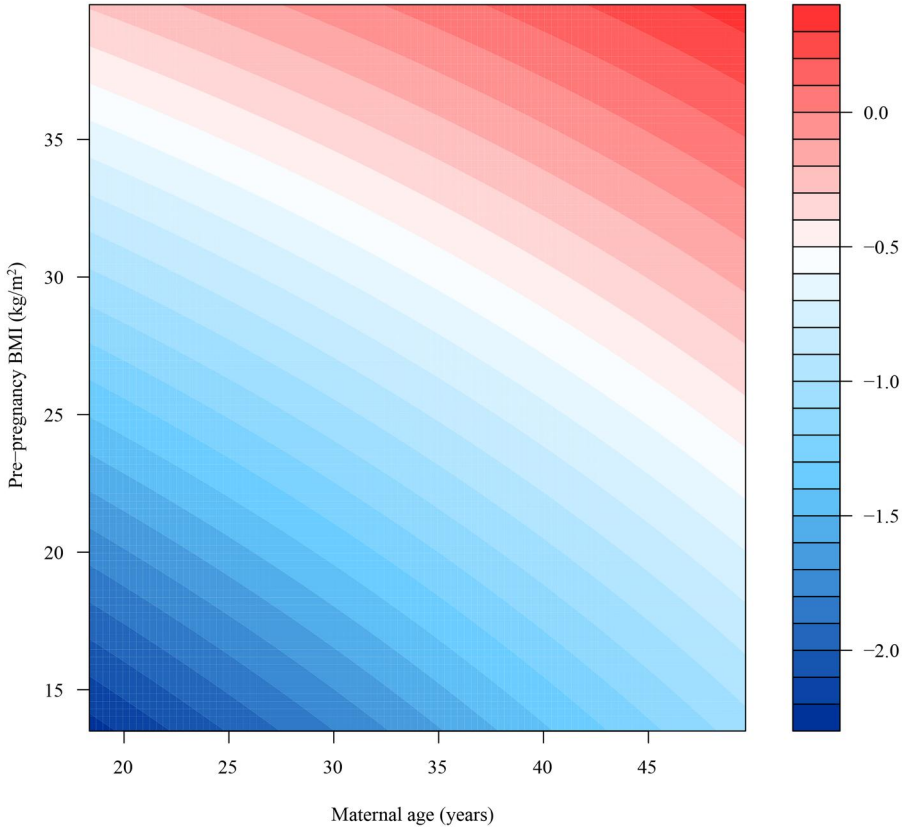

Figure 3. Heatmap of the interaction between pre-pregnancy BMI and maternal age on total pregnancy complications. Blue color represents the low pre-pregnancy BMI and low maternal age, while red color represents the high pre-pregnancy BMI and high maternal age. The scale represents the odds of total pregnancy complications.

Table 4. The interaction of pre-pregnancy BMI and maternal age on the risk of pregnancy complications in parity, race, GWG and preterm births subgroups.

	Univariate model		Multivariate model	
Subgroup	OR (95% CI)	*P*	OR (95% CI)	*P*
Multipara (n = 8420)				
Age <35 & BMI <25	Ref		Ref	
Age ≥35 & BMI <25	1.32 (1.18 – 1.46)	<0.001	1.27 (1.13 – 1.42)	<0.001
Age <35 & BMI ≥25	1.63 (1.48 – 1.79)	<0.001	1.61 (1.46 – 1.77)	<0.001
Age ≥35 & BMI ≥25	2.13 (1.92 – 2.36)	<0.001	2.06 (1.84 – 2.30)	<0.001
Unipara (n = 13350)				
Age <35 & BMI <25	Ref		Ref	
Age ≥35 & BMI <25	1.37 (1.16 – 1.60)	<0.001	1.34 (1.13 – 1.58)	<0.001
Age <35 & BMI ≥25	1.87 (1.60 – 2.18)	<0.001	1.81 (1.55 – 2.12)	<0.001
Age ≥35 & BMI ≥25	2.45 (2.11 – 2.84)	<0.001	2.40 (2.06 – 2.81)	<0.001
White (n = 17114)				
Age <35 & BMI <25	Ref		Ref	
Age ≥35 & BMI <25	1.16 (1.05 – 1.29)	0.004	1.22 (1.10 – 1.36)	<0.001
Age <35 & BMI ≥25	1.72 (1.57 – 1.88)	<0.001	1.68 (1.54 – 1.84)	<0.001
Age ≥35 & BMI ≥25	2.07 (1.89 – 2.27)	<0.001	2.17 (1.96 – 2.39)	<0.001
Black (n = 13350)				
Age <35 & BMI <25	Ref		Ref	
Age ≥35 & BMI <25	1.67 (1.04 – 2.67)	0.034	1.68 (1.03 – 2.76)	0.039
Age <35 & BMI ≥25	1.74 (1.15 – 2.65)	0.009	1.76 (1.14 – 2.70)	0.010
Age ≥35 & BMI ≥25	2.67 (1.78 – 4.00)	<0.001	2.74 (1.78 – 4.20)	<0.001
Other (n = 8420)				
Age <35 & BMI <25	Ref		Ref	
Age ≥35 & BMI <25	1.34 (1.11 – 1.62)	0.003	1.43 (1.16 – 1.75)	0.001
Age <35 & BMI ≥25	1.46 (1.18 – 1.80)	0.001	1.55 (1.25 – 1.93)	<0.001
Age ≥35 & BMI ≥25	1.78 (1.44 – 2.20)	<0.001	2.09 (1.66 – 2.63)	<0.001
Inadequate GWG (n = 8879)				
Age <35 & BMI <25	Ref		Ref	
Age ≥35 & BMI <25	1.40 (1.22 – 1.61)	<0.001	1.37 (1.19 – 1.59)	<0.001
Age <35 & BMI ≥25	1.71 (1.50 – 1.94)	<0.001	1.82 (1.59 – 2.08)	<0.001
Age ≥35 & BMI ≥25	2.12 (1.86 – 2.42)	<0.001	2.35 (2.03 – 2.71)	<0.001
Normal GWG (n = 8969)				
Age <35 & BMI <25	Ref		Ref	
Age ≥35 & BMI <25	1.15 (1.01 – 1.32)	0.036	1.21 (1.04 – 1.39)	0.011
Age <35 & BMI ≥25	1.60 (1.42 – 1.81)	<0.001	1.61 (1.41 – 1.82)	<0.001
Age ≥35 & BMI ≥25	1.85 (1.63 – 2.11)	<0.001	1.96 (1.70 – 2.25)	<0.001
Excessive GWG (n = 3922)				
Age <35 & BMI <25	Ref		Ref	
Age ≥35 & BMI <25	1.18 (0.95 – 1.46)	0.126	1.20 (0.96 – 1.51)	0.105
Age <35 & BMI ≥25	1.49 (1.25 – 1.78)	<0.001	1.50 (1.24 – 1.80)	<0.001
Age ≥35 & BMI ≥25	2.06 (1.71 – 2.47)	<0.001	2.22 (1.82 – 2.71)	<0.001
Preterm births (n = 746)				
Age <35 & BMI <25	Ref		Ref	
Age ≥35 & BMI <25	1.30 (0.77 – 2.22)	0.328	1.31 (0.76 – 2.23)	0.348
Age <35 & BMI ≥25	1.88 (1.15 – 3.06)	0.012	1.94 (1.17 – 3.23)	0.011
Age ≥35 & BMI ≥25	3.29 (2.07 – 5.22)	<0.001	3.54 (2.13 – 5.89)	<0.001
Non-preterm births (n= 21024)				
Age <35 & BMI <25	Ref		Ref	
Age ≥35 & BMI <25	1.24 (1.14 – 1.36)	<0.001	1.29 (1.17 – 1.41)	0.001
Age <35 & BMI ≥25	1.64 (1.52 – 1.78)	<0.001	1.66 (1.52 – 1.80)	<0.001
Age ≥35 & BMI ≥25	1.99 (1.83 – 2.16)	<0.001	2.12 (1.94 – 2.33)	<0.001

BMI: body mass index, GWG: gestational weight gain, OR: odds ratio, CI: confidence interval, Ref: reference.
Univariate model: the crude model;.
Multivariate model for parity subgroup: adjusted for mother's race, mother's education level, timing of initiation of prenatal care, smoke during pregnancy, previous cesarean, gestational age and GWG;.
Multivariate model for race subgroup: adjusted for mother's education level, timing of initiation of prenatal care, smoke during pregnancy, previous cesarean, gestational age, parity and GWG;.
Multivariate model for GWG subgroup: adjusted for mother's race, mother's education level, timing of initiation of prenatal care, smoke during pregnancy, previous cesarean, gestational age and parity;.
Multivariate model for preterm births subgroup: adjusted for mother's race, mother's education level, timing of initiation of prenatal care, smoke during pregnancy, previous cesarean, gestational age, parity and GWG.

Discussion

This retrospective cohort study explored the interaction effect between pre-pregnancy BMI and maternal age on the risk of pregnancy complications in twin pregnancies after ART. The results showed a potential additive effect between pre-pregnancy BMI and maternal age on pregnancy complications. This relationship was also found in women with different races, multipara/unipara, different GWG levels, and preterm births/non-preterm births.

To our knowledge, few studies have explored the interaction effect between pre-pregnancy BMI and maternal age on the risk of pregnancy complications in twin pregnancies after ART. Our results indicated that higher maternal age, combined with higher pre-pregnancy BMI, was associated with increased odds of pregnancy complications. Guarga et al. [19] showed that women with maternal age >35 years old had increased rates of hypertensive disorders and DM compared to younger women. Smithson et al. [20] found that women of very AMA (≥45 years old) had a significantly higher risk of chronic hypertension, gestational hypertension, preeclampsia with and without severe features, superimposed preeclampsia, and eclampsia (at least 2-fold) than the AMA (35-44 years old) group. Scime et al. [21] also reported that pregnancy complications were more common among women aged ≥35 years old.

Twin pregnancy, *in vitro* fertilization, and AMA (often defined as ≥35 years) are independent indicators of many adverse obstetric outcomes and lead to the aggravation of obstetric risk due to their coexistence [22]. Zhu et al. [23] observed a significantly higher rate of diastolic function decline in maternal women aged ≥35 years old and suggested the susceptibility of diastolic function to cardiac maladaptation of pregnancy in advanced age. GDM is a common pregnancy complication in women with AMA, and the potential mechanism of the increased incidence may be due to changes in blood volume, vascular endothelial injury, insulin receptor, and decreased insulin affinity with aging [24,25]. Gestational hypertensive disorders are the most prevalent complications within gestation, and preeclampsia is relatively severe and closely related to pregnancy outcomes [26]. Preeclampsia appears after almost 20 weeks, while those involved in pathogenetic mechanisms may last starting from an early stage, thus leading to a hemodynamic change in maternal circulation, and cardiac diastolic function is sensitive to the change [27]. Pathogenetic mechanisms involved in preeclampsia include oxidative and endoplasmic reticulum stress, intravascular inflammation, and endothelial dysfunction [28]. Thus, women with AMA who intend to undergo ART should pay great attention to the dynamic monitoring of cardiovascular deconditioning or insulin function. However, the difference of pathogenetic mechanisms in pregnancy complications between single and twin pregnancy after ART is needed further exploration.

Pre-pregnancy BMI is a risk factor for GDM complicated by preeclampsia, preterm delivery, gestational hypertension, and macrosomia [29]. In this study, a total of 4,053 (59.37%) women with pre-pregnancy BMI ≥25 among those who had pregnancy complications, but most of the one who without pregnancy complications had a BMI <25. A retrospective cohort study of women with twin pregnancies found that, in the normal-weight group, GWG above recommendations was associated with an increased risk of hypertensive disorders [30]. Another population-based observational cohort study showed that women with pre-pregnancy BMI classified as overweight or obese had an increased risk of preeclampsia and gestational hypertension [31]. Ren et al. [32] indicated that pre-pregnancy BMI and GWG affected the risk of preeclampsia and its clinical subtypes. The mechanisms underlying the adverse effects of pre-pregnancy obesity/overweight on pregnancy complications remain unclear, and recent studies have implicated that perturbations in the metabolome during pregnancy may play an important role [33,34]. Women who had a high pre-pregnancy BMI, diagnosed as GDM or preeclampsia seemed to have alterations in blood or urinary metabolome, in which several lipoprotein-related variables, triglycerides, specific amino acids, fatty acids, and inflammatory markers changed [35,36]. Researchers believed that women with overweight or obesity had baseline excessive vascular inflammation, and the observed higher risk of late-onset preeclampsia with rising BMI may be secondary to intraplacental (intervillous) malperfusion and hypoxia due to mechanical restrictions as the growing placenta reaches its size limit [37,38]. These results suggested women who are preparing for pregnancy to maintain a normal BMI through a combination of proper diet and proper exercise to reduce the risk of pregnancy complications.

We additionally explored the potential interaction effect between pre-pregnancy BMI and maternal age on total pregnancy complications in subgroups of races, parity, GWG, and preterm births. Liu et al. [15] showed that maternal pre-pregnancy obesity is significantly related to an increased risk of preterm birth; however, the risk differs according to maternal age, race, and ethnicity. In non-Hispanic white, Hispanic, and non-Hispanic black women, maternal obesity was inversely associated with preterm birth among those older than 30 years old [15]. A retrospective cohort study indicated that among women with overweight/obesity, Hispanic and NH Native-Hawaiian/other Pacific Islander had a lower risk of preeclampsia, whereas the risk of GDM increased among all race/ethnicities except NH American Indian/Alaskan Native and NH Native-Hawaiian/Other Pacific Islander, respectively [39]. We presumed that complicated factors such as

diet, physical and social environments, health behaviors, and access to prenatal care may account for these differences. There are well-recognized associations between excessive GWG and adverse pregnancy outcomes, including preeclampsia, GDM, and cesarean birth [40]. In our study, 6,337 (42.41%) of women without pregnancy complications had an inadequate GWG. We think a possible explanation for this is that nutritional therapy and exercise interventions are the first-line treatments to control blood glucose levels after GDM diagnosis. However, in fact, some patients may overlimit their diet to achieve satisfactory blood glucose control, which limits weight gain and even leads to weight loss [41]. Besides, Luo et al. [42] indicated that nulliparous women with AMA showed increased risks for gestational hypertension, preeclampsia/eclampsia, and premature rupture of membranes, whereas multiparous women with AMA showed an increased risk for GDM. The pathophysiology of hypertensive disease in nulliparous and multiparous pregnant women has been elucidated so far, and it may involve immune maladaptation, although no conclusion [43]. It has also been reported that multiparity is linked to an increased risk of GDM [44], although the effects of increasing parity on insulin sensitivity or β-cell function have not been detected [45]. In the current study, most of women not have a history of preterm births, in detail, 14,445 (96.67%) in the non-pregnancy complications group while 6,579 (96.37%) in the pregnancy complications group. Preterm delivery in the medical history of women has been demonstrated to be associated with increased cardiovascular risk, such as higher systolic and/or diastolic blood pressure [46], hypertension [47], coronary artery calcification related systolic blood pressure [48], an altered atherogenic lipid profile or hypercholesterolemia [49], and Type 2 DM [50]. We assumed that women with a previous preterm delivery may have an increased risk of pregnancy complications due to cardiovascular damage from preterm birth.

Data in this retrospective cohort study was extracted from the NVSS database so that the sample size was large and partly representative. Our study explored the potential interaction effect between pre-pregnancy BMI and maternal age on pregnancy complications in twin pregnancies after ART, which may provide some references for the opportune administration of ART and preparation for pregnancy. However, there are also some limitations. Information of women, such as pre-pregnancy BMI and pregnancy complications, was obtained from medical records in this retrospective study, in which biases are exist. In addition, the NVSS database does not provide information on twins, whereas we used the twin matching method based on data from fathers and mothers to reduce the rate of mistakes. We only explored the interaction effect in women with twin pregnancies after ART; however, the risk of pregnancy complications was significantly different in singleton pregnancies and multiparous pregnancies [51]. Therefore, further researches focus on the interaction effect between pre-pregnancy BMI and maternal age on pregnancy complications in women with different pregnancy statuses are still needed.

Conclusion

Medical providers should counsel patients on the risks of ART based on pre-pregnancy BMI and maternal age, and monitor more closely for complications based on these risk factors.

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Data availability statement

NVSS database is publicly available and the data are de-identified, more details please visit the website: https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm).

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