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Maternal obesity and the incidence of large-for-gestational-age newborns in isolated hypothyroxinemia pregnancies: a comparative cohort study

Bin Zhang[1†], Sijie Xi[1†], Zhaolong Zhan[1], Yinglu Zhang[1], Fengying Lu[1] and Xiaosong Yuan[1*]

Abstract

Background The synergistic impact of isolate maternal hypothyroxinaemia (IMH) and other modulators on fetal growth outcomes is unknown. This study was aimed to determine whether third trimester IMH [free thyroxine level (FT4) below the the 5th percentile and thyroid stimulating hormone (TSH) between the 5th and 95th percentiles] and prenatal body mass index (BMI) jointly increase the risk of large for gestational age (LGA) deliveries.

Methods A retrospective analysis was conducted on 11,478 Chinese pregnant women with laboratory data (including thyroid hormone levels and routine biochemical tests) and hospitalization records from a specialized hospital.

Results The prevalence of obesity (BMI ≥ 30 kg/m^2) and IMH was 20.1% (2312/11478) and 4.5% (519/11478), retrospectively. Women with obesity had a 6.96-fold greater risk of IMH (95% CI: 4.58, 10.58) and a 5.88-fold increased risk of LGA (95% CI: 4.87, 7.11) than those with normal weight (BMI < 25 kg/m^2), while women with IMH had a 1.32-fold increased risk of LGA (95% CI: 1.05, 1.65) than euthyroid women. The positive associations of LGA risk with obesity and IMH remained robust in sensitivity analyses conducted among women aged < 35 years, primiparas, and those without pregnancy complications. Compared to euthyroid women with normal weight, women with obesity and IMH had a 7.60-fold higher risk of LGA (95% CI: 5.26, 10.97). Additionally, a significant interaction between BMI categories and IMH on LGA was observed ($P < 0.013$). Subgroup analyses validated this interaction among women with aged < 35 years, multiparity, and non-pregnancy complications.

Conclusions Obesity and IMH in late pregnancy are both associated with an increased risk of LGA newborns, and their coexistence may further amplifies this risk; prenatal BMI and thyroid hormone levels could serve as potential indicators for identifying individuals at elevated LGA risk.

Keywords Obesity, Body mass index, Thyroid hormone, Isolate maternal hypothyroxinaemia, Large for gestational age, Birthweight

[†]Bin Zhang and Sijie Xi contributed equally to this work.

*Correspondence:
Xiaosong Yuan
xiaosongyuan@njmu.edu.cn

[1]Department of Medical Genetics, Changzhou Maternal and Child Health Care Hospital, Changzhou Medical Center, Nanjing Medical University, Changzhou, China

Introduction

Birth weight is a key indicator of fetal growth and has long-term health implications, as highlighted by the developmental origins of health and disease theory [1]. Newborns classified as large for gestational age (LGA, >90th percentile) or small for gestational age (SGA, <10th percentile) face increased risks of adverse outcomes [2, 3]. LGA infants are more prone to obesity, diabetes, cardiovascular issues, and certain cancers, while SGA infants are at higher risk of neurodevelopmental disorders, metabolic dysfunction, and hepatic tumors [4–6]. The prevalence of LGA has risen in developed countries, whereas SGA rates have increased in developing nations [2]. Interventions to prevent SGA and LGA are crucial for improving neonatal health and promoting socioeconomic development.

Thyroid hormones are vital for fetal development, especially before 20 weeks of gestation when the fetus depends on maternal thyroid hormones [7, 8]. Maternal thyroid dysfunction, particularly isolated maternal hypothyroxinemia (IMH), has garnered increasing attention due to its potential impact on fetal growth [9]. While overt maternal hyperthyroidism and hypothyroidism are linked to low birth weight, the effects of IMH on birthweight remain controversial [10]. Most studies associate first- or second-trimester IMH with increased birthweight, macrosomia, or LGA [11–17], while a few suggest a link to lower birthweight (LBW) and SGA [18–20]. Other studies find no significant correlation between IMH and fetal growth outcomes, underscoring the need for further research to clarify these relationships [21–27].

Given the critical role of maternal thyroid function in late pregnancy on fetal thyroid status, there is a pressing need for research focusing on isolated maternal hypothyroxinemia (IMH) during this period [28]. This retrospective study aimed to determine whether IMH in late pregnancy increases the prevalence of SGA or LGA newborns among Chinese women. Additionally, since maternal weight at delivery is a known determinant of fetal birth weight [29, 30], we explored the potential synergistic effects of IMH and prenatal body weight status on fetal growth outcomes.

Materials and methods

Data source and study design

Utilizing the comprehensive data repository sourced from Changzhou Maternal and Child Health Care Hospital, we performed this retrospective, observational cohort study. The research protocol was reviewed and approved by the Ethics Committee of the hospital, with approval number ZD201803. Given the anonymous nature of the data used in this study, the requirement for informed consent from individual participants was waived. The original database comprised 13,275 consecutive subjects who delivered babies in the hospital from the start of April 2016 to the end of March 2017. During this timeframe, free thyroid testing (funded by the reagent supplier and hospital research grants) was widely adopted by pregnant women admitted for delivery, enabling robust data collection. Outside this period, testing required fees, limiting accessibility. The 12-month window provided sufficient sample size to detect associations between IMH and LGA/SGA while minimizing seasonal variability in maternal behaviors. The following criteria were used for excluding participants from the final analysis: (i) history of pre-pregnancy illnesses that may modulate thyroid hormone levels and affect subsequent birth outcomes, including thyroid disease, chronic conditions (hypertension, heart, liver and kidney diseases), diabetes mellitus, syphilis and immune rheumatic disease; (ii) harmful habits during pregnancy (smoking, drinking alcohol, and using illegal drugs); (iii) multiple pregnancy; (iv) failure of live birth; (v) absence of thyroid function assessment and height/weight measurement. A total of 1,797 participants who presented with a history of pre-pregnancy diseases ($n=488$), plural gestations ($n=335$), congenital malformations ($n=68$), non-live birth ($n=28$), and missing thyroid hormones levels and height/weight values ($n=878$) were ultimately excluded from the current study (Fig. 1). Data regarding to maternal demographics and neonatal characteristics, such as maternal age, height, weight, parity status, blood pressure (BP), medical history, harmful habits, pregnancy complications, fetal sex, gestational week at delivery, as well as birth length and weight of the neonates, were meticulously checked and retrieved from the hospital's medical records. The results of thyroid function tests and other routine laboratory assessments conducted upon admission to the hospital were comprehensively reviewed and extracted from the hospital's laboratory information system.

Laboratory measurements and definition of thyroid function

Maternal blood samples were collected at the time of admission for hospital delivery and transferred to the laboratory for subsequent thyroid function testing and biochemical analysis. Serum free triiodothyronine (FT3), free thyroxin (FT4), thyroid-stimulating hormone (TSH) and thyroid peroxidase antibody (TPO-Ab) were assayed utilizing the electrochemiluminescence technique on an automated immunoassay analyzer (Cobas Elecsys 601, Roche Diagnostics, Switzerland). Routine measurements of serum liver and kidney function, as well as whole blood cell counts, were conducted utilizing advanced automatic analyzers and their respective, suitable reagents. For liver and kidney function evaluations, the AU5800 analyzer from Beckman Coulter Inc. (Japan) was employed, while for blood cell counts, the XN550 analyzer from Sysmex

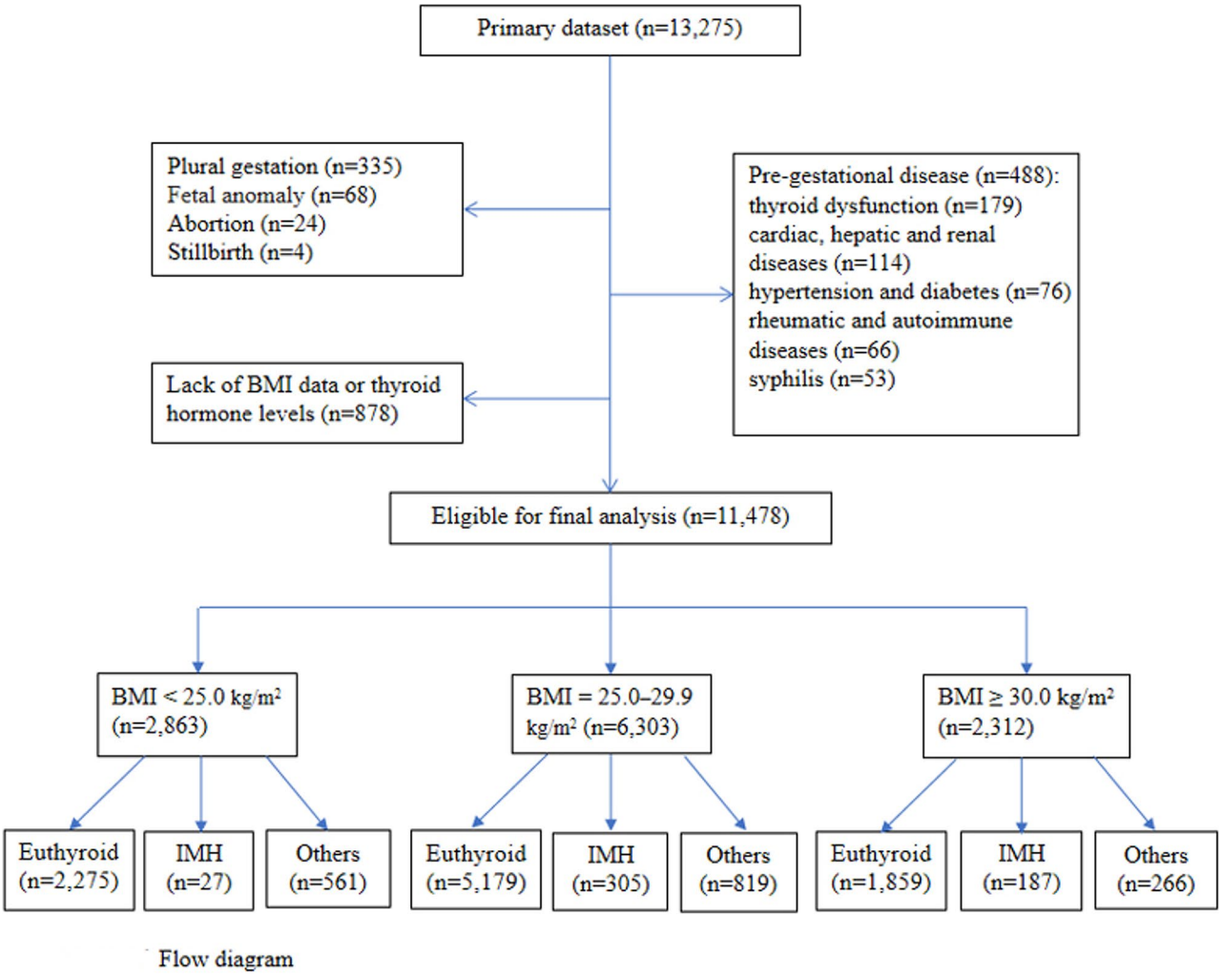

Fig. 1 Flow diagram

Inc. (Japan) was utilized. Based on the manufacturer's specifications, a TPO-Ab level exceeding 34.0 mIU/L was designated as positive. According to the percentiles distribution of FT4 and TSH levels among participants with negative TPO-Ab status, maternal thyroid function was categorized as follows: Euthyroid, normal TSH and FT4 (5th -95th percentiles); hypothyroxinaemia, normal TSH and low FT4 (< 5th percentile); hypothyroidism, normal/low FT4 FT4 and high TSH (> 95th percentile); hyperthyroxinaemia, normal TSH and high FT4; and hyperthyroidism, normal/high FT4 and low TSH. Due to the lack of manufacturer-provided trimester-specific reference ranges for TSH/FT4, we established regional thresholds using our laboratory's pregnancy-specific thyroid hormone data. The 5th -95th percentile cutoffs were selected to align with current evidence and ensure comparability with prior studies, thereby supporting standardized clinical decisions [31], and to optimize clinical practicality. Narrower cutoffs (10th – 90th percentiles) risk overdiagnosing mild hypothyroxinemia in iodine-sufficient populations, potentially leading to unnecessary interventions, while broader cutoffs (2.5th -97.5th percentiles) reduce sensitivity and increase the risk of missed diagnoses. By contrast, the 5th -95th percentiles strike a balance between specificity and sensitivity, minimizing the misclassification of transient or subclinical deviations while effectively detecting clinically significant abnormalities.

Definitions of covariates and outcomes

Maternal age was dichotomized into two categories: ≥35 years and < 35 years. Additionally, maternal prenatal body mass index (BMI) was stratified into three distinct groups: normal weight (BMI < 25 kg/m²), overweight (BMI ≥ 25 kg/m² and < 30 kg/m²), and obese (BMI ≥ 30 kg/m²) [32]. Pre-eclampsia (PE), pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), and intrahepatic cholestasis of pregnancy (ICP)

were recognized as pivotal complications during gestation, with their diagnoses relying on well-established criteria outlined in a previous report [33]. The newborns were stratified into three categories based on their birthweight and gestational week, employing the methodology devised by Mikolajczyk: (i) SGA, identified by a birthweight falling below the 10th percentile of the gestational age-specific reference range within the study cohort; (ii) AGA, characterized by a birthweight lying within the 10th to 90th percentile; (iii) LGA, designated by a birthweight exceeding the 90th percentile [2]. To establish reference percentiles, the cohort-specific mean birthweight (3513.8 g) and standard deviation (SD: 402.3 g) for term infants (40 weeks) were first calculated. The coefficient of variation (CV = 11.45%) was then derived as (SD/mean)×100. These parameters were input into a predefined Microsoft Excel algorithm (Web Appendix 2) [2], which generated continuous birthweight percentiles across gestational ages from 24 to 41 weeks, ensuring age-specific classification accuracy.

Statistical analysis

Data were presented as mean (standard deviation, SD) for continuous variables, and as frequency (percentage) for categorical variables. The pregnant women were stratified into three groups based on the categories of prenatal BMI at the time of admission. Difference across groups were tested by ANOVA/Kruskal Wallis tests for continuous variables, and Chi-square/Fisher's exact tests for categorical variables. Spearman's correlation test was employed to examine the relationships between maternal BMI and thyroid hormone levels. Linear regression models, tailored for continuous variables, and logistic regression models, designed specifically for dichotomous outcomes, were applied to evaluate the associations of BMI (continuous and categorized) with thyroid hormone levels and IMH. Furthermore, these models were leveraged to calculate both regression coefficients (β) and odds ratios (OR) to quantify the impact of various indexes (BMI, BMI categories and IMH) on birth length, birthweight, as well as SGA/LGA risk. To validate the robustness of the observed associations, sensitivity analyses utilizing logistic regression models were conducted exclusively among participants without advanced age, multipara, or pregnancy complications. Adjusted covariates in the regression analyses included maternal age, parity, blood pressure (BP), gestational week, assisted reproduction, pregnancy complications, fetal sex, and laboratory findings (routine blood tests, hepatic and renal function, FT3, and TPO-Ab status). Similarly, the ORs of LGA across each subgroup classified by BMI categories and euthyroid/IMH status were calculated, and their potential interactions were investigated. Additionally, these interactions were validated in subgroup analyses stratified by maternal clinical characteristics.

Statistical analyses were performed using R (http://www.R-project.org) and Empower Stats (X&Y Solutions, Inc. Boston, Massachusetts), and statistical significance was determined by a *P*-value threshold of less than 0.05.

Results

Participants' characteristics

The process of participants' screening is depicted in Fig. 1. The final analysis comprised 11,478 consecutive subjects. Among these pregnant women, the mean (standard deviation, SD) age at the time of admission for labor was 28.6 (4.4) years old, with a majority of 6,903 individuals (60.1%) being primipara. The prevalence of pregnancy complications was 8.4% for GDM, 6.2% for ICP, 3.4% for PE, and 2.1% for PIH, respectively. In addition, 4.5% (519) of mothers were defined as IMH. Of the 11,478 singleton neonates, 15.5% (1781) were defined as LGA and 8.8% (1012) as SGA. The mean prenatal BMI in our study was 27.3 (SD 3.4) kg/m^2, with 20.1% (2312) being obesity.

The participants were assigned into three groups according to BMI categories (normal weight, overweight, and obesity, Table 1). A significant step-wise increase among BMI categories was observed in terms of maternal age, blood pressure (BP), multipara rate, assisted reproduction rate, cesarean section rate, the prevalence of GDM, PE, and PIH, fetal birth length and weight, platelet counts, and the levels of hemoglobin and FT3. On the contrary, the opposite findings were detected in the variables of FT4, total bilirubin, direct bilirubin, total protein, and albumin. Notably, a positive relationship of BMI categories with IMH prevalence and the incidence of LGA deliveries was found (0.9% and 6.2% in normal weight group, and increased to 4.8% and 15.2% in overweight group, and 8.1% and 28.0% in obesity group). In addition, there was a negative relationship between BMI categories and SGA incidence (15.5% in normal weight group, and decreased to 7.3% and 4.5% in overweight and obesity groups).

Relationships of BMI with thyroid hormone levels and IMH

The distribution of thyroid hormone levels grouped by maternal TPO-Ab status is shown in Table S1. Among the 11,478 mothers with singleton, 5.6% (640), 4.5% (519), 4.8% (547), 4.4% (501), and 4.8% (547) of mothers were defined as TPO-Ab positive, hypothyroxinaemia, hypothyroidism, hyperthyroxinaemia, and hyperthyroidism, respectively. Spearman's correlation analysis revealed significant negative correlation of BMI with TSH (r = -0.044, P < 0.001) and FT4 (r = -0.279, P < 0.001) levels and positive correlation between BMI and FT3 levels (r = 0.169, P < 0.001) in late pregnancy. Regression coefficients for thyroid hormone levels associated with BMI categories

Table 1 Descriptive statistics for characteristics of the study population ($n = 11,478$)

Characteristics	Normal weight ($n = 2,863$)	Overweight ($n = 6,303$)	Obesity ($n = 2,312$)	*P* value
Age (years)	27.7 ± 4.0	28.8 ± 4.4	29.2 ± 4.7	< 0.001
<35	2656 (92.8%)	5535 (87.8%)	1973 (85.3%)	< 0.001
≥35	207 (7.2%)	768 (12.2%)	339 (14.7%)	
Height (cm)	161.8 ± 4.6	161.6 ± 4.6	161.4 ± 4.6	0.001
Weight (kg)	61.4 ± 4.8	71.2 ± 5.4	84.4 ± 7.6	< 0.001
BMI (kg/m^2)	23.4 ± 1.2	27.3 ± 1.4	32.4 ± 2.2	< 0.001
Systolic BP (mmHg)	118.5 ± 10.7	120.8 ± 11.6	124.6 ± 13.8	< 0.001
Diastolic BP (mmHg)	73.3 ± 7.6	74.4 ± 8.0	76.5 ± 9.4	< 0.001
Parity				
No child	1926 (67.3%)	3725 (59.1%)	1252 (54.2%)	< 0.001
≥1 child	937 (32.7%)	2578 (40.9%)	1060 (45.8%)	
Gestational age (week)	38.6 ± 1.8	38.8 ± 1.5	38.7 ± 1.6	0.010
Assisted reproduction	41 (1.4%)	144 (2.3%)	77 (3.3%)	< 0.001
Delivery mode				
Vaginal delivery	1933 (67.5%)	3629 (57.6%)	1027 (44.4%)	< 0.001
Cesarean section	930 (32.5%)	2674 (42.4%)	1285 (55.6%)	
PTB	241 (8.4%)	366 (5.8%)	149 (6.4%)	< 0.001
Pregnancy complications				
GDM	174 (6.1%)	494 (7.8%)	295 (12.8%)	< 0.001
ICP	208 (7.3%)	371 (5.9%)	130 (5.6%)	0.018
PE	38 (1.3%)	174 (2.8%)	180 (7.8%)	< 0.001
PIH	21 (0.7%)	112 (1.8%)	110 (4.8%)	< 0.001
IMH	27 (0.9%)	305 (4.8%)	187 (8.1%)	< 0.001
Neonatal sex				
Female	1370 (47.9%)	2948 (46.8%)	1093 (47.3%)	0.624
Male	1493 (52.1%)	3355 (53.2%)	1219 (52.7%)	
Neonatal birth height (cm)	49.6 ± 1.6	49.9 ± 1.2	50.0 ± 1.4	< 0.001
Neonatal birth weight (gram)	3159.3 ± 462.6	3368.5 ± 463.3	3517.9 ± 527.4	< 0.001
Weight for gestational age				
SGA	444 (15.5%)	463 (7.3%)	105 (4.5%)	< 0.001
AGA	2241 (78.3%)	4884 (77.5%)	1560 (67.5%)	
LGA	178 (6.2%)	956 (15.2%)	647 (28.0%)	
Laboratory findings				
FT3 (pmol/L)	3.9 ± 0.6	4.1 ± 0.6	4.2 ± 0.6	< 0.001
FT4 (pmol/L)	13.5 ± 1.9	12.6 ± 1.8	12.1 ± 1.9	< 0.001
TSH (mIU/L)	3.1 ± 1.9	3.0 ± 1.7	3.9 ± 1.6	< 0.001
TPO-Ab (mIU/L)	17.7 ± 34.1	17.3 ± 30.6	18.5 ± 33.9	0.191
RBC ($10^{12}/L$)	4.0 ± 0.4	4.0 ± 0.3	4.1 ± 0.4	< 0.001
WBC ($10^9/L$)	8.7 ± 2.2	8.8 ± 2.2	8.8 ± 2.2	0.070
Platelet ($10^9/L$)	197.0 ± 54.0	202.9 ± 55.5	209.6 ± 56.5	< 0.001
Hemoglobin (g/L)	118.1 ± 11.8	118.7 ± 11.9	120.0 ± 11.7	< 0.001
Total bilirubin (μmol/L)	8.2 ± 3.3	7.9 ± 2.9	7.5 ± 2.8	< 0.001
Direct bilirubin (μmol/L)	1.7 ± 1.1	1.6 ± 1.0	1.5 ± 0.9	< 0.001
ALT (U/L)	12.0 ± 16.2	11.2 ± 11.6	11.8 ± 15.0	0.041
AST (U/L)	20.9 ± 12.2	19.7 ± 9.4	20.4 ± 28.6	0.003
Total protein (g/L)	64.0 ± 4.5	63.6 ± 4.3	62.9 ± 4.2	< 0.001
Albumin (g/L)	36.9 ± 2.5	36.5 ± 2.5	35.9 ± 2.5	< 0.001
Urea nitrogen (mmol/L)	3.6 ± 1.0	3.5 ± 0.9	3.5 ± 0.9	0.310
Creatinine (umol/L)	60.4 ± 8.8	60.2 ± 8.9	59.9 ± 9.6	0.142

BMI, body mass index; BP, blood pressure; PTB, preterm birth; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, preeclampsia; PIH, pregnancy induced hypertension; IMH, isolated maternal hypothyroxinaemia; SGA/AGA/LGA, small/appropriate/large for gestational age; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TPO-Ab, thyroid peroxidase antibody; RBC, red blood cells; WBC, white blood cells; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 2 Association of BMI with thyroid hormone levels and IMH

	FT3 (pmol/L)		FT4 (pmol/L)		TSH (mIU/L)		IMH	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	OR (95% CI)	*P* value
Model 1								
Normal weight	0		0		0		1	
Overweight	0.11 (0.09, 0.14)	< 0.001	-0.89 (-0.97, -0.81)	< 0.001	-0.13 (-0.20, -0.05)	0.002	4.96 (3.34, 7.38)	< 0.001
Obese	0.25 (0.21, 0.28)	< 0.001	-1.37 (-1.47, -1.27)	< 0.001	-0.24 (-0.34, -0.14)	< 0.001	8.48 (5.64, 12.75)	< 0.001
Per-1 kg/m^2 increase	0.03 (0.02, 0.03)	< 0.001	-0.15 (-0.16, -0.14)	< 0.001	-0.03 (-0.04, -0.02)	< 0.001	1.16 (1.13, 1.18)	< 0.001
Model 2								
Normal weight	0		0		0		1	
Overweight	0.11 (0.08, 0.13)	< 0.001	-0.79 (-0.87, -0.71)	< 0.001	-0.11 (-0.19, -0.03)	0.005	4.63 (3.10, 6.91)	< 0.001
Obese	0.21 (0.18, 0.25)	< 0.001	-1.20 (-1.31, -1.10)	< 0.001	-0.24 (-0.34, -0.14)	< 0.001	6.96 (4.58, 10.58)	< 0.001
Per-1 kg/m^2 increase	0.02 (0.02, 0.03)	< 0.001	-0.13 (-0.14, -0.12)	< 0.001	-0.03 (-0.04, -0.02)	< 0.001	1.13 (1.10, 1.16)	< 0.001

Model 1 was unadjusted. Model 2 was adjusted for age, parity, BP, gestational age, assisted reproduction, pregnancy complications, and laboratory findings (WBC, RBC, platelet, hemoglobin, hepatic and renal function, and TPO-Ab status). BMI, body mass index; IMH, isolated maternal hypothyroxinaemia; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; CI, confidence interval; OR, odds ratio; RBC, red blood cell; WBC, white blood cell; TPO-Ab, thyroid peroxidase antibody.

Table 3 Association of BMI and IMH with fetal growth and SGA/LGA risk

	Birth length		Birth weight		SGA		LGA	
	β (95% CI)	*P* value	β (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Model 1								
Normal weight	0		0		1		1	
Overweight	0.26 (0.20, 0.32)	< 0.001	212.91 (192.16, 233.67)	< 0.001	0.44 (0.38, 0.50)	< 0.001	2.74 (2.33, 3.22)	< 0.001
Obese	0.39 (0.31, 0.46)	< 0.001	360.26 (334.52, 386.00)	< 0.001	0.26 (0.21, 0.33)	< 0.001	5.80 (4.88, 6.89)	< 0.001
Per-1 kg/m^2 increase	0.04 (0.03, 0.05)	< 0.001	39.45 (36.92, 41.98)	< 0.001	0.84 (0.82, 0.86)	< 0.001	1.18 (1.17, 1.20)	< 0.001
Euthyroid	0		0		1		1	
IMH	0.01 (-0.11, 0.14)	0.839	43.54 (0.15, 86.93)	0.049	0.90 (0.65, 1.24)	0.516	1.41 (1.14, 1.76)	0.002
Model 2								
Normal weight	0		0		1		1	
Overweight	0.14 (0.09, 0.18)	< 0.001	167.01 (150.14, 183.88)	< 0.001	0.40 (0.35, 0.47)	< 0.001	2.67 (2.24, 3.17)	< 0.001
Obese	0.30 (0.24, 0.36)	< 0.001	323.96 (302.24, 345.68)	< 0.001	0.19 (0.15, 0.25)	< 0.001	5.88 (4.87, 7.11)	< 0.001
Per-1 kg/m^2 increase	0.04 (0.03, 0.04)	< 0.001	37.79 (35.63, 39.95)	< 0.001	0.81 (0.79, 0.83)	< 0.001	1.20 (1.18, 1.22)	< 0.001
Euthyroid	0		0		1		1	
IMH	0.10 (-0.00, 0.19)	0.052	53.29 (18.89, 87.69)	0.002	0.79 (0.56, 1.11)	0.169	1.32 (1.05, 1.65)	0.019

Model 1 was unadjusted. Model 2 was adjusted for age, parity, BP, gestational age, assisted reproduction, pregnancy complications, neonatal sex, and laboratory findings (WBC, RBC, platelet, hemoglobin, hepatic and renal function, FT3, and TPO-Ab status). BMI, body mass index; IMH, isolated maternal hypothyroxinaemia; SGA/LGA, small/large for gestational age; CI, confidence interval; OR, odds ratio; RBC, red blood cell; WBC, white blood cell; FT3, free triiodothyronine; TPO-Ab, thyroid peroxidase antibody.

are presented in Table 2. Adjusted linear regression models displayed that a 1-kg/m^2 increase in BMI during late pregnancy was associated with a 0.13-pmol/L decrease in FT4 level (95% CI:–0.14,–0.12), a 0.03-mIU/L decrease in TSH level (95% CI:–0.04,–0.02), and a 0.02-pmol/L increase in FT3 level (95% CI: 0.02, 0.03). In comparison to women with a normal weight, overweight and obesity respectively exhibited decreased median levels of FT4 by 0.79 (95% CI: -0.87, -0.71) pmol/L and 1.20 (95% CI: -1.31, -1.10) pmol/L and TSH by 0.11 (95% CI: -1.31, -1.10) mIU/L and 0.24 (95% CI: -0.34, -0.14) mIU/L and increased median levels of FT3 by 0.11 (95% CI: 0.08, 0.13) pmol/L and 0.21 (95% CI: 0.18, 0.25) pmol/L (all $P < 0.001$). In addition, women with obesity had a remarkably higher risk of IMH compared to those of normal weight (crude OR: 8.48, 95% CI: 5.64, 12.75; adjusted OR: 6.96, 95% CI: 4.58, 10.58).

Association of BMI and IMH with fetal growth and SGA/LGA risk

As shown in Table 3, maternal BMI in overweight and obese categories was associated with higher birth length and weight relative to normal-weight category with approximate mean increases of 0.14 cm (95% CI: 0.09, 0.18) and 167.01 g (95% CI: 150.14, 183.88), and 0.30 cm (95% CI: 0.24, 0.36) and 323.96 g (95% CI: 1302.24, 345.68), respectively. Obesity conferred an increased LGA risk and a decreased SGA risk relative to normal weight in both the unadjusted (OR for LGA: 5.80, 95% CI: 4.88, 6.89; OR for SGA: 0.26, 95% CI: 0.21, 0.33) and adjusted logistic regression models (OR for LGA: 5.88,

Table 4 Modification effect of BMI on associations between IMH and LGA neonates

	Euthyroid		IMH		Crude		*P* value [a] for Interaction	Adjusted [b]		*P* value [a] for Interaction
	Total	LGA (%)	Total	LGA (%)	OR (95% CI)	*P* value		OR (95%CI)	*P* value	
Normal weight	2275	147 (6.5%)	27	5 (18.5%)	3.29 (1.23, 8.81)	0.018		2.86 (1.01, 8.12)	0.048	
Overweight	5179	794 (15.3%)	305	38 (12.5%)	2.06 (1.41, 3.01)	< 0.001		2.00 (1.36, 2.96)	< 0.001	
Obese	1859	512 (27.5%)	187	64 (34.2%)	7.53 (5.33, 10.64)	< 0.001	0.009	7.60 (5.26, 10.97)	< 0.001	0.013

[a] Interaction test for BMI (normal weight vs. Overweight/obese) and IMH (euthyroid vs. IMH) on LGA risk. [b] Adjusted for adjusted for age, parity, BP, gestational age, assisted reproduction, pregnancy complications, neonatal sex, and laboratory findings (WBC, RBC, platelet, hemoglobin, hepatic and renal function, FT3, and TPO-Ab status). BMI, body mass index; IMH, isolated maternal hypothyroxinaemia; LGA, large for gestational age; CI, confidence interval; OR, odds ratio; RBC, red blood cell; WBC, white blood cell; FT3, free triiodothyronine; TPO-Ab, thyroid peroxidase antibody.

Table 5 Subgroup analysis of modified effect of BMI on associations between IMH and LGA neonates

	Euthyroid		IMH		Crude		*P* value [a] for Interaction	Adjusted [b]		*P* value [a] for Interaction
	Total	LGA (%)	Total	LGA (%)	OR (95% CI)	*P* value		OR (95%CI)	*P* value	
Age < 35 years										
Normal weight	2101	131 (6.2%)	22	4 (18.2%)	3.34 (1.11, 10.02)	0.031		3.59 (1.17, 11.07)	0.026	
Overweight	4566	649 (14.2%)	251	28 (11.2%)	1.89 (1.23, 2.91)	0.004		1.96 (1.26, 3.05)	< 0.001	
Obese	1581	411 (26.0%)	153	51 (33.3%)	7.52 (5.14, 10.99)	< 0.001	0.013	7.78 (5.19, 11.66)	< 0.001	0.015
Age ≥ 35 years										
Normal weight	174	16 (9.2%)	5	1 (20.0%)	2.47 (0.26, 23.44)	0.431		1.72 (0.16, 19.05)	0.658	
Overweight	613	145 (23.7%)	54	10 (18.5%)	2.24 (0.95, 5.29)	0.065		2.66 (1.09, 6.45)	0.031	
Obese	278	101 (36.3%)	34	13 (38.2%)	6.11 (2.58, 14.47)	< 0.001	0.547	7.60 (3.04, 19.04)	< 0.001	0.661
Primipara										
Normal weight	1513	70 (4.6%)	16	1 (6.2%)	1.37 (0.18, 10.55)	0.760		1.51 (0.19, 11.77)	0.694	
Overweight	3045	353 (11.6%)	188	22 (11.7%)	2.73 (1.65, 4.53)	< 0.001		2.74 (1.63, 4.59)	< 0.001	
Obese	999	239 (23.9%)	103	29 (28.2%)	8.08 (4.94, 13.21)	< 0.001	0.801	7.50 (4.46, 12.62)	< 0.001	0.877
Multipara										
Normal weight	762	77 (10.1%)	11	4 (36.4%)	5.08 (1.46, 17.76)	0.011		4.11 (1.12, 15.12)	0.033	
Overweight	2134	441 (20.7%)	117	16 (13.7%)	1.41 (0.79, 2.51)	0.244		1.29 (0.71, 2.32)	0.405	
Obese	860	273 (31.7%)	84	35 (41.7%)	6.35 (3.88, 10.41)	< 0.001	0.002	6.45 (3.83, 10.88)	< 0.001	0.003
NPC										
Normal weight	1952	123 (6.3%)	23	5 (21.7%)	4.13 (1.51, 11.31)	0.006		3.97 (1.36, 11.63)	0.012	
Overweight	4324	633 (14.6%)	248	29 (11.7%)	1.97 (1.28, 3.02)	0.002		1.98 (1.27, 3.07)	0.002	
Obese	1387	345 (24.9%)	123	42 (34.1%)	7.71 (5.09, 11.68)	< 0.001	0.003	7.63 (4.93, 11.82)	< 0.001	0.006

[a] Interaction test for BMI (normal weight vs. Overweight/obese) and IMH (euthyroid vs. IMH) on LGA risk. [b] Adjusted for adjusted for age, parity, BP, gestational age, assisted reproduction, pregnancy complications, neonatal sex, and laboratory findings (WBC, RBC, platelet, hemoglobin, hepatic and renal function, FT3, and TPO-Ab status). BMI, body mass index; IMH, isolated maternal hypothyroxinaemia; LGA, large for gestational age; NPC, non-pregnancy complications; CI, confidence interval; OR, odds ratio; RBC, red blood cell; WBC, white blood cell; FT3, free triiodothyronine; TPO-Ab, thyroid peroxidase antibody.

95% CI: 4.87, 7.11; OR for SGA: 0.19, 95% CI: 0.15, 0.25). Additionally, IMH also increased the birthweight (crude β: 43.54, 95% CI: 0.15, 86.93; adjusted β: 53.29, 95% CI: 18.89, 87.69) and was positively associated with LGA risk (crude OR: 1.41, 95% CI: 1.14, 1.76; adjusted OR: 1.32, 95% CI:1.05, 1.65). The robustness of these associations were demonstrated in sensitivity analyses among the participants with non-advanced age (Table S2), primipara (Table S3), and non-pregnancy complications (Table S4).

Joint effect of obesity and IMH on LGA risk

Table 4 presents the modified effects of BMI categories on the association between IMH and LGA risk. The lowest prevalence of LGA (6.5%) was observed in participants with normal weight and euthyroid, whereas the highest prevalence (34.2%) was observed in those with obesity and IMH, representing a 7.6-fold increase in LGA risk (adjusted OR: 7.60; 95% CI: 5.26, 10.97). Interaction tests between BMI categories and IMH on LGA yielded statistically significant results (crude *P* for interaction: 0.009; adjusted *P* for interaction: 0.013). In addition, consistent interactions were detected in these subgroups (non-advanced age, multipara, and non-pregnancy complications; Table 5).

Discussion

Main findings

To the best of our knowledge, this is the largest retrospective study to date, revealing a significant link between prenatal BMI, thyroid hormone, and the risk of LGA deliveries. We observed a positive relationship between BMI categories (normal weight, overweight, and obesity) and the incidence of IMH, which was 0.9% in normal weight, and increased to 4.8% in overweight

and 8.1% in obesity. With the elevation of BMI categories, FT3 increased by 0.11 and 0.21 pmol/L, FT4 decreased by 0.79 and 1.20 pmol/L. Additionally, there were significant differences in the risk of LGA deliveries across subgroups classified by BMI categories and euthyroid/IMH status. The lowest incidence of LGA (6.5%) was found in the subgroup with low BMI category (normal weight) and euthyroid, whereas the highest incidence (34.2%) was observed in the subgroup with high BMI category (obesity) and IMH, representing that the absolute risk of LGA increased by 27.8% and the OR increased by 7.6-fold (95% CI: 5.26, 10.97; *P* for interaction = 0.013). A similar interaction was validated in participants with non-advantage age, multipara, and non-pregnancy complications. Taken together, these findings indicated that women with obesity and IMH in late pregnancy had a higher risk of LGA, emphasizing the importance of tailored clinical settings and management for them.

Interpretation

Previous epidemiological investigations have examined potential alterations in birth weight associated with IMH. Su et al. found that newborns born to mothers with IMH during the initial 20 weeks of pregnancy are at an increased risk of SGA (adjusted OR: 3.55) among 1,017 Chinese women [18]. Nazarpour et al. and Sankoda et al. also observed an increased likelihood of LBW (adjusted OR = 2.53) in 1,843 Iranian women and of SGA (adjusted OR = 12.51) in 1,105 Japanese women, respectively, who were identified as IMH during early pregnancy [19, 20]. By contrast, Cleary-Goldman et al. showed that IMH during the first trimester is associated with macrosomia (adjusted OR = 1.97) among 10,990 American women [11]. Evidence from van Mil et al. also indicated that IMH in the first trimester is associated with increased head sizes (β = 1.38) among fetuses and infants of 4,894 Dutch women [34]. In Spain, León et al. showed that IMH before 13 weeks of gestation contributes to higher birthweight (β = 109) among 2,644 participants [12]. In China, Zhu et al. and Gong et al. observed an increased risk of LGA (adjusted OR = 2.08) and macrosomia (adjusted OR = 1.94) among IMH women in the second trimester (rather than the first trimester), identified from 2,999 participants in Anhui and 3,398 participants in Liaoning, respectively [13, 14]. Additionally, Liu et al., Du et al., and Li et al. also found that first-trimester IMH, identified from studies involving 34,930 participants in Shanghai, 1,236 participants in Beijing, and 7,051 participants in Guangdong, is independently associated with an increased risk of macrosomia (with ORs of 2.48 and 3.89, respectively) and LGA (adjusted OR = 1.27) [15–17]. Our hospital-based observational study demonstrated that IMH during late pregnancy is associated with both higher birthweight (β = 53) and an increased risk of LGA (adjusted OR = 1.32) compared with those in the context of euthyroidism among 11,478 consecutive participants in Jiangsu, China. This finding is in agreement with the prior reports and recent meta-analyses [10, 35, 36]. However, Casey et al. in the USA, Hamm et al. in Canada, and Ong et al. in Australia reported that IMH during early pregnancy has no adverse impact on fetal growth (SGA) and pregnancy outcomes among 17,298 participants, 879 participants, and 2,411 participants, respectively [21–23]. Furthermore, four studies conducted in China have revealed no significant correlation between IMH occurring either during the first and second trimesters or in the third trimester and adverse fetal growth outcomes such as LBW or SGA, macrosomia, or LGA [24–27]. At present, existing studies that examine the association between IMH and fetal growth outcomes may not yield consistent conclusions [37]. This discrepancy may be attributed to differences in study design (prospective vs. retrospective), study location (as an indicator for race/ethnicity and iodine status), sample size (ranging from hundreds to tens of thousands), cut-off values (FT4 < 2.5th percentile vs. FT4 < 5th percentile vs. FT4 < 10th percentile) and gestational age (first trimester vs. second trimester vs. third trimester) for identifying IMH, maternal TPO-Ab status, and the control for potential confounders including maternal age, BMI, gestational weight gain (GWG), pregnancy complications, and iodine status [37]. In addition, maternal TSH reference intervals vary across different ethnic populations during pregnancy, with over 90% of post-2005 studies reporting upper limits exceeding fixed cut-offs by 0.13–2.17 mU/L [31]. The 2017 guidelines of the American Thyroid Association (ATA) recommend using pregnancy-specific, population-based reference ranges or, if unavailable, an adjusted upper limit (4 mIU/L) [38]. In our study, the group with obesity exhibited significantly higher mean TSH levels (3.9 mIU/L), approaching the ATA-recommended threshold (4 mIU/L), and lower mean FT4 levels, which may contribute to elevated IMH prevalence and subsequent LGA risk in this population.

Obesity has emerged as a global epidemic, with its prevalence rising dramatically worldwide. Prior research indicates that elevated BMI may serve as a proxy for IMH in pregnancy, and individuals with high BMI during early pregnancy demonstrate an increased risk of developing IMH [39–42]. The current study further revealed that the incidence of IMH among individuals with overweight or obesity during late pregnancy was significantly higher compared to those with normal weight (0.9% in normal weight vs. 4.8% in overweight vs. 8.1% in obesity), with relative risks increasing by 4.63-fold and 6.96-fold, respectively. Additionally, our findings suggest that maternal obesity is associated with reduced serum FT4 levels (β = -1.20) and elevated serum FT3 levels (β = 0.21).

This phenomenon may be explained by the adaptive response of obesity stimulating peripheral deiodinase activity to enhance energy expenditure, thereby promoting the conversion of FT4 to FT3 [43]. Furthermore, studies by Li et al. and Liu et al. demonstrate that prepregnancy overweight or obesity is not only more prevalent among individuals with IMH but also independently associated with IMH development during pregnancy [17, 44]. A large-scale prospective cohort study of 34,930 pregnant women in China revealed a significant synergistic interaction between prepregnancy overweight/obesity and first-trimester IMH regarding macrosomia risk (adjusted OR = 1.65 for prepregnancy overweight/obesity; adjusted OR = 2.48 for IMH; adjusted OR = 5.26 for coexisting IMH and prepregnancy overweight/obesity) [15]. The present study provides further evidence that prenatal overweight/obesity, when coexisting with third-trimester IMH, may synergistically elevate the risk of LGA infants. Specifically, the adjusted ORs were 5.88 for prenatal overweight/obesity, 1.32 for third-trimester IMH, and 7.60 when both conditions were present. Based on the aforementioned findings and our results, we propose a hypothesis that that both pre-pregnancy BMI and prenatal BMI (shaped by GWG) interact with IMH at various gestational stages, thereby multiplicatively increasing the risk of LGA newborns. The identification of stage-specific synergistic interactions between maternal obesity (prepregnancy or prenatal) and IMH carries profound clinical implications for antenatal care: (1) stratified risk screening and prevention; (2) intervention timing and modalities; (3) multidisciplinary care models; (4) patient education; and (5) policy and guideline revisions. By adopting a time-sensitive, stratified care approach that includes early thyroid optimization for pre-pregnancy obesity and late metabolic surveillance for prenatal obesity, clinicians can disrupt the multiplicative risk pathways.

The direct mechanisms by which IMH and prenatal obesity may potentially impact LGA, as well as the combined additive effect of these two unfavorable conditions on LGA, remain elusive. However, these mechanisms might serve as plausible explanations. On the one hand, thyroid hormones are essential for maintaining the delicate balance between the catabolic breakdown and anabolic synthesis of glucose, fat, and protein, and they also have the potential to directly modulate insulin secretion and its sensitivity, thereby significantly affecting overall metabolic processes [45]. Lower FT4 levels, the primary manifestation of IMH, may be linked to higher circulating glucose concentrations, leading to an increased glucose transfer from the placenta to the fetus and thereby contributing to fetal weight gain through continuous nutrient accumulation [46]. On the other hand, previous study has show that elevated maternal BMI may promote placental growth and result in an expanded placental surface, facilitating greater nutrient transfer [47]. Maternal overweight or obesity could contribute to increased levels of glucose, fatty acids, andamino acids in pregnancy, enabling them to be passed across the placenta to the fetus on a more regular basis [48, 49]. These phenomena may lead to excessive fetal nutrition and elevated synthesis of insulin and insulin-like growth factors, together with insulin resistance and GDM, thereby enhancing the possibility of fetal overgrowth [50]. In general, both IMH and prenatal obesity in pregnant individuals might affect the risk of LGA by altering the intrauterine nutritional environment through the regulation of growth-promoting hormone levels, their sensitivity, and fetal nutrient uptake [15]. Moreover, prenatal obesity has the potential to predispose individuals to IMH, ultimately leading to a cumulative impact on the risk of LGA. Consequently, the synergistic effect of IMH and prenatal obesity on LGA is biologically reasonable.

Strengths and limitations

Our results enrich the literature concerning the adverse impact of prenatal obesity on thyroid hormone levels, which might contribute to an increased risk for fetal impairment linked to IMH and LGA. This retrospective analysis of a vast sample size drawn from real-world data empowered us to take into consideration major confounders, including maternal demographic characteristics and routine laboratory findings. Importantly, we considered maternal pregnancy complications and TPO-Ab status. Additionally, we carried out multiple sensitivity analyses and subgroup analyses in this study to guarantee the reliability of the findings. For instance, GDM, a prevalent pregnancy complication, plays a significant role in the pathogenesis of LGA infants, and women with obesity are at a higher risk of developing GDM. Although subgroup and sensitivity analyses were conducted among women without pregnancy complications, the potential influence of GDM cannot be overlooked when evaluating the combined effects of obesity and IMH on LGA. Finally, to the best of our knowledge, this is the first study to focus on antenatal obesity and IMH, with interaction, on the risk of LGA deliveries in Chinese women. However, the following limitations should be mentioned: First, given the retrospective and observational nature of this study, we are unable to definitively establish the precise causal relationship. Second, as is the case with all retrospective observational studies, despite adjustments made for known potential confounders, such as maternal factors and laboratory results, the possibility of unadjusted or unmeasured confounders (e.g., pregestational BMI and GWG) remains. For example, our study lacked data on iodine concentrations and thyroid medication during pregnancy, which could potentially impact

our results. Notably, Changzhou is an iodine-sufficient area, and Chinese pregnant women generally maintain adequate iodine intake due to the implementation of a salt iodization program since 1996 [51]. Third, in this study, thyroid hormone levels were measured only once late in pregnancy, whereas the regulation of fetal growth occurs throughout the entire gestation period. Finally, this single-institution, retrospective analysis uncovers an association within the Chinese population, but its generalizability to other centers and populations remains to be confirmed.

Conclusion

In a cohort of Chinese pregnant women from a large tertiary hospital, we observed that the subgroup with obesity and IMH in late pregnancy demonstrated an elevated likelihood of delivering LGA newborns. If validated, these findings may have important public health and clinical relevance, particularly given the growing global focus on LGA-related health outcomes. Our results suggest that integrating BMI evaluation with thyroid hormone profiling may assist in identifying individuals at higher risk of LGA deliveries.

Abbreviations

IMH	Isolate maternal hypothyroxinaemia
SGA/AGA/LGA	Small/appropriate/large for gestational age
BMI	Body mass index
BP	Blood pressure
GDM	Gestational diabetes mellitus
ICP	Intrahepatic cholestasis of pregnancy
PE	Preeclampsia
PIH	Pregnancy-induced hypertension
PTB	Preterm birth
FT3	Free triiodothyronine
FT4	Free thyroxine
TSH	Thyroid stimulating hormone
TPO-Ab	Thyroid peroxidase antibody
RBC	Red blood cells
WBC	White blood cells
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
SD	Standard deviation
IQR	Interquartile range
CI	Confidence interval
OR	Odds ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-025-01394-z.

Supplementary Material 1

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Author contributions

BZ and XY conceived and designed this study. X Y wrote the manuscript. SX collected the data. ZZ and YZ analyzed and interpreted data. All authors reviewed and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethical Committee of Changzhou Maternal and Child Health Care Hospital (ZD201803). Due to anonymous data recorded in the present study, the requirements for written informed consent were waived by the Ethical Committee of Changzhou Maternal and Child Health Care Hospital. All methods in this study were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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