ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2021 September 26; 9(27): 7963-8279

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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Thrice Monthly Volume 9 Number 27 September 26, 2021

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

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https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
September 26, 2021

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World J Clin Cases 2021 September 26; 9(27): 8008-8019

DOI: 10.12998/wjcc.v9.i27.8008

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Case Control Study

Association of gestational anemia with pregnancy conditions and outcomes: A nested case-control study

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Supported by Beijing Municipal Science and Technology Commission Capital Clinical Characteristic Application Research, No. Z161100000516117.

Institutional review board statement: The study was approved by the Ethics Committee of Peking Union Medical College

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Abstract

BACKGROUND

Gestational anemia is a serious public health problem that affects pregnant women worldwide. Pregnancy conditions and outcomes might be associated with the presence of gestational anemia. This study investigated the association of pregnancy characteristics with anemia, exploring the potential etiology of the disease.

AIM

To assess the association of pregnancy parameters with gestational anemia.

METHODS

A nested case-control study was conducted based on the Chinese Pregnant Women Cohort Study-Peking Union Medical College Project (CPWCS-PUMC). A total of 3172 women were included. Patient characteristics and gestational anemia occurrence were extracted, and univariable and multivariable logistic regression models were used to analyze the association of pregnancy parameters with gestational anemia.

RESULTS

Among the 3172 women, 14.0% were anemic, 46.4% were 25-30 years of age,

Hospital, Chinese Academy of Medical Sciences (No. JS-1060).

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at maliangkun2019@163.com.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Manuscript source: Unsolicited manuscript

Specialty type: Obstetrics and gynecology

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 29, 2021
Peer-review started: April 29, 2021
First decision: May 23, 2021
Revised: June 1, 2021

21.9% resided in eastern, 15.7% in middle, 12.4% in western 18.0% in southern and 32.0% in northern regions of China. Most women (65.0%) had a normal prepregnancy body mass index. Multivariable analysis found that the occurrence of gestational anemia was lower in the middle and western regions than that in the eastern region [odds ratio (OR) = 0.406, 95% confidence interval (CI): 0.309-0.533, $P < 0.001$)], higher in the northern than in the southern region (OR = 7.169, 95%CI: 5.139-10.003, $P < 0.001$), lower in full-term than in premature births (OR = 0.491, 95%CI: 0.316-0.763, $P = 0.002$), and higher in cases with premature membrane rupture (OR=1.404, 95%CI: 1.051-1.876, $P = 0.02$).

CONCLUSION

Gestational anemia continues to be a health problem in China, and geographical factors may contribute to the situation. Premature birth and premature membrane rupture may be associated with gestational anemia. Therefore, we should vigorously promote local policy reformation to adapt to the demographic characteristics of at-risk pregnant women, which would potentially reduce the occurrence of gestational anemia.

Key Words: Anemia; Body mass index; Gestational weight gain; Pregnancy; Pregnancy outcomes

Core Tip: This nested case-control study assessed pregnant women who delivered in 2018. Most women (65.0%) had a normal prepregnancy body mass index. Gestational anemia occurrence was lower in the middle and western regions, higher in the northern than in the southern region, lower in full-term than premature births, and higher in cases with than without premature membrane rupture.

Citation: Sun Y, Shen ZZ, Huang FL, Jiang Y, Wang YW, Zhang SH, Ma S, Liu JT, Zhan YL, Lin H, Chen YL, Shi YJ, Ma LK. Association of gestational anemia with pregnancy conditions and outcomes: A nested case-control study. *World J Clin Cases* 2021; 9(27): 8008-8019
URL: https://www.wjgnet.com/2307-8960/full/v9/i27/8008.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i27.8008

INTRODUCTION

Gestational anemia is a common complication of pregnancy and a serious global public health problem. The World Health Organization (WHO) estimates that 38% of pregnant women worldwide are anemic[1]. It is reported that the incidence rate ranges from 5.4% in developed countries to as high as 80% in developing nations[2-7]. Several socio-demographic and economic characteristics of women also influence the distribution of gestational anemia[8] and should be taken into consideration in prenatal care. According to the WHO definition, anemia in pregnancy refers to hemoglobin (Hb) < 110 g/L in the first trimester, < 105 g/L in the second and third trimesters, and < 100 g/L in the postpartum period[4-7,9].

Decreased Hb content is a normal physiological phenomenon in pregnancy because of a nearly 50% increase in plasma volume and an increased iron demand[10,11]. However, a much more pronounced decrease of Hb can lead to detrimental pregnancy outcomes such as preterm birth, low birth weight, and small for gestational age[3,12]. The main reason is that gestational anemia is primarily caused by iron-deficiency, which results in reduced Hb levels and decreased oxygen-carrying capacity. That leaves the fetus in a state of chronic hypoxia that alters fetal growth and development [13]. Very few studies have investigated the effects of gestational anemia on pregnancy and birth outcomes, and cohort studies with long-term follow-up are even rarer[14]. The development of gestational anemia in low- and middle-income developing countries is affected by various factors. Previous studies focused on the association of gestational anemia with elemental iron, while the demographic characteristics of anemic pregnant women are usually overlooked[2]. We hypothesized that pregnancy

Accepted: August 6, 2021
Article in press: August 6, 2021
Published online: September 26, 2021

P-Reviewer: Kurniawan A, Skrypnik D
S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Li JH

conditions and outcomes might be associated with gestational anemia. Therefore, the aim of this study was to investigate the association of pregnancy characteristics with anemia during pregnancy, exploring potential etiological factors of the disease. The results could be of significance for the prevention and management of gestational anemia, which might help to reduce adverse pregnancy outcomes and improve birth outcomes.

MATERIALS AND METHODS

Study design and subjects

This was a nested case-control study that evaluated data were from the Chinese Pregnant Women Cohort Study-Peking Union Medical College Project (CPWCS-PUMC), a prospective, multi-center cohort study including subjects from 24 hospitals in 15 provinces (autonomous regions or direct-controlled municipalities) of China. The study population was a representative sample of the Chinese general population. The study was approved by the Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences (No. JS-1060). Written informed consent was obtained from each participant. Pregnant women enrolled in the CPWCS-PUMC between July 25, 2017 and July 24, 2018 and delivered before December 31, 2018 were included in this study. Not all CPWCS-PUMC participants were included in this study, only a certain period of enrollment in the CPWCS-PUMC was included in final analysis, so that the women were all involved in the study at the same time. The inclusion criteria were (1) Chinese nationality, (2) gestational week < 13 at enrollment, (3) singleton pregnancy; and (4) registration and regular prenatal examinations at one of the participating hospitals. The exclusion criteria were (1) a history of anemia, (2) hematological disease, (3) blood transfusion within the past 6 mon, or (4) a history of immune disease before pregnancy.

Data collection

The demographic characteristics and pregnancy-related data of the women were analyzed. The demographic characteristics assessed included the region of residence in China, urban/rural dwelling, age, weeks of gestation, ethnicity, education level, occupation, family size, annual personal income of the pregnant woman, annual family income, height and weight before pregnancy, body mass index (BMI) before pregnancy, and gestational weight gain. Pregnancy-related parameters included premature rupture of membranes (PROM), gestational diabetes mellitus, and gestational hypertension.

Definitions

Anemia of pregnancy was determined during outpatient visits. Gestational anemia was diagnosed when Hb levels were < 110 g/L at any time during pregnancy[4-7,9]. Prepregnancy BMI was calculated as weight before pregnancy (kg)/height squared (m^2), and classified as low (BMI < 18.5 kg/m^2), normal (BMI = 18.5-24.0 kg/m^2), overweight (BMI = 24.0-28.0 kg/m^2), and obese (BMI > 28.0 kg/m^2)[15]. Gestational weight gain was the increase of body weight during pregnancy, calculated by subtracting the weight before pregnancy (kg) from that at delivery. The gestational weight gain was divided into 12 subgroups by increments of 2.5 kg between two consecutive groups. Age was calculated as 2018 minus the year of birth, and the patients were divided into six subgroups, < 20, 20-24, 25-29, 30-34, 35-39 and ≥ 40 years of age.

Statistical analysis

SPSS 25.0 (IBM, Armonk, NY, United States) was used for the statistical analysis. Continuous data were reported as means ± SD. Categorical data were reported as numbers and percentages. Univariable logistic regression was first conducted to identify factors potentially associated with gestational anemia. Then, clinically relevant factors with $P < 0.05$ were included in multivariable logistic regression analysis. Odds ratios (ORs) and adjusted (A)ORs and their 95% confidence intervals (CIs) were calculated. A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

General characteristics of the pregnant women

This study included 3172 women with singleton pregnancies, of whom 14.0% were diagnosed as anemia. Of the 3172 women, 97.2% were Han Chinese. Women 25-30 years of age were the most represented (46.4%), followed by 30-35 (28.6%), 20-25 (10.0%), 35-40 (9.54%), < 20 (3.3%), and ≥ 40 (2.1%) years of age. The most common education level was college (56.2%), followed by high school (20.7%), junior middle school (15.5%), master's degree (6.5%), primary school (0.6%), and doctoral degree (0.5%). Unemployed pregnant women were most represented (29.3%), followed by business services and industry employees (19.1%). The number of permanent family members in the households of the pregnant women were two (30.0%), three (22.3%), and four (22.9%); only 1.2% of families had only one permanent resident. As for geographic distribution, 21.9% of the women resided in eastern, 15.7% in middle, 12.4% in western 18.0% in southern, and 32.0% in northern regions. The place of residence was rural for 57.6% of the women. A personal annual income of 40,000-50,000 Yuan was the most represented among the women (18.0%) and the most prevalent family annual income (20.8%) was 80,000-100,000 Yuan. Most women (65.0%) had normal prepregnancy BMIs, followed by overweight (17.5%), low weight (13.2%), and obese (4.2%). A gestational weight gain of 15.0-17.5 kg was the most frequent (24.0%), followed by 10.0-12.5 kg (22.60%, Table 1).

Association of gestational anemia with various parameters in univariable logistic regression analysis

Table 2 shows the results of univariable analysis. With the eastern region as a reference for eastern-middle-western distribution, the ORs for anemia in the middle and west regions were 0.60 (95%CI: 0.47-0.76) and 0.66 (95%CI: 0.51-0.85), respectively. With the south region as a reference for south-north distribution, the OR for anemia in the north region was 5.95 (95%CI: 4.33-8.18). With < 20 years as the reference age, the ORs in the 20-25, 25-30, 30-35, and 35-40 groups were 5.93 (95%CI: 2.10-16.74), 4.12 (95%CI: 1.50-11.32), 3.96 (95%CI: 1.43-10.94), and 4.48 (95%CI: 1.57-12.78), respectively. With preterm birth as the reference, the OR of full-term birth was 0.59 (95%CI: 0.39-0.88). With urban residence as reference, the OR of rural residence was 1.58 (95%CI: 1.28-1.95). With primary school or lower as the reference, the ORs of the junior middle school, high school, college, master's degree, and doctoral degree were 1.01 (95%CI: 0.33-3.12), 0.65 (95%CI: 0.21-2.01), 0.49 (95%CI: 0.16-1.49), 0.54 (95%CI: 0.17-1.76), and 1.87 (95%CI: 0.40-8.74), respectively. Employment, personal annual income, family annual income, and PROM were all statistically significant ($P < 0.05$). BMI and gestational weight gain were not significantly associated with anemia.

Factors associated with gestational anemia in multivariable logistic regression analysis

Variables with statistical significance ($P < 0.05$) in the single-factor logistic regression analysis were included in the multivariate logistic regression model. Two variables with clinical significance, prepregnancy BMI and gestational weight gain, were also included in the model, although no statistical significance was shown in univariable analysis. Table 3 shows that anemia occurrence was lower in the middle and western regions than in the eastern region (OR = 0.406, 95%CI: 0.309-0.533, $P < 0.001$), higher in the northern region than in the southern region (OR = 7.169, 95%CI: 5.139-10.003, $P < 0.001$), lower for full-term birth than for premature birth (OR = 0.491, 95%CI: 0.316-0.763, $P = 0.002$), and higher for PROM cases (OR = 1.404, 95%CI: 1.051-1.876, $P = 0.02$).

DISCUSSION

Anemia in pregnancy is a common complication that requires intervention. Regarding the mechanisms involved in the development of gestational anemia, pregnancy induces inflammation that can induce anemia[16]. In addition, gestational anemia is a normal physiological phenomenon caused by changes of hematologic parameters during pregnancy[17,18]. Anemia in pregnancy increases the risk of maternal and fetal death, influences the cognitive and physical development of the offspring, results in long-term effects on the neonates, and increases the risk of poor health in adulthood [19]. Successful reduction in the prevalence of anemia improves pregnancy outcomes for mothers and infants, resulting in intergenerational benefits for individual health,

Table 1 General characteristics of the pregnant women who participated in this study

Characteristics	*n* = 3172	Percentage
Ethnicity		
Han	3082	97.2
Others	90	2.8
Age in yr		
< 20	106	3.3
20-25	318	10.0
25-30	1473	46.4
30-35	908	28.6
35-40	301	9.5
≥40	66	2.1
Educational level		
Primary school or lower	19	0.6
Junior middle school	493	15.5
High school	655	20.7
College	1784	56.2
Master's degree	206	6.5
Doctoral degree	15	0.5
Number of permanent residents in family		
1	37	1.2
2	951	30.0
3	706	22.3
4	725	22.9
5	550	17.3
6	119	3.8
≥ 7	68	2.1
Unknown	16	0.5
Geographic distribution		
East	694	21.9
Middle	498	15.7
West	394	12.4
South	572	18.0
North	1014	32.0
Place of residence		
Urban registration	1346	42.4
Rural registration	1826	57.6
Clinical characteristics		
Anemia	443	14.0
Premature rupture of membrane	398	12.6
Gestational diabetes mellitus	372	11.7
Gestational hypertension	84	2.7
Occupation		

Unemployed	929	29.3
Administration	319	10.1
Professional	504	15.9
Office clerk	312	9.8
Business services industry	607	19.1
Agricultural industry	64	2.0
Others	437	13.8
Personal annual income (Yuan, thousands)		
0	207	6.5
≤ 10	214	6.8
≤ 20	308	9.7
≤ 30	486	15.3
≤ 40	362	11.4
≤ 50	571	18.0
≤ 60	281	8.9
≤ 70	82	2.6
≤ 80	145	4.6
≤ 90	18	0.6
≤ 100	295	9.3
≤ 150	94	3.0
> 150	73	2.3
Unknown	36	1.1
Family annual income, in Yuan, thousands		
0	25	0.8
≤ 20	115	3.6
≤ 40	206	6.5
≤ 60	451	14.2
≤ 80	317	10.0
≤ 100	661	20.8
≤ 120	144	4.5
≤ 140	52	1.6
≤ 160	302	9.5
≤ 180	68	2.1
≤ 200	404	12.7
≤ 250	88	2.8
≤ 300	159	5.0
> 300	136	4.3
Unknown	44	1.4
Body mass index in kg/m^2		
< 18.5	420	13.2
18.5-24.0	2062	65.0
24.0-28.0	556	17.5
≥ 28.0	134	4.2

Gestational weight gain in kg		
< 2.5	46	1.5
2.5-5.0	25	0.8
5.0-7.5	169	5.3
7.5-10.0	202	6.4
10.0-12.5	717	22.6
12.5-15.0	479	15.1
15.0-17.5	760	24.0
17.5-20.0	286	9.0
20.0-22.5	302	9.5
22.5-25.0	67	2.1
25.0-27.5	83	2.6
≥ 27.5	36	1.1

well-being, economic potential, community development[1]. However, factors affecting the development of gestational anemia remain debatable[2,20-23]. Therefore, investigating the association of prepregnancy BMI with gestational anemia has important significance in prenatal care.

To our knowledge, this study is the first to compare the prevalence of anemia in five regions of China (*i.e.* eastern, middle, western, southern, and northern). In this study, we found that the overall occurrence of gestational anemia was 14.0%. Gestational anemia occurrence was lower in the middle and western regions than in the eastern region, and higher in the northern region than in the southern region. This result was comparable to a study that compared the prevalence of anemia in three big cities, and found that the prevalence of anemia in Guangzhou (38.8%) and in Chengdu (23.9%) were both significantly higher than the overall prevalence, and the prevalence in Beijing (19.3%) was lower[23]. The results may be related to regional differences in local economic development, lifestyle, and diet, which may also help to boost local policy reformation to adapt to the demographic characteristics.

Univariable analysis showed that prepregnancy BMI and gestational weight gain were not associated with gestational anemia in Chinese women. Previous studies have reported the association of prepregnancy BMI and gestational weight gain with gestational anemia[2,20-23]. Therefore, these two factors were included in the multivariable analysis, but still showed no significant associations with gestational anemia. The findings suggested that prepregnancy BMI and gestational weight gain may not be associated with gestational anemia, at least in Chinese women. Previous studies have shown that in some countries, obesity was associated with anemia in adults[24-26]. The underlying mechanism may involve the influence of obesity on the expression of hepcidin, which in turn inhibits iron absorption, consequently leading to anemia[27]. Anemia in obese women was reported to be associated with the obesity-related inflammatory status or complications[28]. In contrast, other studies demonstrated that obesity did not induce anemia[14,29]. In a study of gestational diabetes in Chinese women, Lin *et al*[23] showed that a prepregnancy BMI of < 18.5 kg/m^2 was associated with anemia. That also conflicts with the results of this study, but the anemia prevalence was lower in this study compared with Lin *et al*[23] (14% *vs* 24%). The exact reasons for the discrepancies are unknown and deserve further investigation.

In this study, univariable analysis found that age, education level, type of family residence, occupation, and family income were associated with gestational anemia. Nevertheless, those factors showed no significant associations in multivariable analysis, suggesting potential confounding factors or interactions among parameters. Geographic or spatial differences have also been demonstrated to be associated with anemia[30], corroborating our findings. In this study, no urban-rural differences were found, which does not agreement with the findings of Lin *et al*[23].

Hb levels in pregnant women decrease with advancing pregnancy, and consequently increase the severity of gestational anemia[2,20-23]. It has been reported that anemia in pregnancy is associated with an increased risk of several adverse pregnancy outcomes, such as preterm birth, hypertensive disorders, and low birth

Table 2 Results of univariable logistic regression analysis

Characteristics	*P* value	OR	95%CI of OR	
			Lower	Upper
East region	< 0.01			
Middle region	< 0.01	0.6	0.47	0.76
West region	< 0.01	0.66	0.51	0.85
North region	< 0.01	5.95	4.33	8.18
< 20 yr	0.01			
20-25 yr	< 0.01	5.93	2.1	16.74
25-30 yr	0.01	4.12	1.5	11.32
30-35 yr	0.01	3.96	1.43	10.94
35-40 yr	0.01	4.48	1.57	12.78
> 40 yr	0.09	3.03	0.85	10.77
Preterm	0.03			
Full-term birth	0.01	0.59	0.39	0.88
Rural registration	< 0.01	1.58	1.28	1.95
PROM	< 0.01	1.61	1.23	2.11
BMI classification	0.41			
Gestational weight gain classification	0.57			
Primary school or lower	< 0.01			
Junior middle school	0.98	1.01	0.33	3.12
High school	0.46	0.65	0.21	2.01
College	0.21	0.49	0.16	1.49
Master's degree	0.31	0.54	0.17	1.76
Doctoral degree	0.42	1.87	0.4	8.74
Unemployed	0.02			
Administration	0.2	0.79	0.54	1.14
Professionals	0.1	0.77	0.56	1.05
Office clerk	0.07	0.7	0.48	1.03
Business services industry	0.06	0.75	0.56	1.01
Agricultural industry	0.03	1.88	1.05	3.36
Others	0.09	0.75	0.54	1.04
Personal annual income	< 0.01			
Family annual income	< 0.01			

BMI: Body mass index; CI: Confidence interval; OR: Odds ratio; PROM: Premature rupture of membranes.

weight[31-33]. The incidence of anemia in pregnancy was shown to be associated with preterm birth (AOR = 1.32; 95%CI: 1.14-1.53) and small for gestational age (AOR = 1.27; 95%CI: 1.04-1.55)[17]. These results were in accordance with our findings. We found that full-term delivery was inversely correlated with gestational anemia, suggesting that the absence of anemia was associated with favorable pregnancy outcomes. The findings also indirectly indicate that gestational anemia might increase the risk of preterm birth. As shown above, PROM was associated with gestational anemia, again supporting adverse pregnancy outcomes in case of anemia[12,34,35].

Our study has several strengths. In this nationwide survey, a defined time period within the population of a prospective cohort was involved. The strict study criteria

Table 3 Results of multivariable logistic regression analysis

Characteristics	*P* value	OR	95%CI of OR	
			Lower limit	Upper limit
East region	< 0.001			
Middle region	< 0.001	0.428	0.331	0.553
West region	< 0.001	0.406	0.309	0.533
North region	< 0.001	7.169	5.139	10.003
< 20 yr	0.07			
20-25 yr	0.077	2.635	0.900	7.711
25-30 yr	0.245	1.856	0.654	5.269
30-35 yr	0.367	1.623	0.567	4.646
35-40 yr	0.399	1.596	0.538	4.738
> 40 yr	0.961	0.968	0.259	3.617
Full-term birth	0.002	0.491	0.316	0.763
PROM	0.022	1.404	1.051	1.876

CI: Confidence interval; OR: Odds ratio; PROM: Premature rupture of membranes.

excluded women with a history of anemia, hematological disease, blood transfusion within the past 6 mon, or immune diseases before pregnancy, to eliminate possible factors that were associated with anemia. The large sample size has enabled us to estimate the overall prevalence of gestational anemia, as well as to compare the rates among regions and population subgroups. Moreover, prepregnancy BMI was classified as low, normal, overweight, and obese. Gestational weight gain was divided into 12 subgroups. Age was divided into six subgroups. Subgroup analysis was performed to minimize selection bias. Univariable logistic regression was first conducted to identify factors potentially associated with gestational anemia. Multivariable logistic regression analysis was used to identify the factors associated with gestational anemia.

The study limitations included the following. Data for some factors such as tea consumption during pregnancy, which could affect anemia occurrence[36], was not assessed. In addition, parameters such as gravidity, parity, abortion history, and prepregnancy comorbidities can also affect the incidence of gestational anemia[12,34,35], and might have helped establish a more accurate model, but were not evaluated. Additional studies are necessary to determine the exact etiology and consequences of gestational anemia.

CONCLUSION

This study showed that gestational anemia continues to be a health problem in China, and geographical factors may contribute to the situation. Premature birth, and PROM may be associated with gestational anemia. Therefore, we should vigorously promote local policy reformation to adapt to the demographic characteristics of at-risk pregnant women, which would potentially reduce the occurrence of gestational anemia.

ARTICLE HIGHLIGHTS

Research background

Gestational anemia is a common complication of pregnancy and a serious public health problem worldwide. Several socio-demographic and economic characteristics of women influence the distribution of gestational anemia and should be taken into consideration in prenatal care. We hypothesized that pregnancy conditions and outcomes might be associated with gestational anemia.

Research motivation

The study aim was to investigate the association of pregnancy characteristics with anemia during pregnancy, exploring potential etiological factors of the disease. The results could be of significance for the prevention and management of gestational anemia, which might in turn help reduce adverse pregnancy outcomes and improve birth outcomes.

Research objectives

To assess the association of pregnancy parameters with gestational anemia.

Research methods

A nested case-control study was conducted based on the Chinese Pregnant Women Cohort Study-Peking Union Medical College Project (CPWCS-PUMC). A total of 3172 women were included. Patient characteristics and gestational anemia occurrence were extracted, and univariable and multivariable logistic regression models were used to analyze the association of pregnancy parameters with gestational anemia.

Research results

Of the 3172 women, 14.0% were anemic; 46.4% were 25-30 years of age, and 21.9%resided in eastern, 15.7% in middle, 12.4% in western, 18.0% in southern, and 32.0% in northern regions of China. Most women (65.0%) had normal prepregnancy BMIs. Multivariable analysis showed that gestational anemia occurrence was lower in the middle and western regions than in the eastern region (OR = 0.406, 95%CI: 0.309-0.533, $P < 0.001$), higher in the northern region than that in the southern region (OR = 7.169, 95%CI: 5.139-10.003, $P < 0.001$), lower in full-term births than in premature birth (OR = 0.491, 95%CI: 0.316-0.763, $P = 0.002$), and higher in cases with premature rupture of membranes (OR = 1.404, 95%CI: 1.051-1.876, $P = 0.02$).

Research conclusions

Gestational anemia continues to be a health problem in China, and geographical factors may contribute to the situation. Premature birth, and premature rupture of membranes may be associated with gestational anemia. Therefore, we should vigorously promote local policy reformation to adapt to the demographic characteristics for at-risk pregnant women, which would potentially reduce the occurrence of gestational anemia.

Research perspectives

Local policy reformation of different regions should be made to adapt to the demographic characteristics.

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