High Hemoglobin Level is a Risk Factor for Maternal and Fetal Outcomes of Pregnancy in Chinese Women: A Retrospective Cohort Study

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Abstract

Background

To examine the association of hemoglobin (Hb) levels during gestation with the risk of selected adverse pregnancy outcomes in Chinese women.

Methods

A total of 1911 singleton mothers were included. Hb levels were measured during the second (16-18th weeks) and third (28-30th weeks) trimesters of pregnancy, and pregnancy outcomes were followed. Statistical analysis was performed using multivariate logistic regression.

Results

After multivariable adjustment, Hb levels > 130 g/L in the second trimester increased the risk of low-birth-weight infants (LBW) (odds ratio [OR], 2.54; 95% confidence interval [CI], 1.12–5.77). In the third trimester of gestation, compared with women whose Hb levels between 110–119 g/L, women with Hb levels > 130 g/L had an increased risk of LBW (OR, 2.17; 95% CI, 1.05–4.48) and small-for-gestational-age infants (SGA) (OR, 1.98; 95% CI, 1.04–3.78). In addition, maternal Hb levels of < 110 g/L or > 130 g/L at the second week that were restored vs not restored in the third trimester decreased the risk of preterm birth (PTB) by 80% (95% CI, 0.07–0.58) and 86% (95% CI, 0.03–0.84), respectively.

Conclusion

Maternal Hb > 130 g/L was associated with increased risk of adverse pregnancy outcomes. Reduction of PTB risk was observed with correction of Hb level during the third trimester.

Background

The term “adverse pregnancy outcomes” refers to all pathological pregnancy and delivery complications, which not only significantly affect the physical and mental health of pregnant women and growing fetus but also directly threatens the lives of both mothers and new born[1]. The association of maternal hemoglobin (Hb) concentrations and pregnancy outcomes has been widely recognized by the public[2]. Although many studies have explored the relationship between anemia or high Hb and pregnancy outcomes, the research results have been inconsistent. In both low-income and high-income countries, anemia during pregnancy is one of the main risk factors for maternal death and adverse birth outcomes [3, 4]. While a large amount of studies have extensively documented the fact that anemia could cause a series of adverse maternal and birth outcomes, such as LBW, PTB, small-for-gestational-age infants (SGA), stillbirth, perinatal and neonatal death[3–9], A few studies has shown no correlation[10, 11]. It is

generally accepted that pregnant women with moderate to severe anemia are at higher risk of adverse outcomes comparing to mild anemia[12, 13].

Compared with anemia, elevated maternal Hb levels are usually considered a predictor of well nutritional status and have not received enough attention. In recent decades, some studies have found that elevated Hb levels are associated with adverse maternal and infant outcomes, including gestational diabetes mellitus (GDM), PTB, LBW, SGA, and fetal death[2, 5, 8, 14], while a few studies has reported that high Hb levels are not associated with pregnancy outcomes[15]. In the United States, Switzerland and other developed countries, a U-shaped relationship between Hb concentrations and pregnancy outcomes has been found; that is, women with Hb values at either extreme have a higher risk of adverse birth outcomes[8]. However, the data from developing countries is relatively limited.

In addition, recent reviews have shown that the relationship between Hb levels and adverse pregnancy events is mainly affected by the time point of Hb determination[2]. Some studies have shown that anemia in first-trimester was significantly related to adverse pregnancy outcomes[5, 16, 17], while other studies have shown that this relationship was more significant in the second or third trimesters[18]. Furthermore, there have been few studies on the effect of recovery from low or high levels of hemoglobin during pregnancy on pregnancy outcomes.

In this retrospective cohort study, we aimed to examine the association of Hb levels in the second and third trimesters of pregnancy with adverse pregnancy outcomes, including PROM, fetal intrauterine distress (FIUD), PTB, LBW and SGA in Chinese women and to evaluate the influence of the recovery of Hb levels in the third trimester of gestation on maternal and infant pregnancy outcomes.

Methods

Study design and participants

A total of 1,994 pregnant women who registered and attended their routine first hospital visit in pregnancy at the Antenatal Department of Union Shenzhen Hospital of Huazhong University of Science and Technology (Shenzhen, Guangdong) and planned to give birth at this hospital were recruited from January 2015 to December 2018. The following exclusion criteria were included: smoking or drinking alcohol during pregnancy (n = 4), history of liver disease (n = 12), diabetes or hypertension (n = 45), kidney disease (n = 5), heart disease (n = 3), and twin or multiple pregnancy (n = 14). Finally, a total of 1,911 gravidas with singleton pregnancies were included in the present investigation. Basic information on the participants was collected at the beginning of the study, and Hb concentrations were measured in the second (16–18 weeks) and third (28–30 weeks) trimesters of gestation. In addition, the women were followed up until delivery. Participants signed informed consent forms at the beginning of the study, and all procedures were approved by the Ethics Committee of the Union Shenzhen Hospital of Huazhong University of Science and Technology.

Collection of baseline information

Age (years), education (primary, secondary, college or above), conception method (natural or artificial), parity (primiparity or multiparity), history of miscarriage (yes or no), embryo number and history of disease (e.g., liver disease, diabetes or hypertension, kidney disease, heart disease) were obtained through face-to-face interviews by a well-trained investigator, and questionnaires were completed simultaneously. Height and weight were measured using an electronic scale with the following detailed instructions: take off the shoes, stand up straight with the shoulders parallel and the body naturally relaxed. Height and weight measurements were accurate to 0.1 cm and 0.1 kg, respectively. The prepregnancy body mass index (BMI) (kg/m^2) was calculated as weight (kg) divided by the square of the height (m^2).

Laboratory assays

At 16–18 weeks and 28–30 weeks of pregnancy, fasting venous blood was collected by a professionally trained investigator. Hb levels were measured using an automated colorimetric procedure. All laboratory measurements were performed with a Hitachi 7600 automatic analyzer (Hitachi, Tokyo, Japan).

Assessment of pregnancy outcomes

The adverse pregnancy outcomes of this study included PROM, FIUD, PTB, LBW and SGA. We followed the definition of the International Classification of Diseases, 10th Revision (ICD-10). PROM was defined when the membranes were observed to have ruptured before the onset of labor [19–21]. FIUD refers to a fetus's acute and chronic hypoxic symptoms under the influence of various factors in the uterus [22]. PTB was defined as delivery at ≥ 20 weeks and before 37 weeks of gestation. Low birth weight was defined as a newborn with a birth weight less than 2500 g [23]. Smallness for gestational age was generally defined as below the 10th percentile on the growth chart [24].

Statistical analyses

Baseline information is presented as the mean (SD) for continuous variables and as the proportion (%) for categorical variables. Statistical differences between groups were tested using analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. Hb levels were categorized into four groups as follows: <110 g/L, 110–119 g/L, 120–130 g/L, and >130 g/L. The second group ($110 \text{ g/L} \leq \text{Hb} < 119 \text{ g/L}$) was defined as the reference group. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated by using logistic regression models to examine the association of Hb levels at gestation with the risk of adverse pregnancy outcomes. Two models were included in the present study: Model 1 was unadjusted; Model 2 was adjusted for age, education, conception method, parity, history of miscarriage, GDM, hypertension and thyroid disease. Furthermore, pregnant women with low Hb levels (<110 g/L) or high Hb levels (>130 g/L) at 16–18 weeks were divided into two groups: restored and not restored according to Hb levels at 28–30 weeks. Age subgrouping (<35 and ≥ 35 years) was performed because advanced maternal age is a known risk factor for adverse pregnancy outcomes [25]. Finally, to eliminate the influence of pregnancy diseases on pregnancy outcome, we performed a sensitivity analysis, that is, excluding pregnant women with gestational diabetes, hypertension and thyroid diseases, and repeated the above analysis. All analyses

were carried out by using SPSS 24.0 (SPSS Inc., Chicago, IL, USA), and a two-sided P-value < 0.05 was considered statistically significant. Graphic production was completed by using R version 3.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

A total of 1911 singleton pregnant women aged 31.51 (3.91) years were included in the study with 384 cases of PROM, 84 cases of FIUD, 108 cases of PTB, 66 cases of LBW and 65 cases of SGA. As presented in Table 1, the differences in prepregnancy BMI, conception method, prevalence of GDM, and Hb levels in the second and third trimesters of gestation were statistically significant ($P < 0.05$) among the four Hb levels. There was no significant difference in other indicators.

Table 1
Baseline characteristics of mothers and infants by hemoglobin (Hb) levels in the second trimester in this study.

	Total	Hb levels (g/L)				<i>P</i> value
		< 110	110–119	120–129	> 130	
No. of maternal cases	1911	405	779	583	144	
Maternal age (years)	31.51 ± 3.91	31.68 ± 4.10	31.47 ± 3.80	31.41 ± 3.82	31.58 ± 4.29	0.748
Age categories						0.278
< 35	1445 (75.6)	297 (73.3)	592 (76.0)	451 (77.4)	105 (72.9)	
≥ 35	466 (24.4)	108 (26.7)	187 (24.0)	132 (22.6)	39 (27.1)	
Prepregnancy BMI (kg/m ²)	20.82 ± 3.26	20.12 ± 2.29	20.72 ± 2.82	21.18 ± 4.24	21.82 ± 2.79	< 0.001
Education						0.493
Primary	78 (4.1)	20 (4.9)	27 (3.5)	24 (4.1)	7 (4.9)	
Secondary	285 (14.9)	68 (16.8)	122 (15.7)	78 (13.4)	17 (11.8)	
College or above	1548 (81.0)	317 (78.3)	630 (80.9)	481 (82.5)	120 (83.3)	
Conception method						0.015
Natural	1869 (97.8)	383 (94.6)	768 (98.6)	576 (98.8)	142 (98.6)	
Artificial	26 (1.4)	12 (3.0)	7 (0.9)	5 (0.9)	2 (1.2)	
Parity						0.113
Primiparity	815 (42.6)	180 (44.4)	314 (40.3)	257 (44.1)	64 (44.4)	
Multiparity	1096 (57.4)	225 (55.5)	465 (59.7)	326 (55.9)	80 (55.6)	
History of miscarriage	819 (42.9)	173 (42.7)	340 (43.6)	242 (41.5)	80 (55.6)	0.854
GDM	372 (19.5)	59 (14.6)	154 (19.8)	126 (21.6)	33 (22.9)	0.029

Data are presented as the mean ± SD for continuous variables and as n (%) for categorical variables. Abbreviations: BMI: body mass index; GDM: gestational diabetes mellitus; PROM: premature rupture of membranes; FIUD: fetal intrauterine distress; LBW: low-birth-weight infants; PTB: preterm birth; SGA: small-for-gestational-age infants.

	Total	Hb levels (g/L)				<i>P</i> value
		< 110	110–119	120–129	> 130	
Gestational hypertension	5 (0.3)	2 (0.5)	2 (0.3)	1 (0.2)	0 (0)	0.706
Gestational thyroid disease	21 (1.1)	7 (1.7)	7 (0.9)	7 (1.2)	0 (0)	0.331
Hemoglobin (g/L)						
2nd trimester	116.83 ± 9.11	104.31 ± 4.98	114.9 ± 2.83	123.93 ± 2.75	133.62 ± 3.37	< 0.001
3rd trimester	117.69 ± 10.15	110.19 ± 9.28	116.73 ± 8.53	121.88 ± 8.59	126.97 ± 10.62	< 0.001
Adverse maternal and fetal outcomes						
PROM	384 (20.1)	80 (19.8)	145 (18.6)	128 (22.0)	31 (21.5)	0.469
FIUD	84 (4.4)	15 (3.7)	30 (3.9)	30 (5.1)	9 (6.3)	0.396
PTB	108 (5.7)	23 (5.7)	44 (5.6)	31 (5.3)	10 (6.9)	0.902
LBW	66 (3.5)	15 (3.7)	21 (2.7)	21 (3.6)	9 (6.3)	0.184
SGA	86 (4.5)	24 (5.9)	31 (4.0)	24 (4.1)	7 (4.9)	0.449
Data are presented as the mean ± SD for continuous variables and as n (%) for categorical variables. Abbreviations: BMI: body mass index; GDM: gestational diabetes mellitus; PROM: premature rupture of membranes; FIUD: fetal intrauterine distress; LBW: low-birth-weight infants; PTB: preterm birth; SGA: small-for-gestational-age infants.						

Association of Hb levels with adverse pregnancy outcomes

The associations of Hb levels in the second trimester with adverse pregnancy outcomes are shown in Table 2. The second-trimester Hb levels were not significantly associated with PROM, PTB, FIUD or SGA. However, mothers with Hb levels > 130 g/L had a 154% (95% CI, 1.12–5.77) higher risk of PROM than those with Hb levels of 110–119 g/L.

Table 2 ORs (95% CIs) for adverse pregnancy outcomes according to the hemoglobin (Hb) levels at the second trimester.

Hb levels (g/L)					
	<110	110-119	120-129	>130	<i>P_{trend}</i>
PROM					
Case/N	80/405	145/779	128/583	31/144	
Model 1	1.08 (0.79, 1.46)	1	1.23 (0.94, 1.61)	1.20 (0.78, 1.86)	0.284
Model 2	1.06 (0.73, 1.55)	1	1.19 (0.86, 1.66)	1.09 (0.60, 1.99)	0.663
FIUD					
Case/N	15/405	30/779	30/583	9/144	
Model 1	0.96 (0.51, 1.81)	1	1.35 (0.81, 2.27)	1.66 (0.77, 3.58)	0.110
Model 2	0.85 (0.37, 1.79)	1	1.34 (0.78, 2.86)	1.57 (0.72, 3.39)	0.084
PTB					
Case/N	23/405	44/779	31/583	10/144	
Model 1	1.01 (0.60, 1.69)	1	0.94 (0.59, 1.51)	1.25 (0.61, 2.54)	0.850
Model 2	1.05 (0.62, 1.78)	1	0.95 (0.46, 1.47)	1.25 (0.61, 2.57)	0.918
LBW					
Case/N	15/405	21/779	21/583	9/144	
Model 1	1.39 (0.71, 2.72)	1	1.35 (0.73, 2.49)	2.41 (1.08, 5.37)	0.256
Model 2	1.27 (0.64, 2.54)	1	1.39 (0.74, 2.59)	2.54 (1.12, 5.77)	0.146
SGA					
Case/N	24/405	31/779	24/583	7/144	
Model 1	1.52 (0.88, 2.63)	1	1.04 (0.60, 1.79)	1.23 (0.53, 2.86)	0.378
Model 2	1.36 (0.78, 2.38)	1	1.08 (0.62, 1.86)	1.45 (0.62, 3.39)	0.796

Abbreviations: PROM: premature rupture of membranes; FIUD: fetal intrauterine distress; PTB: preterm birth; LBW: low-birth-weight infants; SGA: small-for-gestational-age infants. Model 1: without adjustment. Model 2: adjustment for age, prepregnancy BMI, education, conception method, parity and history of miscarriage, GDM, gestational hypertension and thyroid disease.

The associations of Hb levels in the third trimester with adverse pregnancy outcomes are shown in Table 3. Compared with those for Hb levels of 110–119 g/L, the OR (95% CI) for the risk of LBW at high levels was 2.17 (1.05–4.48), and the OR (95% CI) of SGA at high levels was 1.98 (1.04–3.78).

Table 3

ORs (95% CIs) for adverse pregnancy outcomes according to hemoglobin (Hb) levels in the third trimester.

Hb levels (g/L)					
	< 110	110–119	120–129	> 130	<i>P</i> _{trend}
PROM					
Case/N	82/392	134/698	121/609	47/212	
Model 1	1.11 (0.82, 1.52)	1	1.04 (0.79, 1.37)	1.20 (0.82, 1.74)	0.796
Model 2	1.14 (0.84, 1.56)	1	1.06 (0.80, 1.40)	1.17 (0.80, 1.72)	0.930
FIUD					
Case/N	10/392	34/698	34/609		
Model 1	0.51 (0.25, 1.05)	1	1.16 (0.71, 1.88)	0.57 (0.24, 1.37)	0.345
Model 2	0.52 (0.26, 1.07)	1	1.19 (0.72, 1.94)	0.44 (0.17, 1.17)	0.508
PTB					
Case/N	29/392	37/698	25/609	17/212	
Model 1	1.43 (0.86, 2.36)	1	0.77 (0.46, 1.29)	1.56 (0.86, 2.83)	0.505
Model 2	1.51 (0.91, 2.51)	1	0.79 (0.47, 1.34)	1.65 (0.90, 3.02)	0.930
LBW					
Case/N	16/392	22/698	15/609	6/212	
Model 1	1.31 (0.68, 2.52)	1	0.78 (0.40, 1.51)	2.01 (0.99, 4.07)	0.698
Model 2	1.41 (0.72, 2.74)	1	0.83 (0.42, 1.63)	2.17 (1.05, 4.48)	0.650
SGA					
Case/N	18/392	29/698	23/609	16/212	
Model 1	1.11 (0.61, 2.03)	1	0.91 (0.52, 1.58)	1.88 (1.01, 3.54)	0.331
Model 2	1.11 (0.61, 2.05)	1	0.96 (0.54, 1.68)	1.98 (1.04, 3.78)	0.257
Abbreviations: PROM: premature rupture of membranes; FIUD: fetal intrauterine distress; PTB: preterm birth; LBW: low-birth-weight infants; SGA: small-for-gestational-age infants. Model 1: without adjustment. Model 2: adjustment for age, prepregnancy BMI, education, conception method, number of pregnancies, parity, history of miscarriage, gestational diabetes, hypertension and thyroid disease.					

Association of recovery of Hb levels with adverse pregnancy outcomes

Figure 1 shows that women with Hb levels < 110 g/L in the second trimester of pregnancy that were restored to 110–120 g/L vs not restored in the third trimester of pregnancy had a reduced risk of PTB (OR, 0.20; 95% CI, 0.07–0.58). The same results were found in women with Hb levels > 130 g/L in the second trimester of pregnancy (OR, 0.14; 95% CI, 0.03–0.84).

Subgroup and sensitivity analysis

As shown in Supplementary Table 1, subgroups younger than 35 years with Hb levels > 130 g/L in the second trimester had an increased risk of LBW (OR, 2.86; 95% CI, 1.12–7.32), while those older than 35 years were not significantly different (OR, 1.92; 95% CI, 0.34–10.66). In the third trimester, subgroups older than 35 years with Hb levels > 130 g/L had an increased risk of SGA (OR, 4.19; 95% CI, 1.08–16.25). The other groups were not significantly different. Moreover, statistical tests for interactions between Hb levels and age with respect to outcome did not reveal significant differences (all P-interaction > 0.05).

After removing the data for pregnant women with GDM, hypertension and thyroid diseases, the results were basically consistent with the main findings. However, there was no significant relationship between Hb levels and any of the abovementioned adverse pregnancy outcomes in the second trimester (Supplementary Table 2).

Discussion

In this retrospective cohort study, we observed an increased risk of LBW in pregnant women with elevated Hb levels during the 16–18th weeks of gestation. During the 28–30th weeks of gestation, pregnant women with higher Hb levels exhibited an increased risk of LBW and SGA. In addition, mothers whose Hb levels were corrected to normal in the third trimester had a lower risk of PTB than those whose Hb levels were not corrected.

High levels of Hb during pregnancy are generally considered to be caused by failure of the plasma volume to expand, which increases maternal blood viscosity[26]. Hyperviscosity is negatively affected on the intervillous space, leading to poor maternal-fetal exchange[27]. This could directly cause fetal growth disorders through the reduction in nutrient transfer or may indirectly lead to fetal growth disorders through the release of fetal corticosteroids in response to chronic fetal hypoxia[26]. Recently, experimental studies have found that Hb levels have the ability to bind and inactivate nitric oxide (NO), which is an endothelial-derived smooth muscle relaxing factor[28]. With the increased hematocrit and decreased oxygen level, this ability becomes counterproductive[29]. The deactivation of NO then leads to oxidative stress, vascular endothelial injury, vasoconstriction and placental ischemia[30]. In addition, Magnus Centlow, Stefan R. Hansson and M Centlow et al. suggested that fetal Hb at the placental level is overproduced and leaks into the maternal circulation, further damaging placental function[31–33]. More than a decade ago, both Georg-Friedrich von Tempelhoff and Rasmussen found a negative correlation between Hb levels in the second trimester of pregnancy and birth weight[34]. In a recent study of 31,906 Australian pregnant women, Deborah A. Randall showed that pregnant women with a high concentration of Hb (≥ 140 g/L) had higher incidence of adverse events such as PTB and very low birth weight[35].

Similarly, Justiina Ronkainen et al. recently confirmed that high Hb levels (above the 90th percentile) in late pregnancy were associated with an increased risk of SGA (OR 1.60, 95% CI [1.26, 2.02]) in two Finnish birth cohorts[18]. In contrast, a population-based study in Chinese by A. Ren et al. reported that high Hb levels play no role in adverse pregnancy outcomes[36]. These findings from previous studies are inconsistent and there are few studies on the association between high Hb and adverse pregnancy outcomes among Chinese women. Previous studies have demonstrated that ethnicity potentially modifies the relationship between Hb and pregnancy outcomes[37]. We extended these findings in a relatively large cohort of pregnant Chinese women and observed that women with high Hb levels during the 16-18th week of pregnancy exhibited a 154% higher risk of LBW and during the 28-30th week of pregnancy exhibited a 117% and 98% higher risk of LBW and SGA, respectively. The heterogeneous nature of the results reported in previous studies may be due to variations in study design, sample size, the time points of Hb determination, the level of grading, or other confounding factors.

It has long been noted that anemia is a risk factor for various adverse maternal, fetal and neonatal outcomes. Low Hb levels could limit the oxygen circulation in the body, resulting in oxidative stress or chronic hypoxia, which could then cause adverse maternal and infant outcomes[16]. The WHO defines the Hb threshold for maternal anemia as follows: 100 to 110 g/L for mild anemia, 70 to 100 g/L for moderate, and 70 g/L for severe. But in the second trimester of pregnancy, the threshold of anemia was reduced to 105 g/L. A meta-analysis by Naoko Kozuki et al. suggested that mild anemia showed no significant relationship with SGA and that both the < 90 categories were associated with a 53% increase in the risk of SGA (OR = 1.53, 95% CI: 1.24–1.87)[13]. In another investigation, pregnant women with mild anemia with Hb concentrations of 8-10.9 g/L had no increased risk of PTB and LBW[12]. The majority of the pregnant women with Hb < 110g / L in the second trimester were diagnosed with mild anemia, and there were few cases of moderate or severe anemia, which may be one of the reasons why low levels of Hb category in this study were not associated with adverse pregnancy outcomes. With the plasma volume increase during pregnancy, the Hb concentration continues to fall until the second trimester, then increases slightly around the 30th week. Therefore, measurements taken during or after the second trimester of pregnancy are likely to weaken the link between low Hb and adverse maternal and infant outcomes, which may be another reasons for the current results.

The measures taken to restore low Hb were not collection in this study, and only inferred the treatment method based on previous investigations and clinical experience. We assume that the recovery of low Hb was the result of iron supplementation because most pregnant women receive iron supplementation when they are diagnosed with anemia. A novel clinical trial conducted by Mary E Cogswell suggested that prophylactic iron supplementation led to significantly longer gestation durations (+ 0.6week)[38]. A clinical trial carried out by Hemminiki and Rimpela also found that routine iron supplementation among pregnant women prolonged the gestational duration (+ 0.2week)[39]. However, both trials were conducted in pregnant women without anemia. Since elevated Hb (> 130g/L) was usually overlooked in most Chinese physicians, the methods to correct high Hb concentrations were not recorded. The underlying mechanism of influence on Hb recovery and the risk of PTB remains unclear. The possible mechanism is that the recovery of Hb levels alleviates the hypoxia and stress response caused by low or

high Hb, thereby reducing the corticotrophin releasing hormone (CRH) released by the placenta and the secretion of cortisol associated with preterm birth. There are few articles on the relationship between Hb recovery during pregnancy and pregnancy outcomes[38]. Deborah A. Randal et al.[35] reported that the recovery of Hb level above 110g/ L in pregnant women with HB < 110g/L 20 weeks ago could reduce the risk of postpartum blood transfusion, but it has no significant impact on other results. The inconsistency may caused by measurement timing. In previous studies, Hb was measure before 20 weeks of pregnancy. In addition, our data lack transfusion information and can not be compared with the previous one.

We found that subgroups younger than 35 years with Hb levels > 130 g/L in the second trimester had an increased risk of LBW, while those older than 35 years were not significantly different. In the third trimester, subgroups older than 35 years with Hb levels > 130 g/L had an increased risk of SGA. The other Hb groups were not significantly different. However, there was no evidence of a statistically significant interaction between age and Hb levels (p : 0.079–0.996). Further studies with larger sample sizes are required to determine how the relationship between Hb levels and the risk of adverse pregnancy outcomes is influenced by age.

Although our study comprehensively explored the association between maternal Hb concentrations and the risk of adverse pregnancy outcomes in a relatively large sample size, some limitations in this study remain. First, the small size of the subgroup of women aged > 35 years and with BMI > 24 kg/m² limited the statistical power. Second, the analytic cohort was from China, which may limit the generalizability of the study results. Finally, although we accounted for known confounders, some unmeasured or unknown residual confounders remained (either unmeasured or unknown).

Conclusions

High levels of Hb in the second and third trimesters of pregnancy increase the risk of adverse pregnancy outcomes. Correcting the Hb levels after the second trimester may reduce the risk of premature birth. Active treatment could help to reduce some adverse maternal and infant events, such as PTB, when abnormal Hb levels are found during mid-term pregnancy examinations.

Abbreviations

ANOVA

analysis of variance; BMI:Body mass index; CRH:Corticotrophin releasing hormone; FIUD:fetal intrauterine distress; GDM:Gestational diabetes mellitus; Hb:Hemoglobin; LBW:Low-birth-weight infants; LGA:Large for gestational age infants; NO:nitric oxide; OR:Odds ratio; 95% CIs:95% confidence intervals; SCr:Serum creatinine; SD:standard deviation; SGA:Small for gestational age infants; PROM:Premature rupture of membranes; PTB:preterm birth.

Declarations

Ethics approval and consent to participate

Participants written informed consent forms at the beginning of the study. The protocol for this study was approved by the Ethics Committee of the Union Shenzhen Hospital of Huazhong University of Science and Technology (No. 2019072644) and all methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

GD, ZL and LW conceived and designed the study. YW and RS assisted with study design. LW contributed to statistical analysis and wrote the manuscript. YL and HC provided statistical advice and assisted with data analysis. GD and SS reviewed and edited the manuscript. All authors read and approved the final manuscript.

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References

1. Regan AK, Gissler M, Magnus MC, Håberg SE, Ball S, Malacova E, Nassar N, Leonard H, Pereira G. Association between interpregnancy interval and adverse birth outcomes in women with a previous stillbirth: an international cohort study. *The Lancet* 2019, 393(10180):1527–1535.

2. Young MF, Oaks BM, Tandon S, Martorell R, Dewey KG, Wendt AS. Maternal hemoglobin concentrations across pregnancy and maternal and child health: a systematic review and meta-analysis. *Ann N Y Acad Sci* 2019, 1450(1):47–68.
3. Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, Ota E, Gilmour S, Shibuya K. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. *Am J Clin Nutr* 2016, 103(2):495–504.
4. Benson CS, Shah A, Stanworth SJ, Frise CJ, Spiiby H, Lax SJ, Murray J, Klein AA. The effect of iron deficiency and anaemia on women's health. *Anaesthesia* 2021, 76 Suppl 4:84–95.
5. Scanlon KS, Yip R, Schieve LA, Cogswell ME. High and low hemoglobin levels during pregnancy: differential risks for preterm birth and small for gestational age. *Obstetrics & Gynecology* 2000, 96(5 Pt 1):741–748.
6. Ronnenberg AG, Wood RJ, Wang X, Xing H, Chen C, Chen D, Guang W, Huang A, Wang L, Xu X. Preconception hemoglobin and ferritin concentrations are associated with pregnancy outcome in a prospective cohort of Chinese women. *Journal of Nutrition* 2004, 134(10):2586–2591.
7. Parks S, Hoffman MK, Goudar SS, Patel A, Saleem S, Ali SA, Goldenberg RL, Hibberd PL, Moore J, Wallace D *et al.* Maternal anaemia and maternal, fetal, and neonatal outcomes in a prospective cohort study in India and Pakistan. *BJOG* 2019, 126(6):737–743.
8. Dewey KG, Oaks BM. U-shaped curve for risk associated with maternal hemoglobin, iron status, or iron supplementation. *Am J Clin Nutr* 2017, 106(Suppl 6):1694S-1702S.
9. Chu FC, Shaw SW, Lo LM, Hsieh TT, Hung TH. Association between maternal anemia at admission for delivery and adverse perinatal outcomes. *J Chin Med Assoc* 2020, 83(4):402–407.
10. Hamalainen H. Anaemia in the first but not in the second or third trimester is a risk factor for low birth weight. *Clinical Nutrition* 2003, 22(3):271–275.
11. Rasmussen S, Øian P. First- and second-trimester hemoglobin levels. Relation to birth weight and gestational age. *Acta obstetrica et gynecologica Scandinavica* 1993, 72(4):246–251.
12. Sehgal R, Kriplani A, Vanamail P, Maiti L, Kumar N. Assessment and comparison of pregnancy outcome among anaemic and non anaemic primigravida mothers. *Indian J Public Health* 2016, 60(3):188–194.
13. Kozuki N, Lee AC, Katz J, Group CHEDMR. Moderate to Severe, but Not Mild, Maternal Anemia Is Associated with Increased Risk of Small-for-Gestational-Age Outcomes. *The Journal of Nutrition* 2012, 142(2):358–362.
14. Gao CJ, Huang XM, Chen ZP, Sheng L, Xu J, Li Y, Li XY, Zhang R, Yu ZY, Zha BB *et al.* [High level of hemoglobin during the first trimester of pregnancy associated with the risk of gestational diabetes mellitus]. *Zhonghua Fu Chan Ke Za Zhi* 2019, 54(10):654–659.
15. Ren A, Wang J, Ye RW, Li S, Liu JM, Li Z. Low first-trimester hemoglobin and low birth weight, preterm birth and small for gestational age newborns. *Int J Gynaecol Obstet* 2007, 98(2):124–128.
16. Zhang Q, Ananth CV, Zhu L, Smulian JC. Maternal anaemia and preterm birth: A prospective cohort study. *International Journal of Epidemiology* 2009, 38(5):1380–1389.

17. Zhang Q, Ananth CV, Rhoads GG, Zhu L. The Impact of Maternal Anemia on Perinatal Mortality: A Population-based, Prospective Cohort Study in China. *Annals of Epidemiology* 2009, 19(11):793–799.
18. Ronkainen J, Lowry E, Heiskala A, Uusitalo I, Koivunen P, Kajantie E, Vaarasmaki M, Jarvelin MR, Sebert S. Maternal hemoglobin associates with preterm delivery and small for gestational age in two Finnish birth cohorts. *Eur J Obstet Gynecol Reprod Biol* 2019, 238:44–48.
19. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008, 371(9606):75–84.
20. Liu J, Feng ZC, Wu J. The incidence rate of premature rupture of membranes and its influence on fetal-neonatal health: a report from mainland China. *J Trop Pediatr* 2010, 56(1):36–42.
21. Zhou Q, Zhang W, Xu H, Liang H, Ruan Y, Zhou S, Li X. Risk factors for preterm premature rupture of membranes in Chinese women from urban cities. *Int J Gynaecol Obstet* 2014, 127(3):254–259.
22. Liu Q, Li B. The diagnostic value of ultrasound detection of the fetal middle cerebral artery, umbilical artery blood flow and fetal movement reduction in fetal distress. *American journal of translational research* 2021, 13(4):3529–3535.
23. Glodean DM, Miclea D, Popa AR. Macrosomia. A Systematic Review of Recent Literature. *Romanian Journal of Diabetes Nutrition and Metabolic Diseases* 2018, 25(2):187–195.
24. He JR, Xia HM, Liu Y, Xia XY, Mo WJ, Wang P, Cheng KK, Leung GM, Feng Q, Schooling CM *et al.* A new birthweight reference in Guangzhou, southern China, and its comparison with the global reference. *Arch Dis Child* 2014, 99(12):1091–1097.
25. Frederiksen LE, Ernst A, Brix N, Braskhoj Lauridsen LL, Roos L, Ramlau-Hansen CH, Ekelund CK. Risk of Adverse Pregnancy Outcomes at Advanced Maternal Age. *Obstet Gynecol* 2018, 131(3):457–463.
26. Heilmann L. [Hemorheologic findings in severe gestosis]. *Geburtshilfe Frauenheilkd* 1987, 47(11):764–769.
27. Buchan PC. Rheology of Normal and Abnormal Pregnancy: Clinical Blood Rheology; 2019.
28. Gonzalez, Daniel, R., Treuer, Adriana, V. Nitric oxide synthases, S-nitrosylation and cardiovascular health: From molecular mechanisms to therapeutic opportunities. *Molecular medicine reports* 2015, 11(3):1555–1565.
29. Azarov I, Huang KT, Basu S, Gladwin MT, Hogg N, Kim-Shapiro DB. Nitric Oxide Scavenging by Red Blood Cells as a Function of Hematocrit and Oxygenation. *Journal of Biological Chemistry* 2005, 280(47):39024–39032.
30. Kim-Shapiro, D. B. Unraveling the Reactions of Nitric Oxide, Nitrite, and Hemoglobin in Physiology and Therapeutics. *Arterioscler Thromb Vasc Biol* 2006, 26(4):697–705.
31. Centlow M, Carninci P, Nemeth K, Mezey E, Brownstein M, Hansson SR. Placental expression profiling in preeclampsia: local overproduction of hemoglobin may drive pathological changes. *FERTILITY AND STERILITY-INTERNATIONAL EDITION*-2008.

32. Hansson SR, N?ð?ðV, Erlandsson L. Oxidative stress in preeclampsia and the role of free fetal hemoglobin. *Frontiers in Physiology* 2015, 5(516):516.
33. M., Centlow, K., Junus, H., Nystrm, K., May, I., Larsson. Perfusion of the Human Placenta with Red Blood Cells and Xanthine Oxidase Mimics Preeclampsia in-vitro. *Zeitschrift für Geburtshilfe und Neonatologie* 2009, 213(03):89–95.
34. Rasmussen S, Oian P. First- and second-trimester hemoglobin levels. Relation to birth weight and gestational age. *Acta obstetrica et gynecologica Scandinavica* 1993, 72(4):246–251.
35. Randall DA, Patterson JA, Gallimore F, Morris JM, McGee TM, Ford JB, Obstetric Transfusion Steering G. The association between haemoglobin levels in the first 20 weeks of pregnancy and pregnancy outcomes. *PLoS One* 2019, 14(11):e0225123.
36. Ren A, Wang J, Ye RW, Li S, Liu JM, Li Z. Low first-trimester hemoglobin and low birth weight, preterm birth and small for gestational age newborns. *International Journal of Gynecology & Obstetrics* 2007, 98(2):124–128.
37. Steer P, Alam MA, Wadsworth J, Welch A. Relation between maternal haemoglobin concentration and birth weight in different ethnic groups. *British Medical Journal* 1995, 310(6978):p.489–491.
38. Cogswell ME, Ibrahim P, Liza I, Ray Y, Brittenham GM. Iron supplementation during pregnancy, anemia, and birth weight: a randomized controlled trial. *American Journal of Clinical Nutrition* 2003(4):773–781.
39. Hemminki E, Meriläinen J. Long-term follow-up of mothers and their infants in a randomized trial on iron prophylaxis during pregnancy. *American Journal of Obstetrics & Gynecology* 1995, 173(1):205–209.

Figures

Figure 1

Pregnancy outcomes of pregnant women with low or high Hb in the second trimester according to whether Hb was restored in the third trimester. The model was adjusted for age, prepregnancy BMI, education, conception method, number of pregnancies, parity, history of miscarriage, gestational diabetes, hypertension and thyroid disease.

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