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Article

Maternal and Neonatal Outcomes of Twin Pregnant Women With Anemia

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Abstract

The aim of this study was to investigate the prevalence of anemia in twin pregnancies and the influence of anemia on maternal and neonatal outcomes. This retrospective study included twin pregnant women who delivered in a tertiary hospital in China from January 2018 to December 2018. Patients were divided by WHO criteria (hemoglobin <11.0 g/dL): the anemic and nonanemic groups. Patients with anemia were further classified as recovered or unrecovered subgroup after oral iron therapy. Maternal and neonatal outcomes in women carrying twins were compared using Student's *t* test and the chi-squared test or the Fisher exact test. Univariable and multivariable logistic regression models were used to determine the association of maternal and neonatal characteristics with anemia. Linear regression analysis was used to estimate mean birth weight and gestational week. The prevalence of anemia was 42.6% (182/427) in twin pregnancies. The anemic group had higher rates of low 1-minute Apgar score (4.4% vs. 1.8%, $p = .028$), perinatal death (1.9% vs. 0.2%, $p = .012$) and neonatal intensive care unit (NICU) admission (27.2% vs. 20.2%, $p = .017$; adjusted *OR*, 1.478; 95% CI [1.07, 2.044]). The recovered subgroup had lower NICU admission rate (13.5% vs. 30.3%, $p = .006$; *OR*, 0.388; 95% CI [0.186, 0.809]), higher gestational week and birth weight (β, 0.954 week; 95% CI [0.114, 1.794] and β, 171.01 g; 95% CI [9.894, 332.126] respectively). The prevalence of anemia in twin gestation is high. Anemia is associated with adverse neonatal outcomes, and correction of anemia significantly improved the pregnancy outcomes.

Keywords: Maternal anemia; twin gestation; hemoglobin; pregnancy outcomes

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Maternal anemia is a common pregnancy complication worldwide. The World Health Organization (WHO) defines maternal anemia as a hemoglobin (Hb) concentration of less than 11 g/dL (WHO, 2011). Globally, 36.5% of pregnant patients have anemia (WHO, 2022). Maternal anemia increases the risk of low birth weight (LBW), preterm birth, perinatal mortality, stillbirth, and maternal mortality (Breymann et al., 2011; Jung et al., 2019; Rahman et al., 2016).

Twin pregnancies are at a higher risk for maternal and neonatal complications (Gibson et al., 2020). Recently, twin gestations are increasing worldwide because of the development and application of assisted reproductive technology. The proportion of twin gestations constitutes 2%−4% of total pregnancies (Ananth et al., 2012; Fell et al., 2012; Russell et al., 2003). However, the prevalence of anemia and adverse maternal and neonatal outcomes in twin pregnancies have been rarely studied. The present study aimed to investigate the prevalence of anemia in twin pregnancies, and to examine whether maternal anemia is associated with adverse maternal and neonatal outcomes in twin gestations. We further evaluated changes in outcomes based on successful anemia treatment.

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Materials and Methods

Study Subjects and Design

This was a retrospective study in a tertiary hospital in China. The study was approved by the ethics committee of the hospital, and was conducted in accordance with the ethical standards of the Declaration of Helsinki. Since this was a retrospective study and had minimal risk for patients, a waiver of informed consent was approved by the ethics committee of our hospital. All twin pregnancies were eligible for inclusion. Pregnancies complicated by twin-to-twin transfusion syndrome, second trimester deliveries (< 28 weeks gestation), and substance use were excluded. In our hospital, patients routinely received folic acid during pregnancy. Based on the criteria of Hb <11 g/dL as pregnancy anemia, the twin pregnant women were divided into two groups: patients with Hb <11 g/dL were in the anemic group and patients with Hb ≥11 g/dL served as controls. Anemic patients were treated with supplemental iron therapy and the serum ferritin levels were measured for the remainder of the pregnancy. After early diagnosis and treatment, patients with anemia in the second trimester were further subcategorized by whether they had normal Hb in the third trimester. We also compared the maternal and neonatal outcomes between the recovered and unrecovered subgroups.

Data Collection

Baseline characteristics and comorbidities were analyzed for all eligible participants. This included maternal age, mode of conception, chorionicity, parity, and history of cesarean. Perinatal outcomes assessed included incidence of preterm birth, gestational diabetes (GDM), preeclampsia, preterm premature rupture of membranes (PPROM), cesarean delivery, and postpartum hemorrhage. Neonatal outcomes evaluated included birth weight, incidence of low birth weight (LBW), small for gestational age (SGA), birth weight discordance, congenital malformations, Apgar score at 1 min and at 5 min, neonatal intensive care unit (NICU) admission rate and perinatal mortality.

Definitions

Severity of anemia was categorized as mild (Hb 10.0−10.9 g/dL), moderate (Hb 7.0−9.9 g/dL) and severe (Hb <7.0 g/dL) based on the WHO recommendation (WHO, 2011). Chorionicity was determined by ultrasound at 10–14 weeks of gestation. SGA was defined as birth weight below the sex-specific 10th percentile of weights for gestational age (Kibel et al., 2017). LBW was defined as birth weight <2500 g (Hughes et al., 2017). Perinatal death was defined as the occurrence of intrauterine death and neonatal death. Birth weight discordance was defined as a 20% difference in birth weight between the larger and the smaller twin and calculated by the following equation: (larger actual weight–smaller actual weight)/larger actual weight (American College of Obstetricians and Gynecologists [ACOG], 2021b; Qiao et al., 2020).

Statistical Analysis

Categorical variables were represented as number and percentage. The rates or proportions of different group were compared by the chi-squared test or the Fisher exact test (if the variable contained fewer than five measurements). Student's t test was used for differences between continuous variables.

Univariable and multivariable logistic regression models were used to determine the association of maternal and neonatal characteristics with anemia. Odds ratios (*OR*s) and 95% confidence intervals (CIs) were calculated for each variable. Unadjusted *OR*s and adjusted *OR*s were reported. Linear regression analysis was used to estimate mean birth weight and gestational week.

A $p < .05$ or confidence interval excluding 1.0 was considered statistically significant. All analyses were performed using the Statistical Package for Social Science (SPSS Inc., Chicago, IL, version 20).

Results

Prevalence of Anemia and Demographic Characteristics of Participants

Of the total 427 women with twin pregnancy, 182 were diagnosed with anemia, with an overall anemia prevalence of 42.6% (95% CI [37.9, 47.3]). Of the anemic pregnant patients, 90 (49.5%) were diagnosed in the second trimester, and 92 (50.5%) were diagnosed in the third trimester (Figure 1). The anemia was mild in 127 (69.8%), moderate in 55 (30.2%), and severe in none of the 182 anemic patients.

The maternal demographic characteristics are shown in Table 1. None of the patients in the cohort were younger than 18 years old. Maternal ages and chorionicity were comparable between the anemia and control groups. Patients with anemia were more likely to have higher parity ($p = .012$), spontaneous conception ($p = .028$), and history of cesarean ($p = .02$). The two subgroups of twin pregnant women diagnosed with anemia in the second trimester had similar demographics (Table S1).

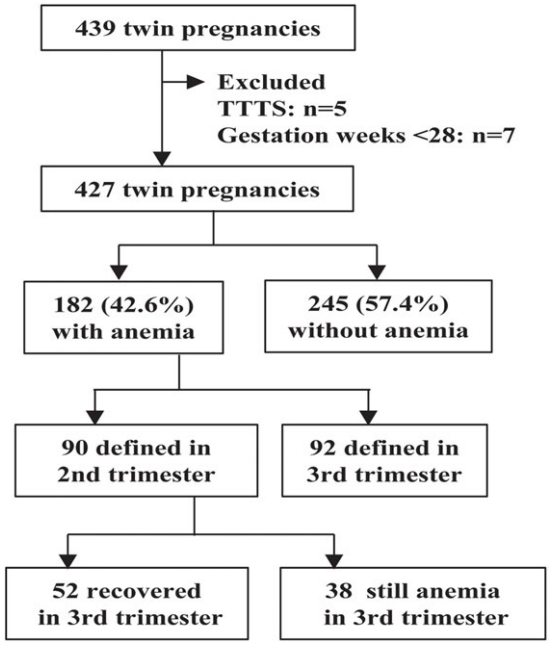

Figure 1. Flow diagram of study participants.
Note: TTTS, twin-to-twin transfusion syndrome.

Maternal Outcomes of Twin Pregnancies With Anemia

Tables 2 and 3 show the maternal outcomes in the two groups. There were no maternal deaths in the cohort. Patients with anemia were less likely to have GDM, compared with nonanemic patients (11.0% vs. 18.0%, $p < .05$). After adjusting for confounders, there was no significant difference in the odds of GDM, preeclampsia, PPROM, postpartum hemorrhage, cesarean delivery, or preterm birth (Table 3).

Neonatal Outcomes of Twin Pregnancies With Anemia

Tables 4 and 5 show the detailed neonatal outcomes of infants born to anemic and nonanemic patients. A higher rate of Apgar score ≤7 at 1 min (4.4% vs. 1.8%, $p = .028$) was observed in twins from the anemic group. Perinatal death was significantly higher among offspring born to anemic patients (1.9% vs. 0.2%, $p = .012$). Notably, newborn infants of patients with anemia were more likely to be admitted to NICU (27.2% vs. 20.2%, $p < .05$); this finding persisted after adjusting for confounders (adjusted *OR*, 1.478; 95% CI [1.07, 2.044]).

Maternal and Neonatal Outcomes of Recovered and Unrecovered Anemic Pregnant Women

The 90 patients diagnosed with anemia during the second trimester were treated with iron supplements, and 52 had normal Hb in the third trimester and the remaining 38 still had anemia. There was a significant reduction in the odds of PPROM (*OR*, 0.233; 95% CI [0.067, 0.814]) among the successfully treated patients. As shown in Table 6, the recovered group had lower rates of preterm birth (32.7% vs. 55.3%, $p = .032$) and LBW (36.5% vs.

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Table 1. Demographic characteristics of twin pregnancies with and without anemia

Parameters	Anemia, $n = 182$ (%)	No anemia, $n = 245$ (%)	p value
Maternal age	30.66 ± 4.1	30.35 ± 4.0	0.439
<18 years	0 (0)	0 (0)	–
18-35 years	151 (83.0)	204 (83.3)	0.935
≥35 years	31 (17.0)	41 (16.7)	
Mode of conception			
Spontaneous pregnancy	96 (52.7)	103 (42.0)	0.028[a]
Fertility treatment	86 (47.3)	142 (58.0)	
Chorionicity			
Dichorionic	135 (74.2)	197 (80.4)	0.126
Monochorionic	47 (25.8)	48 (19.6)	
Parity			
0	147 (80.8)	219 (89.4)	0.012[a]
1 or above	35 (19.2)	26 (10.6)	
History of cesarean	13 (7.1)	6 (2.4)	0.02[a]

Note: Data are presented as number (percentage) or mean ± standard deviation.
[a]Denotes statistical significance.

Table 2. Adverse maternal outcomes in twin pregnant women with and without anemia

Parameters	Anemia, $n = 182$ (%)	No anemia, $n = 245$ (%)	p value
GDM	20 (11.0)	44 (18.0)	0.046[a]
Preeclampsia	23 (12.6)	32 (13.1)	0.897
PPROM	25 (13.7)	36 (14.7)	0.780
Postpartum hemorrhage	82 (45.0)	119 (48.6)	0.472
Cesarean delivery	161 (88.5)	212 (86.5)	0.553
Preterm birth (<37 weeks)	104 (57.1)	138 (56.3)	0.866
Gestational week	35.7 ± 2.2	36.0 ± 1.9	0.131
Maternal death	0 (0)	0 (0)	–

Note: Data are presented as number (percentage) or mean ± standard deviation. GDM, gestational diabetes mellitus; PPROM, preterm premature rupture of membranes.
[a]Denotes statistical significance.

Table 3. Association of maternal anemia with maternal outcomes in twin pregnancies

Parameters	Unadjusted *OR*	95% CI	Adjusted *OR*[a]	95% CI
GDM	0.087	0.931-2.861	1.636	0.913, 2.930
Preeclampsia	1.018	0.557-1.860	0.973	0.527, 1.797
PPROM	1.088	0.576-2.055	0.949	0.496, 1.819
Postpartum hemorrhage	1.265	0.856-1.871	1.244	0.838, 1.847
Cesarean delivery	0.890	0.468-1.694	0.822	0.429, 1.575
Preterm birth (<37 weeks)	0.971	0.627-1.504	0.998	0.640, 1.557
Maternal death	[b]	[b]	[b]	[b]

Note: *OR*, odds ratio; CI, confidence interval; GDM, gestational diabetes mellitus; PPROM, preterm premature rupture of membranes.
[a]Multivariate logistic regression was adjusted for mode of conception, parity and history of cesarean.
[b]Not reported as minimum number of events not met.

Table 4. Neonatal outcomes in twin pregnant women with and without anemia

Parameters	Anemia ($n = 364$)	No anemia ($n = 490$)	p value
Male	192 (52.7%)	272 (55.5%)	0.423
Birth weight (g)	2354.1 ± 567.0	2429.7 ± 501.1	0.044[a]
LBW	191 (52.5%)	234 (47.8%)	0.173
SGA (<10 percentile)	118 (32.4%)	150 (30.6%)	0.574
Birth weight discordance ≥20%	38 (10.4%)	42 (8.6%)	0.354
Fetal malformation	5 (1.4%)	15 (3.1%)	0.107
Apgar score ≤7 at 1 min	16 (4.4%)	9 (1.8%)	0.028[a]
Apgar score ≤7 at 5 min	9 (2.5%)	8 (1.6%)	0.409
Admission to NICU	99 (27.2%)	99 (20.2%)	0.017[a]
Perinatal deaths	7 (1.9%)	1 (0.2%)	0.012[a]
Intrauterine deaths	3 (0.8%)	1 (0.2%)	0.318
Neonatal deaths	4 (1.1%)	0	0.033[a]

Note: Data are presented as number (percentage) or mean ± standard deviation. LBW, low birth weight; SGA, small for gestational age; NICU, neonatal intensive care unit.
[a]Denotes statistical significance.

51.3%, $p = .048$) than the unrecovered group. Furthermore, NICU admission rate (13.5% vs. 30.3%, $p = .006$; *OR*, 0.388; 95% CI [0.186, 0.809]) was significantly lower in newborns of anemic patients who recovered (Tables 6 and 7). In the linear regression, gestational week and birth weight of newborns significantly increased in the recovered subgroup (β, 0.954 week; 95% CI [0.114, 1.794] and β, 171.01 g; 95% CI [9.894, 332.126] respectively).

Discussion

Principal Findings

Our study showed that the prevalence of anemia was 42.6% in twin pregnancies from a tertiary hospital in China. Although there was no severe anemia in the present study, twin pregnant females with mild or moderate anemia were more likely to experience adverse neonatal outcomes, such as a low 1-minute Apgar score, lower birth weight, admission to NICU and perinatal death compared with nonanemic twin pregnant women. Notably, correction of anemia in the third trimester significantly improved neonatal outcomes of anemic patients with twin gestations.

Comparison With Other Studies and Clinical Implications

In this study, we reviewed the Hb levels of women with twin gestations in prenatal tests, and anemia was diagnosed when Hb value in any trimester was lower than 11g/dL (WHO, 2011). Similar to the prevalence of 44.6% in multiple pregnancies in New York (Ru et al., 2016), the 42.6% prevalence of anemia observed in twin pregnancy is much higher than the prevalence of 27.2% in singleton pregnancies previously reported by our center (Lan et al.,

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Table 5. Unadjusted and adjusted odds ratios for neonatal outcomes of patients with anemia

Parameters	Unadjusted OR	95% CI	Adjusted OR[b]	95%CI
Male	0.891	0.678-1.169	0.924	0.701-1.218
LBW	1.209	0.921-1.586	1.174	0.89-1.550
SGA (<10 percentile)	1.087	0.812-1.455	1.076	0.799-1.450
Birth weight discordance ≥20%	1.275	0.783-2.078	1.229	0.749-2.019
Fetal malformation	0.589	0.253-1.371	0.568	0.242-1.336
Apgar score ≤7 at 1 min	2.457	1.073-5.625[a]	2.051	0.879-4.789
Apgar score ≤7 at 5 min	1.527	0.584-3.998	1.293	0.484-3.458
Admission to NICU	1.475	1.072-2.03[a]	1.478	1.07-2.044[a]
Perinatal deaths	4.784	0.988-23.167	3.666	0.737-18.227

Note: *OR*, odds ratio; CI, confidence interval; LBW, low birth weight; SGA, small for gestational age; NICU, neonatal intensive care unit.
[a]Indicates significant difference;
[b]Multivariate logistic regression was adjusted for mode of conception, parity and history of cesarean.

2016), which suggested that women pregnant with twins may be at particularly high risk of anemia. According to WHO guidelines, a prevalence above 40% is a severe public health problem (WHO, 2017). Considering the high prevalence, anemia among twin pregnancy requires more attention.

Despite high rates of maternal anemia, there are few studies on patients with twin gestations, and they were not identified as an at-risk obstetric population by the last published American College of Obstetricians and Gynecologists Practice Bulletin on anemia in pregnancy (ACOG, 2021a). In the present study, twin-pregnant women with anemia was associated with higher risk of a low 1-minute Apgar score and lower birth weight, which also concurs with that found in singleton pregnancy (Figueiredo et al., 2018; Smith et al., 2019; Tunkyi & Moodley, 2018; Young et al., 2019;). Moreover, we observed increased perinatal deaths and NICU admission among twins born to anemic patients. Therefore, anemia in twin pregnancy is a factor for adverse neonatal outcomes.

Although anemia is known to exacerbate risks of preterm birth (Breymann et al., 2011; Jung et al., 2019; Rahman et al., 2016), our study did not find a statistical difference in the incidence of preterm birth between the anemic and nonanemic twin pregnancies. This is consistent with the results of a previous study in twin pregnancies in Israel (Kosto et al., 2016). Preterm birth is highly prevalent in patients who are carrying twin fetuses (Chauhan et al., 2010; Roman et al., 2022), which may overlap with the rate of preterm birth caused by anemia.

In singleton pregnancies, patients with anemia may experience more postpartum hemorrhage, cesarean delivery, preeclampsia and PPROM than patients without anemia (Kanu et al., 2022; Smith et al., 2019). However, compared to twin pregnant women without anemia, we did not find increased rates of these complications among anemic patients.

We noted that more than half of the anemic patients were recovered following iron therapy. The successful treatment was associated with an increase in gestational age and birth weight and a considerable reduction of NICU admission. The findings highlight the importance of early diagnosis and treatment of anemia in twin pregnancies.

Table 6. Adverse maternal and neonatal outcomes of recovered and unrecovered patients diagnosed with anemia in the second trimester

Parameters	Unrecovered anemic women in the third trimester, $n = 38$	Recovered anemic women in the third trimester, $n = 52$	p value
Maternal outcomes			
GDM	3 (7.9%)	7 (13.5%)	0.509
Preeclampsia	1 (2.6%)	1 (1.9%)	1.000
PPROM	10 (26.3%)	4 (7.7%)	0.016[a]
Postpartum hemorrhage	21 (26.3%)	20 (38.5%)	0.114
Cesarean delivery	34 (89.5%)	49 (94.2%)	0.45
Preterm birth (< 37 weeks)	21 (55.3%)	17 (32.7%)	0.032[a]
Gestational week	35.7 ± 2.2	36.6 ± 1.8	0.032[a]
Neonatal outcomes			
Number[a]	76	104	
Birth weight (g)	2348.8 ± 570.2	2519.8 ± 518.7	0.038[a]
LBW	39 (51.3%)	38 (36.5%)	0.048[a]
SGA (< 10 percentile)	22 (28.9%)	29 (27.9%)	0.876
Male	39 (51.3%)	61 (58.7%)	0.328
Fetal malformation	2 (2.6%)	1 (1.0%)	0.574
Apgar score ≤ 7 at 1 min	3 (3.9%)	1 (1.0%)	0.312
Apgar score ≤ 7 at 5 min	2 (2.6%)	0	0.177
Admission to NICU	23 (30.3%)	14 (13.5%)	0.006[a]
Perinatal deaths	2 (2.6%)	1 (1.0%)	0.574

Note: Data are presented as number (percentage) or mean ± standard deviation. GDM, gestational diabetes mellitus; PPROM, preterm premature rupture of membranes; LBW, low birth weight; SGA, small for gestational age; NICU, neonatal intensive care unit.
[a]Denotes statistical significance.

Strengths and Limitations

The strengths of this study include the focus on the effect of anemia in twin pregnancies and the elaborate study design of subgroups. This study has several limitations. First, we did not investigate the iron status or detailed iron supplement of patients. Second, data were collected retrospectively, and some information such as types of anemia and prepregnancy body mass index was missing. Third, our study did not evaluate the effects of severe anemia (Hb <7 g/dL) on twin pregnancy.

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Table 7. Maternal and neonatal odds ratios for adverse outcomes among patients diagnosed with anemia in the second trimester

Parameters	*OR*	95% CI
Maternal outcomes		
GDM	1.815	0.437, 7.529
Preeclampsia	0.725	0.044, 11.977
PPROM	0.233	0.067, 0.814[a]
Postpartum hemorrhage	0.506	0.216, 1.183
Cesarean delivery	1.922	0.404, 0.140
Preterm birth (< 37 weeks)	0.429	0.182, 1.010
Neonatal outcomes		
LBW	0.569	0.312, 1.037
SGA (< 10 percentile)	0.949	0.493, 1.828
Male	1.346	0.742, 2.441
Fetal malformation	0.919	0.179, 6.743
Apgar score ≤ 7 at 1 min	0.236	0.024 2.317
Admission to NICU	0.388	0.186, 0.809[a]
Perinatal deaths	0.359	0.032, 4.036

Note: *OR*, odds ratio; CI, confidence interval; GDM, gestational diabetes mellitus; PPROM, preterm premature rupture of membranes; LBW, low birth weight; SGA, small for gestational age; NICU, neonatal intensive care unit.
[a]Denotes statistical significance.

Conclusions

In this study, we found that 42.6% of females with a twin pregnancy had anemia. Anemia was associated with adverse neonatal outcomes. Correction of anemia in the third trimester significantly improved the pregnancy outcomes. The findings highlight the importance of early diagnosis and treatment of anemia for pregnant women who are carrying twins. Further studies are needed to validate the present findings.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/thg.2023.33.

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Competing interests. The authors declare that they have no competing interests.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the ethics committee of the hospital (2021-080-01).

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