PERINATAL EPIDEMIOLOGY

Maternal anaemia and preterm birth: a prospective cohort study

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Background The role of maternal anaemia in preterm birth remains poorly defined, and the association between anaemia and preterm birth clinical subtypes remain unclear. We examined if maternal anaemia exposure both within and across trimesters during gestation is associated with preterm birth.

Methods This was a secondary analysis of data from a population-based prospective cohort study in 13 counties of East China (1993–96). All singleton live births delivered at 20–44 weeks to women with at least one haemoglobin measure during pregnancy were included \( (n = 160700) \). Risk of preterm birth (<37 weeks) was examined by clinical subtypes, namely, preterm premature rupture of membranes (PROM), spontaneous preterm labour and medically indicated preterm birth. Haemoglobin changes across trimesters were assessed as proxy of haemo-dilution and haemo-concentration. Multivariable Cox proportional hazards regression models were fitted.

Results Preterm birth rates of preterm birth were 4.1% for anaemic and 5% for non-anaemic women \( (P < 0.05) \). Compared with haemoglobin of 11 g/dl (reference), values ≤5 g/dl in the first trimester were associated with increased risk for preterm PROM [hazard ratio (HR) 3.3, 95% confidence interval (CI) 1.4–7.7], whereas low haemoglobin in the third trimester was associated with reduced risk of spontaneous preterm labour. Haemodilution was associated with reduced risk for preterm birth.

Conclusions Anaemia in early pregnancy was found to be associated with increased risk for preterm PROM, whereas exposure in late pregnancy was associated with reduced risk for spontaneous preterm labour.

Keywords Haemoglobin, maternal anaemia, medically indicated preterm birth, preterm premature rupture of membranes, spontaneous preterm labour

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Introduction

Preterm birth remains one of the greatest causes of perinatal mortality and morbidity worldwide.1,2 The association between maternal anaemia and preterm birth remains equivocal with some,3–8 but not other,9–12 studies documenting increased risk. The findings from Chinese studies4,8,9,13 on the relationship between anaemia and preterm birth are also inconsistent. Studies have suggested that the association between anaemia and preterm birth may vary based on the timing of anaemia during gestation.12 Despite the considerable aetiological heterogeneity in preterm birth clinical subtypes, namely, preterm premature rupture of membranes (PROM), spontaneous preterm labour and medically induted preterm birth, very few studies have attempted to evaluate if associations between anaemia and preterm birth are largely driven by associations with one particular subtype.14 If maternal anaemia is indeed associated with one preterm birth subtype, and not others, the association with preterm birth as an entity may be attenuated.15 Furthermore, an examination of associations within particular preterm birth subtypes may reveal interesting clues to aetiology and biologic mechanisms.

Preterm birth may occur through multiple pathways, with maternal infection, hypoxia and oxidative stress being the three major postulated biological mechanisms.16 Iron deficiency may increase the risk of maternal infections, and low haemoglobin may cause a state of low-grade chronic hypoxia that induces maternal and fetal stress. An activated immune system in the presence of infections and inflammation17 and corticotrophin-releasing hormone or cortisol that are released following a stress responses, can activate the maternal or fetal hypothalamic–pituitary–adrenal axis.18 This, in turn, can initiate labour and eventually result in preterm parturition.16 Finally, iron deficiency may also increase oxidative stress resulting in damage to erythrocytes and the feto-placental unit.19,20

We hypothesized that maternal anaemia may be associated with increased risk of preterm birth, and that an examination of associations within preterm birth clinical subtypes may reveal interesting clues to biologic mechanisms.

Methods

Data source

We designed a secondary analysis of data from a prospective, population-based cohort. Data were obtained from a population-based pregnancy-monitoring system established through a community intervention trial to prevent neural-tube defects in 21 counties of three provinces in China. Every woman who resided in the project area and became pregnant was registered at her marital registration or first prenatal visit. Women who were pregnant and delivered between October 1993 and December 1996 were identified. At the time of registration, a campaign programme of peri-conception folic acid supplementation of 400 µg daily during pre- and early pregnancy was offered to non-pregnant women or those in their first trimester. The project was approved by the institutional review boards of both the Centers for Disease Control and Prevention, and the Chinese Ministry of Health.21,22

The data were documented on a Perinatal Health Care Booklet that was issued to every woman at registration with a unique identification number. The information in the booklet contained parental demographics and family history, maternal medical history and obstetric conditions during the pregnancy, perinatal health outcomes and perinatal health care utilization. Haemoglobin levels were determined at the pre-marital physical exam when applicable, and repeated at each trimester by health care professionals, using the usual clinical methods. For women that had more than one haemoglobin assessment in the second and third trimesters, only the lowest value was recorded. All data recorded in the individual booklets were computerized by trained staff in each county using a standardized data entry application with built-in data checking filters.

Study cohort

This study was restricted to data from 13 counties of Zhejiang and Jiangsu provinces, a relatively wealthy region, in East China. Of the 170 885 women that delivered a singleton live birth between 20 and 44 (completed) weeks of gestation, 163 313 women had at least one haemoglobin value measured during pregnancy. We excluded 2186 births with missing record of birthweight and 427 births with implausible birthweight-gestational age combinations.23 After these exclusions, 160 700 singleton live births remained for analysis.

The population in these 13 counties is relatively homogeneous with respect to ethnicity, smoking, alcohol and geographic altitude. During the time of the project, women were not recommended to routinely take prenatal iron supplements; instead, iron supplements were prescribed only when anaemia was diagnosed.4,5 However, data on iron supplement use were not ascertained.

Maternal anaemia, haemoglobin change and preterm birth

Anaemia in each trimester was defined as haemoglobin <10 g/dl, which was pre-specified in the original protocol and has also been a commonly used cut-off in China.9 We classified women with anaemia as follows: first trimester only, second trimester only, third trimester only, first and second trimesters, first and third trimesters, second and third trimesters, and all three trimesters.
Haemoglobin changes were calculated as the differences of the first and second trimesters; the second and third trimesters; and the first and third trimesters. We reclassified the difference as haemo-dilution when change was 1 g/dl or haemo-concentration when change was = -1 g/dl.

Gestational age, in completed weeks, was estimated based on the last menstrual period. Preterm birth was defined as live births delivered before 37 completed weeks. We further categorized preterm birth as very preterm (<32 weeks), moderately preterm (32–33 weeks) and mild preterm (34–36 weeks). We also examined preterm birth based on three clinical subtypes. These include preterm premature rupture of chorioamnionic membranes (spontaneous rupture of membranes prior to the onset of labour and delivery before 37 weeks), medically indicated preterm birth (preterm birth following labour induction and/or cesarean performed before onset of labour for impending in utero fetal compromise) and spontaneous preterm labour (the remainder of all preterm births).

Statistical analysis
Rates of all preterm birth, as well as of each clinical subtype were estimated among singleton live births. The distribution of gestational age at delivery was contrasted for women with and without anaemia during pregnancy. The proportions of clinical subtypes among preterm births were estimated based on anaemia status and preterm severity. For women who had haemoglobin assessments in all three trimesters, we calculated the preterm birth rates for the seven maternal anaemia status groups as described earlier, both by preterm birth severity and by its clinical subtype.

Associations of haemoglobin in each trimester, as a continuous variable, with preterm birth and its clinical subtypes were assessed based on adjusted hazard ratios derived from multivariable Cox proportional hazards regression models. Each preterm birth clinical subtype was compared with term births. Women who delivered before 28 completed weeks (regardless of outcome) were excluded from the analyses for anaemia exposure in the third trimester. We modelled haemoglobin concentrations following transformations based on restricted cubic spline functions with four knots. This approach avoids the undesirable property of assigning arbitrary categorizations. The optimal number of knots was determined based on the model that resulted in smallest Akaike’s Information Criterion. The four knot locations for haemoglobin level (g/dl) were 9.3, 10.8, 11.7 and 13.4 in the first trimester; 8.8, 10.4, 11.2 and 13.0 in the second trimester; and 8.5, 10.0, 11.0 and 12.7 in the third trimester.

To evaluate the effects of anaemia across trimesters on preterm birth, all live births delivered at ≥37 weeks of gestation were censored in the Cox proportional hazards models. The proportional hazards assumption was tested by examining the interaction terms of haemoglobin measures and week of gestation; no violation of this assumption was detected.

Potential confounding factors were included in the models as covariates. These included maternal age, education (completion of elementary school or less, junior high school and high school or above), occupation (farmer, factory worker and other occupations), parity (nulliparity and multiparity), prepregnancy body mass index (BMI) kg/m², and categorized as < 18.5, 18.5–24 and ≥ 25 and infant sex. We also adjusted for prenatal care utilization, using timing of registration for the project (either before or during pregnancy) and timing of first prenatal visit (first or second trimester). Finally, we adjusted for folic acid use (400 µg daily) either before pregnancy or during the first trimester. As with haemoglobin, a restricted cubic spline function of maternal age with four knots at age 21, 23, 25 and 31 years was applied after we detected the violation of linearity assumption. Interactions between folic acid supplementation and maternal haemoglobin level in each trimester were tested; no interactions at P < 0.15 were detected. To eliminate the potential confounding caused by spacing of birth and previous abortions, we also conducted a subgroup analysis including women who were pregnant for the first time only.

The effects of haemo-dilution (haemoglobin change = 1 g/dl) and haemo-concentration (>1 g/dl) were assessed by the multiple Cox proportional hazards models that included the corresponding indicator variables for haemoglobin changes, the first trimester haemoglobin value as the baseline measure, and confounding factors. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

Results
The overall preterm birth (<37 weeks) rate of singleton live-born infants in this cohort was 4.7%, with 4.1% for anaemic and 5% for non-anaemic pregnancy women (P < 0.05). The most prevalent preterm birth clinical subtype was spontaneous preterm labour (3.6%), accounting for 77% of all preterm births. Table 1 shows the rates of preterm birth by maternal characteristics and fetal gender. Nearly one-third of women (32.7%) had anaemia (haemoglobin <10 g/dl) sometime during their pregnancy, with the prevalence of anaemia being 11, 20 and 26% in the first, second and third trimesters, respectively. The distribution of gestational age at delivery for women with and without anaemia was similar (data not shown). Distribution of preterm birth rates in relation to maternal anaemia status is shown in Tables 2–4. There were relatively more preterm PROM cases among moderate preterm births (32–33 weeks) of anaemic women (P < 0.05), as shown in Figure 1.

Associations between haemoglobin levels in each trimester and risk of preterm birth, and preterm PROM
and spontaneous preterm labour are shown in Figures 2 and 3, respectively. Haemoglobin values 9–10 g/dl in the first trimester was associated with slightly increased risk for all preterm births. Haemoglobin <11 g/dl in the first trimester was particularly associated with increased risk for preterm PROM. Women with lowest haemoglobin levels were at highest risk for preterm PROM [adjusted hazards ratio (HR) 3.3, 95% CI 1.4–7.7 for haemoglobin ≤5 g/dl] with progressively declining risk with increasing haemoglobin levels up to 10 g/dl. In contrast, haemoglobin ≤10 g/dl in the third trimester was associated with reduced risk for all preterm births and spontaneous preterm labour. Medically indicated preterm was not associated with maternal haemoglobin (data not shown). We also observed a stronger association between first trimester anaemia and very to moderate preterm birth (<34 weeks) (data not shown). In the subgroup analysis of women who were pregnant for the first time, the patterns of association were similar.

Haemoglobin increases of ≥1 g/dl from previous trimester, as the proxy of haemo-dilution, were associated with reduced risks for all preterm birth (Figure 4).

Discussion
The various studies on maternal anaemia and adverse reproductive outcomes have produced inconsistent findings. This is largely mitigated by the fact that maternal anaemia has been analysed as an aggregated exposure such as ‘any anaemia during pregnancy’. It is likely that anaemia diagnosed early in pregnancy may exert stronger associations on pregnancy outcomes than anaemia diagnosed later in gestation. Equally, studies on preterm birth have paid little attention to its heterogeneous underpinnings, thereby combining aetiologically distinct endpoints as being homogeneous, and perhaps leading to attenuated association measures. Finally, little attention has been devoted to how anaemia affects the risk for preterm birth clinical subtypes, including previous Chinese studies. Most studies have exclusively focused on spontaneous preterm births. Our study was designed to overcome many of these limitations. In addition, we explored the potential effects of physiological haemo-dilution on preterm birth.

We found anaemia in the first trimester was associated with modestly increased risks for all preterm birth. These associations were considerably stronger for preterm PROM. However, third trimester anaemia was associated with reduced risk for all preterm birth, and this association was largely confined to spontaneous preterm labour. Medically indicated preterm birth, on the other hand, was not associated with anaemia. These results underscore the strong heterogeneity in the risk profile for preterm birth based on
Table 2 Maternal anaemia and all preterm birth (<37 weeks) rates

<table>
<thead>
<tr>
<th>Maternal anaemia status</th>
<th>Total live-born infants</th>
<th>With attribute (%) (95% CI)</th>
<th>Preterm birth rate (%) (95% CI)</th>
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<tr>
<td>All women</td>
<td>160700</td>
<td></td>
<td>4.7 (4.6–4.8)</td>
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<td><strong>Maternal anaemia status</strong></td>
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<td></td>
</tr>
<tr>
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<td>65.1 (64.8–65.4)</td>
<td>4.4 (4.2–4.6)</td>
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<tr>
<td>First trimester only</td>
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<td>2.0 (1.9–2.1)</td>
<td>4.6 (3.7–5.5)</td>
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<tr>
<td>Second trimester only</td>
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<td>5.3 (5.2–5.5)</td>
<td>3.5 (3.0–4.0)</td>
</tr>
<tr>
<td>Third trimester only</td>
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<td>11.9 (11.7–12.1)</td>
<td>2.9 (2.6–3.3)</td>
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<tr>
<td>First and second trimesters</td>
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<td>2.4 (2.3–2.5)</td>
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<td>First and third trimesters</td>
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<td>0.95 (0.89–1.01)</td>
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<tr>
<td>Second and third trimesters</td>
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<td>6.7 (6.5–6.8)</td>
<td>3.5 (3.0–3.9)</td>
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<tr>
<td>All three trimesters</td>
<td>5528</td>
<td>5.7 (5.5–5.7)</td>
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Table 3 Maternal anaemia and preterm birth rates by severity

<table>
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<tr>
<th>Maternal anaemia status</th>
<th>Total live-born infants</th>
<th>Preterm birth rates (%) and 95% CI</th>
</tr>
</thead>
<tbody>
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<td></td>
</tr>
<tr>
<td><strong>Maternal anaemia status</strong></td>
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<td></td>
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<td>0.19 (0.15–0.22)</td>
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<tr>
<td>First trimester only</td>
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<td>0.10 (0.00–0.25)</td>
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<td>Second trimester only</td>
<td>5204</td>
<td>0.04 (0.00–0.09)</td>
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<tr>
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<tr>
<td>First and second trimesters</td>
<td>2318</td>
<td>0.09 (0.00–0.21)</td>
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<tr>
<td>First and third trimesters</td>
<td>927</td>
<td>– 0.43 (0.01–0.85)</td>
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<tr>
<td>Second and third trimesters</td>
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<td>0.09 (0.02–0.17)</td>
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<tr>
<td>All three trimesters</td>
<td>5528</td>
<td>0.29 (0.15–0.43)</td>
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</table>

Table 4 Maternal anaemia and preterm birth rates by clinical subtypes

<table>
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<tr>
<th>Maternal anaemia status</th>
<th>Total live-born infants</th>
<th>Preterm birth rates (%) and 95% CI</th>
</tr>
</thead>
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<td>All women</td>
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<td></td>
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<td><strong>Maternal anaemia status</strong></td>
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<td>First trimester only</td>
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<td>Third trimester only</td>
<td>11627</td>
<td>0.40 (0.29–0.52)</td>
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<td>First and second trimesters</td>
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<td>First and third trimesters</td>
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<td>0.22 (0.00–0.51)</td>
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<tr>
<td>Second and third trimesters</td>
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<td>0.51 (0.33–0.68)</td>
</tr>
<tr>
<td>All three trimesters</td>
<td>5528</td>
<td>0.67 (0.45–0.88)</td>
</tr>
</tbody>
</table>
underlying clinical subtypes, as well as by exposure window, i.e. trimester in pregnancy when anaemia was diagnosed.

Our findings on all preterm birth were consistent with a meta-analysis which concluded that early pregnancy anaemia was associated with slightly increased risk for preterm birth and late pregnancy anaemia was inversely associated with preterm birth. All four previous Chinese studies conducted in the same or nearby regions as the present study, examined the association between anaemia and preterm birth without consideration of associations by preterm birth clinical subtypes. Whereas some reported anaemia in the first trimester to be associated with increased risk of preterm birth, others did not. The last study reported that only the third trimester haemoglobin <7 g/dl (severe anaemia) was associated with a marginally increased risk for preterm birth. Previously, five studies reported associations between maternal anaemia and preterm birth clinical subtypes. All these studies either dichotomized pregnant women as being anaemic or non-anaemic using one cut-off point, or have categorized them into multiple groups using several cut-off points. Categorization of skewed exposures such as anaemia, assumes within-category homogeneity, degrades continuous exposure data and tends to be less accurate than spline analysis. We analysed haemoglobin concentrations as a continuous variable based on flexible spine transformation to account for non-linear effects.

Disaggregating preterm birth into more homogeneous subtypes revealed considerable heterogeneity in their associations with anaemia. Anaemia present in all three trimesters was associated with increased risk for spontaneous preterm labour, whereas anaemia in mid- and late pregnancy was associated with reduced risk. There were trends of increased risks for preterm PROM in relation to anaemia exposure in early half or throughout pregnancy. Anaemia in early pregnancy or throughout pregnancy may represent pre-existing, or early onset and persistent iron deficiency. Iron deficiency anaemia, in turn, could induce maternal infection, hypoxia and oxidative stress, and trigger the spontaneous onset of preterm labour.

Previous studies mentioned the concern that normal physiological haemo-dilution during pregnancy, which usually reaches the nadir at the end of the second trimester and early the third trimester, might mask the true association between anaemia and preterm birth. However, the association between
haemo-dilution in the second and third trimesters and preterm birth had not yet been assessed. In our study, we used the haemoglobin reduction across trimesters as the proxy of haemo-dilution, controlling for the first trimester haemoglobin level as the baseline. We found haemo-dilution was associated with reduced risk for preterm birth. This may partially explain the inverse association between the third trimester anaemia and preterm birth.

The overall preterm birth rate in this Chinese cohort was fairly low (4.7%) with spontaneous preterm labour (77%) being the most common clinical subtype. This rate is consistent with earlier findings for other cohorts in this region. Rates of obstetric interventions at preterm and term gestations were 11.6 and 16.7%, respectively, in our cohort. These rates are lower than reported in other populations and suggest that the threshold for intervention in the presence of impending in utero fetal compromise is far higher than in most industrialized societies. It is therefore likely that differences in practice and threshold for intervention may have played an important, but yet uncharacterized, role in our findings. In addition, gestational age was estimated based on last menstrual period, and errors associated with menstrual dating may have affected our findings to some extent.

The observed association between preterm birth and anaemia in the first trimester possibly related to iron deficiency, which was less likely affected by iron supplementation as iron supplement was given after the diagnosis of anaemia. However, anaemic women in late pregnancy were more likely to take iron supplement as a treatment and receive more medical attention. Besides the effects of the normal physiological haemo-dilution, the observed inverse association between late pregnancy anaemia and spontaneous preterm labour might reflect an artefact partially due to the benefits of medical interventions. Whether early prevention and prompt treatment of maternal anaemia can reduce the risks for spontaneous preterm labour and preterm PROM warrants further investigation.

Biases, limitations and strengths of the data

Haemoglobin was assessed in local laboratories using the usual clinical methods without standardized protocols. Haemoglobin values in the second and third trimesters pertained to the lowest of the assessments, which may blend real anaemia with the physiological haemo-dilution that reaches the nadir near the end of the second and early of the third trimesters in normal pregnancy. Therefore, the observed association between anaemia and preterm birth may have been attenuated. Maternal socio-economic status, dietary factors, smoking and gestational age of each haemoglobin measurement could be related to anaemia and preterm birth. Unfortunately, these data were not collected. Data on individual iron supplementation was unavailable. However, it is likely that iron was prescribed to anaemic women as a treatment, and this may have resulted in an attenuation of the associations noted here. Finally, our estimation of gestational age was largely based on menstrual dates that are prone to some degree of inaccuracy.

The abilities to separate preterm births by its clinical subtypes and to examine associations within more homogeneous groups in relation to maternal anaemia.
Figure 3 Adjusted HR of preterm PROM (left panel) and spontaneous preterm labour (right panel) with 95% CI for haemoglobin level in each trimester (the arrows on the x-axis denote the location of knots derived from restricted cubic splines). HRs were adjusted for maternal age, education, occupation, parity, pre-pregnancy BMI, infant sex, prenatal care and folic acid use.

Figure 4 Haemoglobin change and preterm birth (<37 weeks)
are strengths of our study. Haemoglobin values of women in our large, population-based cohort were prospectively ascertained before pregnancy outcomes were determined, which eliminates the possibility of differential misclassification of anaemia. Our study population was relatively homogeneous, and less likely to be affected by selection and confounding biases.

Conclusions
Maternal anaemia in early pregnancy is associated with increased risk of preterm PROM and anaemia in late pregnancy is associated with reduced risk of spontaneous preterm labour. Adequate physiological haemo-dilution during mid- to late pregnancy may be associated with reduced risk for preterm birth. Early prevention and prompt treatment of maternal anaemia may be one avenue for intervention, and may be a topic worthy for further investigation. To unravel other possible explanations to our findings, and to further investigate the causal link between anaemia and preterm birth, a randomized clinical trial could overcome some of the methodological limitations in the current studies.

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Conflict of interest: None declared.

KEY MESSAGES
- Whether maternal anaemia is associated with risk of preterm birth and their clinical subtypes remains unclear.
- In this prospective cohort study from China, we found anaemia in early pregnancy to be associated with increased risk for preterm PROM, whereas anaemia in late pregnancy was associated with reduced risk for spontaneous preterm labour.
- Adequate physiological haemo-dilution during mid- to late pregnancy may be associated with reduced risk for preterm birth.

References


