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Review Article

Maternal anaemia and risk of adverse obstetric and neonatal outcomes in South Asian countries: A systematic review and meta-analysis

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ABSTRACT

Background: The occurrence of maternal anaemia is common in South Asian countries which increase the risk of adverse maternal obstetric and birth outcomes. This may adversely affect the achievement of the Sustainable Development Goals' (SDG) targets of reducing maternal and under-five deaths by 2030.
Objectives: To summarize the evidence on the association of maternal anaemia with adverse birth and maternal obstetric outcomes.
Methods: We adopted the PRISMA consensus statement. PubMed, CINAHL and Web of Science databases were searched on February 20, 2020. A total of 38 studies was included, of which 25 articles were included in the quantitative synthesis and meta-analysis.
Results: Maternal anaemia was associated with a significantly higher risk of low birth weight (OR, 1.90; 95% CI, 1.06-2.60, $p < 0.05$), preterm birth (OR, 1.96; 95% CI, 1.20-2.41, $p < 0.05$) and perinatal mortality (OR, 2.90; 1.97-3.78, $p < 0.05$). Non-significant associations were seen with neonatal mortality (OR, 1.80; 95% CI, 0.90-27.77, $p = 0.7$), miscarriage (OR, 1.68; 95% CI, 0.48-3.20, $p = 0.08$), preeclampsia (OR, 2.66; 95% CI, 0.61-11.52, $p = 0.6$) and caesarean delivery (OR, 1.18; 95% CI, 0.36-2.80, $p = 0.07$).
Conclusion: Maternal anaemia increases the risk of low birth weight, preterm birth and perinatal mortality. Improving maternal nutritional status and iron supplementation during pregnancy are important for reducing these adverse outcomes.

1. Introduction

The Sustainable Development Goals (SDG) have set ambitious targets to reduce maternal and under-five deaths between 2015 and 2030 [1]. The majority of these deaths occurred in low- and middle-income countries (LMICs). These are associated with higher rates of pregnancy-related complications (responsible for around 303,000 maternal and 2.7 million newborn deaths) during and following the delivery [2]. The occurrence of low birth weight (LBW), stillbirth, preterm birth (PTB) are also common in LMICs; all are factors that further increase under-five mortality [3]. Moreover, all of these adverse consequences increase hospital admissions, therefore create an additional burden on existing healthcare facilities in LMICs which are usually over-crowded with limited resources. Importantly, planned pregnancy and recommended use of maternal healthcare services during and following pregnancy could be keys to reduce these adverse outcomes. However, these are still challenges for LMICs despite having been set as a priority in both the Millennium Development Goals (MDGs, 2000-2015) and SDGs [1].

Anaemia is common worldwide and affects 33% of the global population despite the high priority given to tackle this in the maternal and child health programs [4,5]. This percentage is higher among pregnant women. Around 32 million women become pregnant with anaemia or become anaemic following pregnancy. This represents around 38% of annual pregnancies globally [6]. Importantly, this varies significantly across regions. Whilst the Central and Western Europe (24%) region have a low prevalence, Central and West Africa (56%), South Asia (52%), Oceania and East Africa (36%) regions have much higher prevalence of maternal anaemia [6]. Generally, these are the regions where the occurrence of anaemia during pregnancy and reported adverse maternal obstetric and birth outcomes (including maternal and under-five deaths) are both higher. Therefore, investigation of the associations between maternal anaemia and adverse maternal obstetric and birth outcomes is of public health importance.

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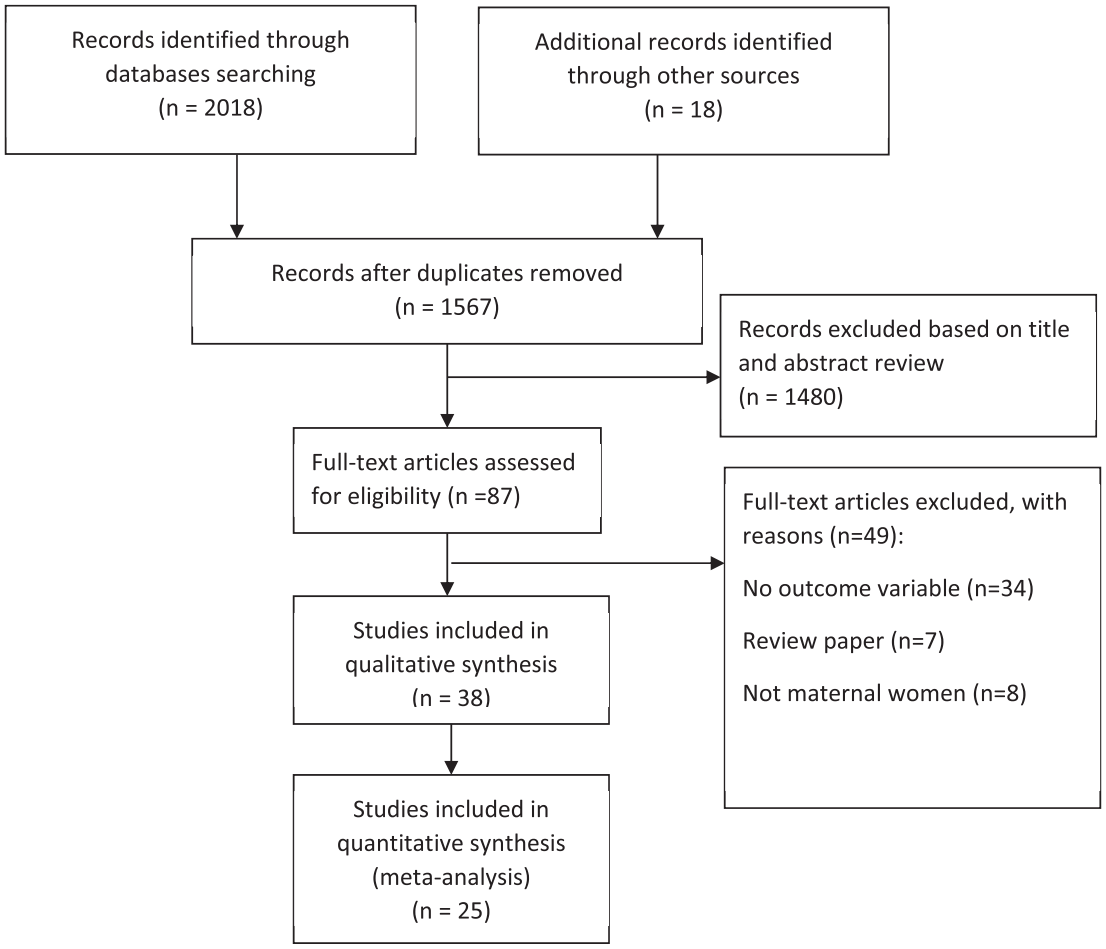

Fig. 1. PRISMA flowchart for selection of studies.

Several primary research studies have been conducted to identify the potential effects of maternal anaemia on adverse maternal obstetric and birth outcomes. However, findings across the studies are not consistent which makes it challenging to form evidence-based policies to reduce these adverse consequences. For instance, maternal anaemia is reported as a risk factor of pre-term birth (PTB) in a few studies [7,8] but other studies reported no significant associations [9,10]. In addition, studies also showed that anaemia during the first trimester of pregnancy is associated with increased risk of PTB [11,12] though contradictory findings are reported in other studies [13,14]. Similar contradictions are also reported for other adverse outcomes, including low birth weight (LBW), stillbirths, small for gestational age (SGA), and perinatal mortality [9,13,15]. These findings may vary depending upon when anaemia is measured in pregnancy (first, second, or third trimester of pregnancy), method and population types investigated, and confounders adjusted for in the models. Therefore, summarizing the actual effects may help policymakers make more effective and targeted policies.

However, there is a lack of research conducted to address these contradictions in LMICs. A broad exploratory search of the literature for this study found only one study that had been conducted in LMICs [16] which examined the effects of maternal anaemia on LBW, PTB, perinatal mortality and neonatal mortality. The major drawback of the study was only inclusion of cohort studies, which are usually rare in resource-poor countries; therefore, it might not be representative of the whole population. Moreover, the authors found higher risks of adverse birth outcomes among anaemic than non-anemic mothers in South Asian countries in their geographic region stratified analysis. However, separate estimates for different adverse birth outcomes are still necessary to solve the existing disagreements in South Asian countries.

We therefore conducted this study to try to ascertain conclusively the true effects of maternal anaemia on adverse maternal obstetric and birth outcomes.

2. Methods

We performed a systematic review and meta-analysis following the PRISMA consensus statement (see Supplement Table S1). Studies conducted in South Asian countries to examine the effects of maternal anaemia on adverse birth and obstetric outcomes were included.

2.1. Search strategy

Systematic computerized literature searches were conducted on February 20, 2020, in three databases: PubMed, CINAHL, and Web of Science. Searches were conducted based on individual comprehensive search strategies separately for each database. We developed search strategies consisting of a combination of free text words, words in titles/abstracts, and medical subject headings for participants, exposure, and settings that were combined using the Boolean operators (AND, OR). The detailed search strategies and search results for PubMed, CINAHL, and Web of Science databases are presented in Tables S2–S4 (in Supplementary file). Further searches for eligible studies were conducted in the reference list of articles and relevant journal websites. We set no time, language, and outcome restrictions to select the studies. The World Health Organization (WHO) guideline of haemoglobin concentration during pregnancy ($<$11 g/dl (anemic) and $\geq$11 g/dl (non-anemic)) was used to diagnose anaemia status [17].

2.2. Inclusion criteria

In this review, comparative studies of the effects of maternal anaemia on adverse birth and obstetric outcomes were included. Moreover, selected studies met the following inclusion criteria: i) maternal anaemia was defined as the exposure variable, ii) gestational age at the time of anaemia measurement was provided, iii) a comparison group of the mother without anaemia with comparable gestational age was also presented, and iv) present at least one of the outcome variables (adverse maternal obstetric and birth outcomes). Additional inclusion criteria were the availability of odds ratios (ORs) and its 95% confidence intervals (CIs) or the raw data that allows us to calculate the ORs and its 95% CIs. The outcome variables were LBW (if birth weight is < 2500 gm), PTB (if the birth occurred <37 weeks), perinatal mortality (include stillbirth and early neonatal mortality), neonatal mortality (defined as deaths within first months of the birth), miscarriages (defined as loss of a pregnancy during the first 23 weeks of pregnancy), small for gestational age (SGA, defined as birth weight below the tenth percentile of the gestational age and sex), preeclampsia (defined as disorder of pregnancy characterized by high blood pressure and a large amount of protein in the urine) and caesarean delivery (defined as the delivery through the surgical procedure).

2.3. Exclusion criteria

We did not search for unpublished papers. We excluded duplicate publications and studies published as abstract only. We excluded studies if they used women's post-pregnancy anaemia. For multiple publications from the same study, if they referred to anaemia at the same gestational age and same predictors' variables, only one publication with high quality was included.

2.4. Data collection process and data items

A data extraction form was designed, trialled, and modified prior to tabulating final data. Two reviewers (Khan MN, and Rahman MA) independently extracted the following data from the selected full-text articles: country of origin, year of study, study design, participant, exposure and their time of assessment, outcome(s), confounders, and measure of association. Inconsistencies were checked and resolved by the third reviewer available as an adjudicator (Rahman MM).

2.5. Quality assessment

We used the Newcastle–Ottawa Scale to assess the methodological quality of all included studies [18]. The scale gives separate measures to assess the methodological quality of cross-sectional, case-control, and cohort studies.

2.6. Data analysis

The odds ratios (ORs) as effect measures were extracted from each selected study. If the OR was unavailable, unadjusted OR with its 95% CI was calculated from raw data extracted from the selected studies. We used fixed-effects or random-effects models to calculate the summary effect of maternal anaemia on specific birth or obstetric outcome. The model was selected based on heterogeneity assessment; I^2 statistics with its p-value was estimated for each meta-analysis to describe the extent of heterogeneity. The random-effects model was used when heterogeneity was moderate (50%) or high (75%), whereas the fixed-effects model was used when heterogeneity was low (<50%) [19].

We explored the sources of heterogeneity through the sub-group and meta-regression analyses across pre-specified subgroups [20]. These were study country, study design, confounding factors, sample size, and maternal age. We also assessed the publication bias through visual inspection of the funnel plot and Egger's regression asymmetry test [21]. Trim-and-Fill procedure was used when evidence of publication bias was found [22]. The Stata software version 15.1 (Stata Corp, College Station, Texas, USA) was used to perform all analyses.

3. Results

3.1. Study selection

Fig. 1 shows the results of the literature search and study selection process. A total of 2,018 potentially eligible articles was identified, of which 1,250 articles were identified from PubMed, 570 articles were identified from Web of Science, and 198 articles were identified from CINAHL. An additional 18 articles were identified through reviewing the reference lists of the selected articles and the relevant journal websites. After removing duplicates, a total of 1,567 potential articles were included to review. Of these, 1,480 articles were removed through screening the titles and abstracts, and the remaining 87 articles were selected for full-text review. A total of 38 articles was finally selected through a detailed review of the articles' full-text; 23 of them were cohort studies, 7 of them were cross-sectional studies, and 8 of them were case-control studies. Of these, 19 (50%) studies were conducted in India, 8 (21.1%) studies were conducted in Pakistan, 6 (15.8%) studies were conducted in Bangladesh, 3 (7.8%) studies were conducted in Nepal, 1 (2.6%) study was conducted in Sri Lanka, and 1 study analysed data from both India and Pakistan (2.6%). We did not find any related study conducted in Afghanistan, Bhutan, or the Maldives.

3.2. Study characteristics

The basic characteristics of the 38 studies included in this systematic review are presented in Table 1. The sample size of the included studies ranged from 76 to 92,247. The sum of the sample size for all included studies was 209,796. All included studies were conducted between 1992 and 2019. Of the 38 included studies, 29 studies reported LBW, 12 studies reported PTB, 9 studies reported perinatal mortality, and 3 studies reported caesarean delivery. Moreover, 4 studies reported miscarriage, SGA, neonatal mortality, and preeclampsia. All included studies in this review were of high quality (in Supplement Tables S5–S7).

3.3. Summary estimate

The pooled odds ratios (ORs) of the 25 studies included are presented in Table 2. Heterogeneity index, publication bias, and Trim-and-Fill estimate for all outcomes were also calculated and presented. Maternal anaemia was found to be associated with the increased likelihood of LBW (OR, 1.90, 95% CI, 1.06-2.60, $p < 0.05$) and the result was consistent in the Trim-and-Fill estimate (OR, 1.80; 95% CI, 1.01-1.98 $p < 0.01$) which accounted for five missing studies. Significantly increased odds of PTB (OR, 1.96, 95% CI, 1.20-2.41 $p < 0.05$) and perinatal mortality (OR, 2.90, 95% CI, 1.97-3.78 $p < 0.05$) among anaemic mothers than their non-anaemic counterparts were also found in our study. These results remained same in the Trim-and-fill estimate once missing studies were adjusted. We found higher odds of caesarean delivery. (OR, 1.18; 95% CI, 0.36-2.80, $p = 0.07$) among anaemic mothers than non-anaemic mothers, however, the association was not significant. Higher odds of other adverse birth and obstetric outcomes including neonatal mortality (OR, 1.80; 95% CI, 0.05-27.77, $p = 0.7$), miscarriage (OR, 1.68; 95% CI, 0.48-3.20, $p = 0.08$) and preeclampsia (OR, 2.66; 95% CI, 0.61-11.52, $p = 0.6$) were also found among anaemic mothers than their non-anaemic counterparts.

Table 3 presents the summary results of the narrative review of 13 additional papers. Our narrative results indicate that the anaemic mothers (Hgb<9 g/dl) were at higher risk of LBW, and the risk was relatively higher among severely anaemic mothers than moderately anaemic mothers. One study also reported around 26.5% higher risk of perinatal deaths among mildly anaemic than non-anaemic mothers.

Table 1
Background information of the included study.

Study (location)	Sample	Study design	Mean age (years)	Measurement of anaemia	Outcomes	Confounding adjustment
Abeysena et al., 2010 [10] [b] (Sri Lanka)	817	Prospective cohort	26.4	First trimester	PTB, LBW, Miscarriage	Adjusted
Bakhtiar et al., 2007 [40] [b] (Pakistan)	860	Prospective cohort	25.0	First, second trimester	PTB, LBW, Perinatal mortality	Unadjusted
Bhalerao et al., 2011 [47] [b] (India)	1200	Prospective cohort	24.9	First, second trimester	PTB, LBW, Perinatal mortality	Unadjusted
Bondevik et al., 2001 [48] [b] (Nepal)	1400	Prospective cohort	23.4	First trimester	LBW, PTB	Unadjusted
Baig et al., 2013 [49] [b] (Pakistan)	600	Case-control	NA	Third trimester	PTB	Unadjusted
Bora et al., 2014 [50] [b] (India)	470	Prospective cohort	24	Third trimester	Caesarean delivery	Unadjusted
Begum et al., 2002 [51] [a] (Bangladesh)	357	Cross-sectional	29.1	Third trimester	Diabetes Mellitus	Unadjusted
Dhar et al., 2003 [52] [b] (Bangladesh)	316	Cross-sectional	23.9	Third trimester	LBW	Maternal age, family income, gestational age, mothers education
Deshmukh et al., 1998 [53] [b] (India)	210	Prospective cohort	22.6	Third trimester	LBW	Unadjusted
Ferdous et al., 2012 [54] [a] (Bangladesh)	4817	Prospective cohort	NA	Third trimester	Perinatal death	Age, parity, maternal education, socio-economic status, place of delivery
Hasin et al., 1996 [55] [b] (Bangladesh)	151	Cross-sectional	25	Third trimester	LBW	Unadjusted
Hossian et al., 2006 [56] [b] (Bangladesh)	350	Prospective cohort	26.5	First trimester	LBW	Unadjusted
Hirve et al., 1994 [57] [b] (India)	1922	Prospective cohort	20.3	First trimester	LBW	Unadjusted
Iltaf et al., 2017 [58] [a] (Pakistan)	1603	Prospective cohort	NA	Third trimester	LBW	Unadjusted
Jehan et al., 2007 [59] [b] (Pakistan)	1369	Prospective cohort	28.8	Second trimester	Stillbirth	Unadjusted
Javed et al., 2018 [60] [a] (Pakistan)	397	Cross-sectional	25.4	Third trimester	LBW	Unadjusted
Kumar et al., 2010 [61] [b] (India)	2027	Prospective cohort	24.6	First trimester	LBW	Adjusted
Kader and Perera, 2014 [62] [b] (India)	20946	Cross-sectional	25.9	Post Pregnancy	LBW	Sex of child, wealth status, antenatal visit, living place
Marahatta, 2007 [63] [b] (Nepal)	863	Prospective cohort	NA	First trimester	LBW, PTB	Unadjusted
Lone et al., 2004 [64] [b] (Pakistan)	629	Prospective cohort	27.0	First, second trimester	PTB, LBW, Perinatal mortality	Adjusted
Malhotra et al., 2002 [65] [b] (India)	447	Prospective cohort	25.3	First trimester	PTB, LBW, still birth, neonatal mortality, Preeclampsia, Caesarean delivery	Unadjusted
Monirujjaman et al., 2014 [66] [a] (Bangladesh)	343	Cross-sectional	NA	Third trimester	LBW	Unadjusted
Mavalankar et al., 1992 [67] [a] (India)	1465	Case-control	NA	Third trimester	PTB	Maternal education, religion, socio economic factors
Nair et al., 2016 [68] [b] (India)	1007	Retrospective cohort	NA	Third trimester	LBW, SGA, prenatal mortality	Adjusted with caste, religion, residence, below poverty line status, women's employment status, tea garden worker, parity, body mass index, maternal age, previous caesarean

(*continued on next page*)

Table 1 (*continued*)

Study (location)	Sample	Study design	Mean age (years)	Measurement of anaemia	Outcomes	Confounding adjustment
						section, previous pregnancy problems, pre-existing medical problems, multiple pregnancies, number of antenatal visits, whether folic acid tablets were received, and mode of delivery
Parks et al., 2019 [69] [a] (India and Pakistan)	92,247	Retrospective cohort	NA	Third trimester	LBW, stillbirth, PTB, neonatal mortality	Adjusted with maternal age, education, and parity
Nair et al., 2018 [70] [a] India	200	Case-control study	NA	First, second, and third trimester	LBW	Unadjusted
Patel et al., 2018 [71] [b] (India)	68,338	Prospective cohort	NA	Third trimester	Caesarean delivery, stillbirths, neonatal deaths, LBW	Adjusted with maternal socio-demographic charecteristics
Rizvi et al., 2007 [72] [a] (Pakistan)	524	Case-control	25.5	Third trimester	LBW	Unadjusted
Shobeiri et al., 2006 [73] [b] (India)	500	Prospective cohort	24.0	First, second, third trimester	LBW	Unadjusted
Swain et al., 1994 [74] [b] (India)	484	Retrospective cohort	NA	Third trimester	LBW	Unadjusted
Singla et al., 1997 [75] [a] (India)	76	Cross-sectional	NA	First trimester	LBW	Unadjusted
Singal et al., 2018 [76] [a] (India)	400	Case-control	NA	Third trimester	PTB	Unadjusted
Sharma et al., 2015 [77] [b] (Nepal)	465	Retrospective case-control	NA	Third trimester	LBW	Adjusted with maternal socio-demographic and pregnancy-related charactersics
Yousaf et al., 2011 [78] [b] (Pakistan)	818	Prospective cohort	27.0	First, second, third trimester	PTB, LBW, Perinatal mortality	Unadjusted
Varsha et al., 2017 [79] [a] (India)	200	Case-control study	NA	Third trimester	LBW	Unadjuted
Ahankari et al., 2017 [80] [b] (India)	615	Retrospective cohort	22	Third trimester	PTB, LBW	Unadjusted
Ahankari et al., 2017 [81] [b] (India)	303	Prospective cohort	NA	Third trimester	LBW	Unadjusted
Daljeet et al., 2016 [82] [a] (India)	60	Case-control	NA	Third trimester	LBW	Unadjusted

LBW, low birth weight; PTB, preterm birth.
[a] Included in narrative review; and.
[b] Study included in meta-analysis.

Table 2
Summary, Publication bias, and Trim and Fill estimates.

Characteristics	No. of studies	Summary estimates		Bias test p-value	Trim and Fill estimates[a]	
		OR (95% CI)	Heterogeneity Index		Missing studies no.	OR (95% CI)
Low birth weight	21	1.90 (1.06–2.60)[b]	86.4	0.01	5	1.80 (1.01–1.98)
Preterm birth	10	1.96 (1.20–2.41)[b]	78.9	0.04	2	1.42 (1.03–2.90)
Perinatal mortality	7	2.90 (1.97–3.78)[c]	84.0	0.05	2	1.98 (1.04–3.05)
Neonatal mortality	2	1.80 (0.90–27.77)[c]	37.0	NA	0	1.80 (0.90–27.77)
Miscarriages	2	1.68 (0.48–3.20)[c]	47.0	NA	0	1.68 (0.48–3.20)
SGA	2	0.98 (0.20–1.60)[c]	43.0	NA	0	0.98 (0.20–1.60)
Preeclampsia	1	2.66 (0.61-11.52)[d]	NA	NA	0	2.66 (0.61-11.52)
Caesarean delivery	3	1.18 (0.36–2.80)[b]	73.3	–	1	1.10 (0.90-1.60)

CI, confidence interval; NA, not applicable; OR, odds ratio.
[a] The trim-and-fill method simulates studies that are likely to be missing from the literature due to publication or other forms of bias. The trim-and-fill OR estimates what the pooled OR would be if these missing studies were included in the analysis.
[b] Summary estimates were based on random-effects methods.
[c] Summary estimates were based on fixed-effects methods.
[d] No pooling method was used due to single study.

Table 3
Narrative review for anaemia and birth and health outcomes.

Study	Study design, Country	Population	Result
Ferdous et al., 2012 [54]	Prospective cohort, Bangladesh	4817 women who delivered during 2007-2008 in the icddr,b field site in Matlab.	About 26.49% perinatal deaths occur in mild anemic group.
Monirujjaman et al., 2014 [66]	Cross-sectional, Bangladesh	343 women aged 18-38 years were enrolled in this study from the district of Khulna division.	Incidence of LBW was comparatively higher (35.5%) in anemic women (hb < 9 g/dl) than normal women.
Begum et al., 2002 [51]	Cross-sectional, Bangladesh	357 women were included from one hospital.	Anemic women had lower prevalence of diabetes (23.4%) than non-anemic women (54.2%). Anaemia was found protective for diabetes.
Mavalankar et al., 1992 [67]	Case-control, India	1317 LBW cases mothers and 1465 controls mothers were selected during 1987 to 1988.	The risk of delivering LBW in serve anemic women was 5.6 (95% CI, 2.1-15.3) and the moderate anemic woman was 1.8 (95% CI, 1.4-2.4).
Rizvi et al., 2007 [72]	Case-control, Pakistan	262 cases (LBW neonates) and 262 controls (normal weight) enrolled during July 2003 to September 2003.	Maternal haemoglobin level was independently associated with LBW. Odds of delivering an LBW baby decreased with increased in maternal haemoglobin (OR:0.70; 95% CI:0.63-0.79)
Singla et al., 1997 [75]	Cross-sectional India	66 pregnant women were selected randomly from a hospital.	Inverse association was found between birth weight maternal anaemia:
Daljeet et al., 2016 [82]	Case-control India	60 pregnant women included in this study; 30 of which were anemic	Maternal anaemia was found significantly correlated with the LBW
Iltaf et al., 2017 [58]	Prospective cohort India	1606 women included in this study of which 161 had given a child classified as LBW	Higher percentage of LBW was found among mothers had low haemoglobin level
Javed et al., 2018 [60]	Cross-sectional Pakistan	397 women included in this study of which 53 had given a child classified as LBW	Maternal anaemia was found significantly associated with the occurrence of LBW.
Parks et al., 2019 [69]	Retrospective cohort India and Pakistan	A total of 92,247 deliveries data was analysed	Maternal anaemia was found associated with LBW, stillbirth, preterm birth, neonatal mortality.
Singal eta l., 2018 [76]	Case-control study India	A total of 400 women given birth were included; 200 of them were anemic	Higher occurrence of preterm birth was found among anemic mother.
Varsha et al., 2017 [79]	Case-control study India	200 mother-baby were included in this study	The occurrence of LBW was found higher among the mothers were anaemic during delivery.
Nair et al., 2018 [70]	Case-control study India	200 pregnant mothers included and followed up delivery occurred	Mothers with anaemia at any time during pregnancy was found to have 4.3 times higher risk of giving birth to low birth weight babies compared to non-anemic mothers

LBW, low birth weight; OR, odds ratio; CI, Confidence interval; hb, haemoglobin.

3.4. Sub-group analysis

We found higher heterogeneity among the selected studies, which reported LBW, PTB, and perinatal mortality (Table 2). We, therefore, conducted the stratified analysis to assess the source of variations. We assess the source of variations across countries, study designs, confounding factors, studies sample size, and maternal age. The results are presented in Table 4. Stratification by countries revealed an increased risk of LBW (OR, 2.04, 95% CI, 1.98-2.45, $p < 0.05$), PTB (OR, 3.30, 95% CI, 2.28-4.79, $p < 0.05$) for Pakistani anaemic mothers compared to the other countries. Studies reporting unadjusted odds reported a higher risk of LBW (OR 1.79, 95% CI, 1.26-1.96, $p < 0.01$), whereas studies citing adjusted odds (OR 1.18, 95% CI, 0.89-1.30) reported a non-significant association. We did not find any evidence of significant variations for LBW, PTB, and perinatal mortality by study designs sample sizes, and maternal ages.

4. Discussion

In this systematic review and meta-analysis, we investigated the effects of maternal anaemia during pregnancy on adverse birth and maternal obstetric outcomes. This is the first comprehensive review of studies of South Asian countries that systematically evaluated the scientific literature to assess the proportion of adverse birth and maternal obstetric outcomes attributed to maternal anaemia during pregnancy. The meta-analysis demonstrated significantly higher risks of adverse birth and maternal obstetric outcomes including LBW, PTB, and perinatal mortality among anaemic mothers than their non-anemic counterparts. We also found higher risks of caesarean delivery, neonatal mortality, miscarriage, preeclampsia among the anaemic than non-anemic mothers, however, the results were not statistically significant.

We found that maternal anaemia during pregnancy increases the risk of occurrence of LBW-a common adverse birth outcome in South Asian countries and known risk factor of under-five mortality. This association between maternal anaemia during pregnancy and the occurrence of LBW is linked with the physiological fall of haemoglobin level during pregnancy that leads to normal plasma volume and red cell mass increase [23,24]. These changes contribute to the change in haemoglobin concentration. For instance, average haemoglobin concentration among the anaemic pregnant women at 36 weeks of gestation was found to be significantly lower (≈110 g/L) than non-anemic women (≈133 g/L) [25–27]. The decrease in maternal haemoglobin concentration may then affect fetal birth weight. This finding is consistent with the findings of other studies [28,29].

Every year an estimated 15 million babies are born preterm, 1 million of them die before reaching their fifth birthday, and many face lifetime disabilities, including learning disabilities, visual and hearing problems [30]. Importantly, more than 60% of these PTBs occur in African and South Asian countries. Moreover, India, Pakistan, and Bangladesh, countries of South Asia included in this review, are ranked among the 10 countries with a higher number of PTB worldwide [30]. This study found maternal anaemia during pregnancy is associated with an elevated risk of occurrence of PTB in South Asia, that is consistent with the previous observations [8,29,31,32] and meta-analysis [33]. The mechanism of higher occurrence of PTB among anaemic than non-anaemic women is comparable with the occurrence of LBW among the anaemic women.

Table 4
Stratified analysis of pooled relative risks of low birth weight, preterm birth, and perinatal mortality for anemic pregnant women.

Characteristics	Low birth weight			Preterm birth			Perinatal mortality		
	Number of study	Pooled OR (95% CI)	Meta regression (p-values)	Number of study	Pooled OR (95% CI)	Meta regression (p-values)	Number of study	Pooled OR (95% CI)	Meta regression (p-values)
Country									
Bangladesh	2	1.74 (1.24-2.44)	0.03			0.05			
India	12	1.80 (1.13-2.20)		3	1.59 (0.0.58-2.78)		3	1.98 (0.78-3.80)	0.40
Nepal	3	1.46 (1.09-1.76)		2	2.28 (0.30-17.32)				
Pakistan	3	2.04 (1.98-2.45)		4	3.30 (2.28-4.79)		4	2.25 (1.14-4.44)	4
Sri lanka	1	0.72 (0.27-1.90)		1	0.72 (0.27-1.90)				
Study design									
Cohort study	18	1.80 (1.04-1.70)	0.51	9	2.70 (1.40-3.60)	0.63			
Cross sectional	2	1.21 (0.87-1.68)		1	1.60 (0.86-2.99)				
Case control	1	0.51 (0.24-1.07)							
Confounding factors									
Adjusted	8	1.18 (0.89-1.30)	0.001	2	1.79 (0.33-9.60)	0.80			
Unadjusted	13	1.79 (1.26-1.96)		8	2.78 (1.48-3.39)				
Sample size									
≤817	11	1.76 (1.21-1.86)	0.26	5	1.98 (0.68-3.40)	0.27	2	2.88 (0.74-11.20)	0.59
>817	9	1.34 (1.30-1.82)		5	2.66 (1.41-5.00)		5	1.91 (1.04-3.50)	
Maternal age, year									
<25	8	1.76 (1.08-1.66)	0.22	3	1.70 (0.64-3.07)	0.40	1	1.70 (0.64-3.07)	0.40
≥25	13	1.78 (1.30-2.40)		7	2.43 (1.43-4.10)		5	2.43 (1.43-4.10)	

Maternal haemoglobin or haematocrit during pregnancy among anaemic women leads to a decline in red cell mass and maternal plasma volume during pregnancy, which contribute to the occurrence of PTB [34]. Moreover, a significant number of studies have observed that the trimester of anaemia onset during pregnancy was associated with PTB occurrence. For instance, some studies reported anaemia in the first trimester of pregnancy is associated with increased risk of PTB [11,12] while others did not [14]. A meta-analysis also reported that early pregnancy anaemia was associated with a slightly increased risk of PTB than late pregnancy anaemia [13]. These differences might be due to various physical factors. However, the aggregate measures of maternal anaemia that were used in the referred studies could be one of the factors associated with these differences [35].

Consistent with other studies [13,29,36,37], this systematic review and meta-analysis reported the strongest significant effect of maternal anaemia during pregnancy on the increased occurrence of perinatal and neonatal mortality. Higher occurrence of LBW and PTB among the anaemic mothers than non-anaemic women are known factors associated with the increased risks of perinatal, neonatal and child mortality. For instance, Goldenberg and colleagues found a 75% higher risk of perinatal mortality following PTB than normal birth, and the WHO reported around 60-80% of all neonatal deaths in LMICs are attributed to the LBW [38]. The other possible factors contributing to the increased risk of perinatal and neonatal mortality are primarily attributed to the anaemia during pregnancy [33,36,39,40]. For instance, the occurrence of anaemia during pregnancy increases the risk of birth asphyxia, a contributor of 26% of the total perinatal mortality in Pakistan [41] and 23% total perinatal deaths in developing countries [42].

Our study found higher risks of LBW and PTB among the anaemic mothers in Pakistan than in other South Asian countries. We could not explain these findings as mechanisms are unclear, and there is a lack of relevant research. However, several available estimates reported a higher incidence of LBW (24.5%) [43] and PTB (15.7%) [44] in Pakistan than the average in South Asian countries (LBW, 15.5% [3] and PTB, 9.6% [45]). Rural residence, lower education, lower use of antenatal care, and larger size of parity may often be cited as common risk factors of such higher occurrences of LBW and PTB in Pakistan [43,46].

4.1. Strengths and limitations

In this study, we did not apply any time, language, or outcome restrictions. This has enabled us to include a large number of studies, which allowed us to determine the number of outcomes attributed to maternal anaemia and finally to draw reasonable conclusions. A very comprehensive analysis also enable us to draw accurate estimates along with possible biases in the estimates. However, several limitations should be mentioned. Firstly, although the WHO developed the standard cut off point for anaemia categorization (anaemic, <11 g/dl, not anemic, ≥ 11 g/dl) during pregnancy, not all studies use this categorization. In the meta-analysis, we considered papers that used this categorization or that had otherwise explained them narratively. Secondly, significant heterogeneity existed in several outcomes that could not be linked with different factors except for the sub-groups in the stratified analysis of this study. This limits our understanding of the association in various settings and restricts the generalization of our findings.

5. Conclusion

Maternal anaemia during pregnancy is associated with the increased risks of adverse birth and obstetric outcomes in South Asian countries. Proper nutrition before and during pregnancy, iron supplements, and screening of anaemia during pregnancy, are recommended to improve

maternal health and to control higher proportions of LBW, PTB, and perinatal mortality in South Asia.

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Authors contributions

Khan MN and Rahman MA developed the study concept and undertook reviews of published studies. Khan MN, and Rahman MM contribute to the study design. Khan MN and Rahman MA screened the studies and extracted data. Khan MN and Rahman MA analysed the data. Khan MN wrote the first draft. Rahman MM and Rahman MA critically reviewed the drafts. All authors have seen and approved the final draft of the study.

Declaration of competing interest

There are no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhip.2020.100021.

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