Maternal hemoglobin and birth weight: systematic review and meta-analysis

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Abstract

A systematic review published in 2000 studied the association between maternal anemia and birth weight; however, some results were inconclusive. A review of randomized control trials and cohort studies published in 2013 concluded that daily prenatal iron use substantially improves birth weight in a linear dose–response manner. Thus, a systematic review and meta-analysis of observational epidemiological studies was conducted to contemporarily estimate the relationship between prenatal maternal hemoglobin and birth weight. We searched four electronic databases for observational epidemiological studies, which reported birth weight as an outcome measure and ascertained prenatal maternal anemia by hemoglobin measurement. Thirty-three studies met inclusion criteria. Meta-analysis of five studies showed that neonates born to women with anemia were, on average, 303 g lighter in birth weight than those born to women without anemia (95% CI: 19.20–588.26; $I^2 = 91\%$; five studies; $p = 0.04$). On the basis of 17 studies, anemia was found to be significantly associated with doubling the risk of low birth weight (OR: 2.37; 95% CI: 1.66–3.38; $I^2 = 81\%$; 17 studies; $p < 0.00001$), and when restricting the analysis to high study score, a higher magnitude of risk was seen (OR: 3.30; 95% CI: 2.24–4.87; $I^2 = 48\%$; 7 studies; $p < 0.00001$). From a subgroup analysis, it was found ($p = 0.02$) that anemia in the first and third trimesters was associated with the increased risk of low birth weight. High hemoglobin levels significantly doubled the risk of low birth weight (OR: 1.84; 95% CI: 1.09–3.12; $I^2 = 62\%$; seven studies, $p = 0.02$). Hemoglobin needs to be routinely investigated during pregnancy, and women with low levels of hemoglobin should be treated and those with significantly high levels should be monitored to minimize harmful impact on neonatal health.

KEY WORDS: Birth weight, hemoglobin, anemia, meta-analysis

Introduction

Anemia is a major health issue affecting both developing and developed countries worldwide.[1] A report of 2005 suggested that globally about 1.62 billion people (95% CI: 1.50–1.74) are affected by anemia, which is about 24.8% of world's population.[1] Pregnant women and preschool children are more prevalent to anemia, and the majority of population with anemia is from developing countries of southeast Asia and sub-Saharan Africa.[1,2] Iron deficiency is the most widespread nutritional disorder and is the major cause of anemia during pregnancy.[1] Published research showed that maternal iron deficiency affects the health of both mother and child, and further it is likely to be responsible for intrauterine growth reduction, preterm births, cognitive impairments, and nutritional deficiencies.[1,3,4] Hemoglobin (Hb) concentration has been widely used in diagnosing anemia[1]; however, there have been modern advances such as pregnancy ferritin value or erythrocyte indices being introduced in the last decade for detailed diagnosis.

A systematic review published in 2000 studied the association between maternal anemia and birth weight; however, some results were inconclusive.[3] A recent review of randomized controlled trials (RCTs) and cohort studies published in 2013 concluded that daily prenatal iron use substantially improves birth weight in a linear dose–response manner.[4] This review showed that iron intake increases mean Hb concentration, reduces the risk of maternal anemia, and importantly also increases the birth weight. Similarly, another systematic review of RCT of iron supplementation published in 2012 outlined that women with iron supplementations were less likely to have low-birth-weight (LBW) babies (weighing

less than 2500 g) compared to non-iron or placebo group.[5] Subsequently, the study suggested that preventive iron supplementation during pregnancy reduced 70% maternal anemia. Findings proposed that prenatal supplementations are of greater benefits to reduce LBW cases and maternal anemia.[5]

A recent review by Sukrat et al.[6] assessed the effect of Hb concentration on variety of outcomes such as preterm birth, small gestation age, and LBW. It obtained about 10 studies published specifically after the year 2000 (with only 9 studies from developing countries), which were included in the LBW analysis. The research was limited to English language, and only two databases namely MEDLINE and Scopus were searched.

Objectives

Apparently, maternal anemia and neonatal health have been one of the important areas of research. Observational studies published over the past decade[7–9] suggested the association between maternal Hb concentration and birth weight: however, findings from some studies are uncertain.[21,29,35,36] However, a recent study has suggested a U-shaped relationship between maternal Hb and birth weight,[10] with contemporary research supporting a potential association between high Hb levels and reduced birth weight. Published reviews of observational studies have certain limitations as mentioned earlier, and no detailed review is published about maternal Hb levels and birth weight. Therefore, we conducted a comprehensive systematic review and meta-analysis focusing mainly on observational epidemiological studies to assess the relationship between maternal Hb levels during pregnancy and birth weight.

Materials and Methods

A comprehensive literature search was conducted through electronic databases using standard guidelines,[11,12] involving CINAHL, Embase, MEDLINE, and Web of Science databases, to identify all observational epidemiological studies published after year 2000, assessing the association between maternal Hb during pregnancy and birth weight (August 2012). We imposed no language limitations during our electronic search. Subsequently, we scanned the reference lists of eligible full-text studies to identify further potentially relevant articles.

Eligibility Criteria
Studies were included based on the following criteria:

1. Cross-sectional survey, case–control design, or cohort design
2. Birth weight listed as an outcome measure
3. Maternal anemia measured using Hb measurements during pregnancy

We excluded RCTs assessing the effect of iron supplementation or iron dosage during pregnancy. Further, studies with thalassemia conditions during pregnancy or malaria in combination with maternal anemia were not considered, as these general conditions could alter the association.[1,2]

Data Extraction and Quality Assessment
We assessed the eligibility of articles by reviewing search independently through title and abstract screening. The full text of the potentially eligible studies were obtained and reviewed independently by us, with discrepancies resolved through consensus. Data extraction was sought individually using a previously piloted form. The Newcastle–Ottawa Scale was used to assess study quality,[11] with a score of 7 or more considered to reflect high-quality scores with case–control and cohort design, and a score less than 7 was considered as low-quality scores (maximum score could be 9 considering these two study designs). Particularly for cross-sectional survey, score of 5 or more was considered for high-quality scores and less than 5 for low-quality scores (maximum score could be 7 awarded in cross-sectional design).[12] Ethical approval was not required for this research.
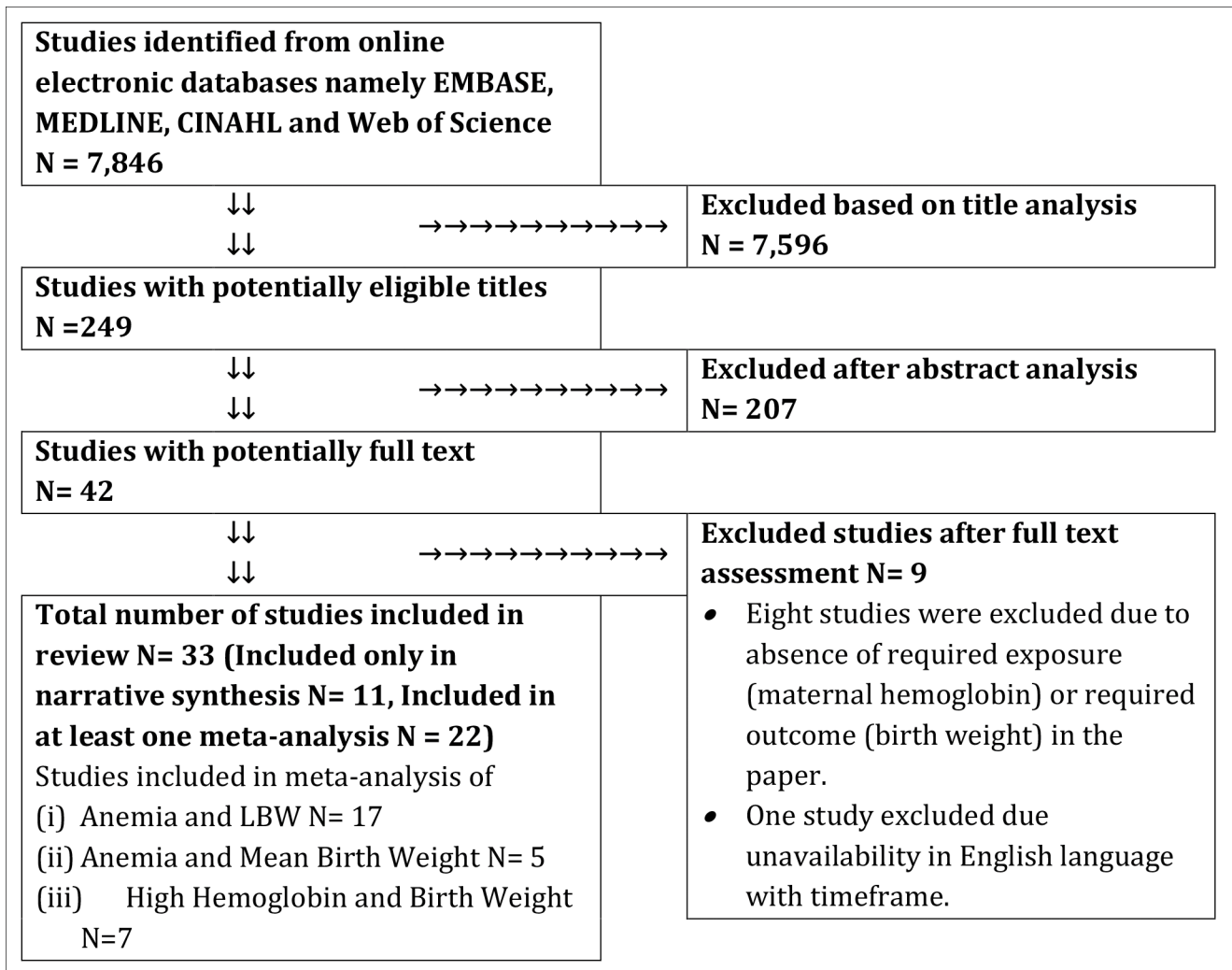
Statistical Analysis
Data were extracted using either adjusted or unadjusted estimates of the association, with 95% confidence intervals 95% CI). Adjusted estimates were preferred where both unadjusted and adjusted estimates were reported. We defined LBW as less than 2500 g at birth,[1] Hb levels less than 11 g/dl as maternal anemia,[1] and high Hb level was defined empirically as implied in the included study. Odds ratios (ORs) were used to describe the risk of LBW and mean differences for continuous measures of birth weight. Meta-analysis was performed using a random effect model because we anticipated a high level of heterogeneity between the estimates of the studies due to inherent biases in study design.

Heterogeneity was quantified using I^2-test.[11] More than 75% was considered as high heterogeneity, above 50% as moderate, and less than 25% as low.[11] Statistical significance was considered at the 0.05 level. Subgroup analysis was performed to explore heterogeneity between the studies by relating analysis to confounders, trimester of pregnancy, and study geographical location. Subgroup analyses were conducted to assess the impact of methodological quality. Publication bias was assessed visually using funnel plot method for meta-analyses. Statistical analyses were conducted using Review Manager software, version 5.1.[12] The review was conducted while adhering to the Meta-analysis of Observational Studies in Epidemiology guidelines.[12]

Results

Overview of Included Studies
The electronic searches produced a total of 7846 hits. On the basis of the title analysis, 7597 articles were excluded, thus leaving 249 articles for abstract screening. Forty-two abstracts were deemed eligible for full-text assessment [Figure 1]. Nine studies[42–50] were excluded after full-text

Studies identified from online electronic databases namely EMBASE, MEDLINE, CINAHL and Web of Science N = 7,846	
↓↓ ↓↓ →→→→→→→→→	Excluded based on title analysis N = 7,596
Studies with potentially eligible titles N =249	
↓↓ ↓↓ →→→→→→→→→	Excluded after abstract analysis N= 207
Studies with potentially full text N= 42	
↓↓ ↓↓ →→→→→→→→→	Excluded studies after full text assessment N= 9 • Eight studies were excluded due to absence of required exposure (maternal hemoglobin) or required outcome (birth weight) in the paper. • One study excluded due unavailability in English language with timeframe.
Total number of studies included in review N= 33 (Included only in narrative synthesis N= 11, Included in at least one meta-analysis N = 22) Studies included in meta-analysis of (i) Anemia and LBW N= 17 (ii) Anemia and Mean Birth Weight N= 5 (iii) High Hemoglobin and Birth Weight N=7	

Figure 1: Flow diagram of included and excluded studies.

assessment as the required exposure measurement and outcome was not reported in eight papers, and unavailability of one study[46] in English language was the primary reason of exclusion. Thus, 33 studies were considered in the review [Table 1]. Studies that clearly assessed iron-deficiency anemia during pregnancy based on Hb concentration and assessed birth weight were included with the strict follow-up of study inclusion criteria. Of 33 studies included, 22 provided sufficient information to be considered in the meta-analysis [Table 1]. The remaining 11 studies were included in the narrative synthesis, as not sufficient information was reported in the publications to be included in meta-analysis.

Description of Included Studies

Of the 33 studies included [Table 1], 12 used cohort designs, 4 applied case–control approach, and 17 were cross-sectional studies. Nineteen studies were conducted in Asia,[7,8,10,13–28] nine in Africa,[9,29–36], one in Europe,[37] two in North America,[38,39] and two in South America.[40,41] Sample size ranged from 50 to 88,149. The majority of studies assessed Hb level based on laboratory findings, and birth weight measurements were considered from hospital records.

The cutoff level for Hb varied considerably in the included studies. The cutoff level of 12 g/dl was used in four studies.[15,21,39,40] Majority of studies (about 25) used the cutoff level ranged between 10 and 11 g/dl.[7–10,13,14,16,18,20, 22–28,30,31,33–38,41] Further, eight studies[8–10,18,27,31,35,37] categorized anemia, such as severe anemia (Hb ≤ 7.0 g/dl), moderate anemia (Hb between 8.0 and 9.0 g/dl) and mild anemia (Hb = 9.0–10.0 g/dl). A study[19] from north India used 8.5 g/dl as cutoff level for anemic and non-anemic divisions. Cutoff levels for Hb were not clearly defined in the remaining three studies.[17,29,32]

The methodological quality of the included studies ranged from 3 to 9, with a median score of 6. Scores below 7 tended

Table 1: Included studies

No.	Author	Study design	Sample size	Study location	Confounder adjustments	Included in meta-analysis	Range of hemoglobin cutoff for anemia
1	Mbazor and Umeora[32]	Cross sectional	483	Nigeria	No adjustment	Anemia and low birth weight	Not clearly defined
2	Makki[17]	Cross sectional	2256 Anemic 648 Non-anemic 1594	Yemen	No adjustment	Anemia and low birth weight	Not clearly defined
3	Hassan et al.[29]	Cross sectional	246	Egypt	Insufficient quantitative data reported	Not applicable	Not clearly defined
4	Ganesh Kumar et al.[8]	Case–control	Cases 150; Controls 300	India	Factors adjusted for not reported	Anemia and low birth weight	Less than 10–11 g/dl Additional categories of mild, moderate, and severe anemia
5	Mumbare et al.[7]	Case–control	Cases 274 Controls 274	India	Adjusted for socioeconomic status	Anemia and low birth weight	Less than 10–11 g/dl
6	Rizvi et al.[28]	Case–control	Cases 262 Controls 262	Pakistan	Factors adjusted for not reported	Not applicable	Less than 10–11 g/dl
7	Akhter et al.[14]	Cohort	50	Bangladesh	No adjustment	1. Anemia and low birth weight 2. High hemoglobin and birth weight	Less than 10–11 g/dl
8	Levario-Carrillo et al.[41]	Cohort	153	Mexico	No adjustment	Anemia and mean birth weight	Less than 10–11 g/dl
9	Sekhavat et al.[20]	Cross sectional	1842 Anemic 328 Non-anemic 1514	Iran	No adjustment	1. Anemia and low birth weight 2. High hemoglobin and birth weight	Less than 10–11 g/dl
10	Nahum and Stanislaw[39]	Cross sectional	235	USA	Insufficient quantitative data reported	Not applicable	12 g/dl
11	Lee et al.[15]	Cohort	248	Korea	Adjusted for gestational age	Anemia and low birth weight	12 g/dl
12	Akinola et al.[36]	Cross sectional	500	Nigeria	Insufficient quantitative data reported	Not applicable	Less than 10–11 g/dl
13	Ma et al.[24]	Cross sectional	6,413	China	Insufficient quantitative data reported	Not applicable	Less than 10–11 g/dl
14	Shobeiri et al.[22]	Cohort	500	India	Insufficient quantitative data reported	Not applicable	Less than 10–11 g/dl
15	Lone et al.[16]	Cohort	619	Pakistan	Factors adjusted for not reported	Anemia and low birth weight	Less than 10–11 g/dl
16	Demmouche et al.[34]	Cohort	207	Algeria	No adjustment	Anemia and mean birth weight	
17	Telatar et al.[27]	Cross sectional	3,688	Turkey	No adjustment	Anemia and mean birth weight	
18	Khan[26]	Cohort	73	Pakistan	Insufficient quantitative data reported	Anemia and mean birth weight	

| No.	Author	Study design	Sample size	Study location	Confounder adjustments	Included in meta-analysis	Range of hemoglobin cutoff for anemia
19	Ugwuja et al.[33]	Cohort	349	Nigeria	No adjustment	Anemia and mean birth weight	
20	Malhotra et al.[18]	Cohort	447	India	Adjusted for age, parity, and induction of labor	1. Anemia and low birth weight 2. High hemoglobin and birth weight	Less than 10–11 g/dl
21	Geelhoed et al.[9]	Cohort	309 157 anemic 153 non-anemic	Ghana	Adjusted for maternal age	1. Anemia and low birth weight 2. High hemoglobin and birth weight	Categories of mild, moderate, and severe anemia
22	Kumar et al.[23]	Cohort	2027	India	Insufficient quantitative data reported	Not applicable	Less than 10–11 g/dl
23	Van Bogaert[35]	Cross sectional	2707	South Africa	Insufficient quantitative data reported	Not applicable	Categories of mild, moderate, and severe anemia
24	Ren et al.[10]	Cross sectional	88,149	China	Adjusted for maternal age, smoking, and weight	1. Anemia and low birth weight 2. High hemoglobin and birth weight	Less than 10–11 g/dl Categories of mild, moderate, and severe anemia
25	Chang et al.[38]	Cross sectional	918	USA	Adjusted for maternal age, BMI, and smoking	1. Anemia and low birth weight 2. High hemoglobin and birth weight	Less than 10–11 g/dl
26	Kidanto et al.[31]	Cross sectional	1721	South Africa	Factors adjusted for not reported	Anemia and low birth weight	Less than 10–11 g/dl Additional categories of mild, moderate, and severe anemia
27	Sachdeva et al.[19]	Cross sectional	254	India	No adjustment	Anemia and low birth weight	8.5 g/dl
28	Hämäläinen et al.[37]	Cross sectional	22,799	Finland	No adjustment	Anemia and low birth weight	Less than 10–11 g/dl Additional categories of mild, moderate, and severe anemia
29	Chumak and Grijbovski[21]	Cross sectional	24,525	Russia	Insufficient quantitative data reported	Not applicable	12 g/dl
30	Laflamme[40]	Cross sectional	79	Bolivia	Insufficient quantitative data reported	Not applicable	12 g/dl
31	Abeysena et al.[13]	Cohort	766	Sri Lanka	Adjusted for maternal and parity	1. Anemia and low birth weight 2. High hemoglobin and birth weight	Less than 10–11 g/dl
32	Elhassan et al.[30]	Case–control	1224	Sudan	Factors adjusted for not reported	Anemia and low birth weight	Less than 11 g/dl
33	Ahmad et al.[25]	Cross sectional	100	Pakistan	Insufficient quantitative data reported	Not applicable	Less than 10–11 g/dl
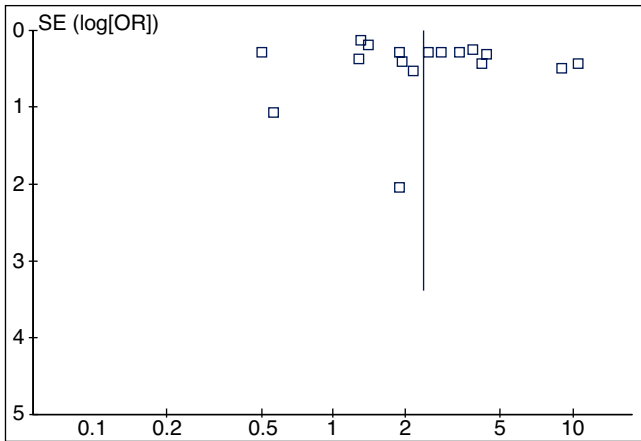
Figure 2: Funnel plot of anemia and low birth weight.

to arise from failure to define LBW criteria and lack of adjustment of confounders in the statistical analysis. Of the included studies, 10 presented their adjusted results for confounders such as maternal age, parity, body mass index, and smoking.[8–10,13,15,16,18,30,31,38] Only one study adjusted its measure of effect for socioeconomic status.[7]

Meta-analysis

Anemia and Low Birth Weight

Of 33 studies, 17 were considered in this meta-analysis of anemia and LBW[7–10,13–20,30–32,37,38] with 13 studies presenting Hb levels of third trimester. A pooled analysis of 17 heterogeneous studies (I^2 = 81%) showed that women with anemia during pregnancy were twice as likely to deliver an LBW baby compared to those without anemia during pregnancy (OR: 2.37; 95% CI: 1.66–3.38; I^2 =81%; p < 0.00001). No evidence of publication bias was observed [Figure 2].
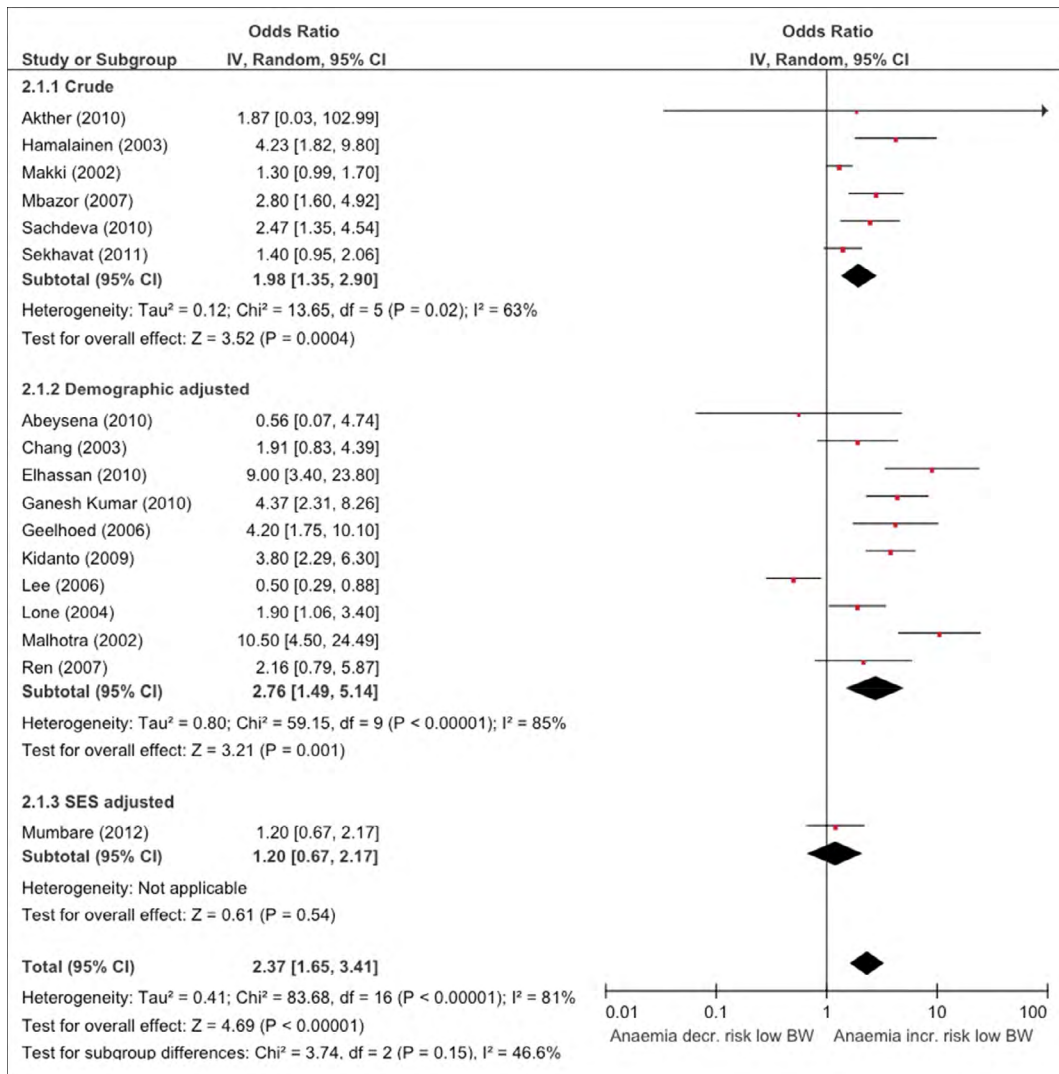

Figure 3: Anemia and the risk of low birth weight- subgroup analysis based on confounder adjustments.

Further, seven studies (mentioned later) assessed the association between low Hb levels and the risk LBW, but could not be included in the meta-analysis due to how studies were reported, thus OR calculations were not possible. Finding from a cross-sectional study in China[24] reported higher number of cases with LBW when Hb was <8 g/dl, and similar results were obtained from a research in Iran.[27] A research in Pakistan[16] suggested that the risk of LBW and preterm delivery is 1.9 and 4 times higher in women with anemia, respectively, compared to those without anemia. However, research in Russia,[21] Egypt,[29] South Africa,[35] and Nigeria[36] found no significant association with Hb levels and the risk of LBW. These studies mainly used qualitative analysis and no OR or sufficient data were presented, hence could not be included in the meta-analysis.

The 17 heterogeneous studies presented in the meta-analysis were further used in four-subgroup analysis outlined in the following sections depending on availability of data.

Subgroup analysis based on adjustment for confounders: In a subgroup analysis assessing the impact of adjustment for confounders on the association between anemia and the risk of LBW, slightly larger estimates of effect were seen for studies that allowed for confounders in their statistical analysis (unadjusted OR 1.98, 95% CI 1.35-2.90, I^2 =63%, 6 studies, 14,17,19,20,32,37) adjusted for demographics (OR 2.76, 95% CI 1.49-5.14, I^2 =85%, 10 studies 8,9,10,13,15,16,18,30,31,38) and for socioeconomic status (OR 3.27, 95% CI 1.81-5.91, 1 study[7]). However, the test of subgroup analysis found no significant difference between the subgroups (p = 0.33) [Figure 3].

Subgroup analysis based on timing of measurement for Hb: In a subgroup analysis relating to the Hb measurement across three trimesters showed significant difference (p = 0.02). In particular, the largest risk of an LBW was found if anemia was recorded in the first trimester (OR: 3.20; 95% CI: 1.68–6.10; I^2 = 2%); however, this estimate was based on only two studies.[10,37] A nonsignificant association was seen between the risk of LBW and anemia when identified in the second trimester (OR: 0.91; 95% CI: 0.47–1.75; I^2 = 42%; two studies[37,38]). When anemia was recorded in the third trimester (14 studies), the risk of having an LBW baby was approximately doubled (OR: 1.97; 95% CI: 1.71–2.28; I^2 = 84%).[7–9,13,15–20,30–32,38]

Subgroup analysis based on the study geographical location: A test for subgroup differences found to be significant in the association of LBW and anemia during pregnancy (p = 0.02), where the largest magnitude of effect was seen in a pooled analysis of African-based studies (OR: 3.96; 95% CI: 2.65–5.92; I^2 = 28%, 4 studies[9,10,30–32]) compared to studies conducted in Asia (OR: 2.04; 95% CI: 1.29–3.21; I^2 = 83%; 11 studies[7,8,10,13–20]) and individual studies conducted in North America (OR: 1.28; 95% CI: 0.63–2.62; 1 study[38]) and in Europe (OR: 1.91; 95% CI: 0.83–4.39; 1 study[37]).

Subgroup analysis based on overall methodological quality: A significant difference was found between low and high study scores, where larger magnitudes of effect were seen for the higher score studies (OR: 3.30; 95% CI: 2.24–4.87; I^2 = 48%) compared to the low scores (OR: 1.55; 95% CI: 1.07–2.25; I^2 = 72%) with significant subgroup difference (p = 0.006).

Anemia and Mean Birth Weight

Of 33 studies, 5 studies[26,27,33,34,41] assessed the association between anemia and mean birth weight, thus including individually in this meta-analysis (B). Result showed that neonates born to women with anemia during pregnancy had significantly reduced birth weights with an average of 303.73 g than those born to women without anemia (95% CI: 19.20–588.26; p = 0.04) [Figure 4]. However, extreme levels of heterogeneity (I^2 = 97%) were detected in the meta-analysis, thus these findings should be interpreted with caution. Heterogeneity observed higher specifically related with two studies,[26,34] which found large reduction in birth weight between women with anemia and those without anemia. Further, with these two studies study scores were low because
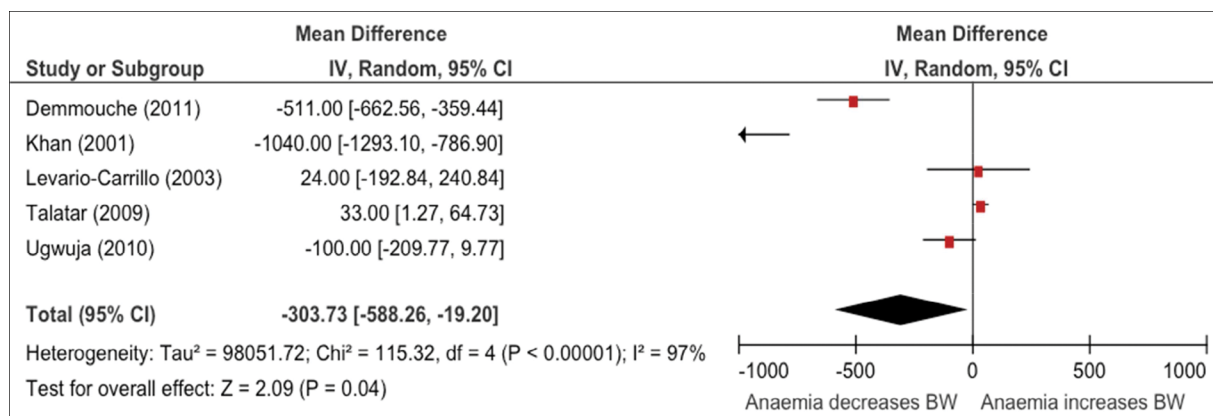
Figure 4: Mean birth weight among anemic and non-anemic participants.

of unadjusted confounders. We understand that the samples among these studies had higher prevalence of anemia, which could be the reason; however, there is no possibility to confirm the findings or further explore root causes of heterogeneity for studies being from different countries. Considering limitations due to study numbers and lack of adjusted measures in these studies, further subgroup analysis could not be performed.

High Hemoglobin Levels and Low Birth Weight

Of 33 studies, 7 papers[9,10,13,14,18,20,38] were identified, assessing the association between high levels of Hb and the risk of LBW. A pooled analysis of seven studies found that women with high Hb levels recorded during pregnancy were 84% significantly more likely to deliver an LBW neonate (OR: 1.84; 95% CI: 1.09–3.12; I^2 = 62%) [Figure 5]. In addition, two studies[24,39] assessed the relation of high Hb levels and the risk of LBW, but could not be considered in meta-analysis due to how results were reported. Findings from cross-sectional survey in China[24] outlined higher incidences of LBW cases when Hb level was more than 14 g/dl. A research about effect of altitude on levels of Hb[39] showed the decrease in birth weight by 89 g with increase in Hb level by 1.0 g/dl. Limited information was published particularly in these two studies, thus could not be included in the meta-analysis. Further subgroup analysis could not be performed due to how data were reported.

Discussion

Strengths and Limitations of This Review

The review has several strengths. The findings from this review are generalizable, because we conducted comprehensive search strategies to obtain maximum number of published studies through electronic databases with no language restrictions. A Spanish study was translated into English to assess the eligibility and then considered in the review as well

as in the meta-analysis.[41] We calculated ORs wherever data were available and included them in the meta-analysis.[14,19] Furthermore, we checked bias visually using funnel plot for both low and high levels of Hb analysis, and found no evidence of possible publication biases. Finally, we attempted to explore reasons for heterogeneity by performing subgroup analyses such as confounder adjustment, study locations, study scores, and timing of measurement of anemia. Subgroup analysis identified that higher quality studies showed larger magnitude of effect than the lower quality studies, which was unusual given that lower quality studies tend to produce larger effect sizes due to biases involved in study designs.[12] Issues related to multiple pregnancies or births, likely to affect the association between anemia and neonates, and they could underestimate the true association.[1,3] However, we did not find any issues related to unit analysis, as studies generally excluded multiple births and pregnancies. Compared to previously published reviews,[3,6] we understand that this review is comprehensive in terms of methodology and database included. Importantly, this review provided a detailed understanding of low and high Hb concentration and its effect on birth weight.

However, the review has certain limitations, which are mainly related to the methodological quality and data availability in included papers. The majority of included studies were scored low, primarily due to lack of adjustments of confounders in their statistical analyses; 11 studies could not be included in at least one meta-analysis because of how data were reported. Second, considering limitation of case–control design or cross-sectional approach, a temporal association cannot be evaluated being the main reason for higher risk of biases.[4] However, we conducted possible subgroup analyses, which were not presented in earlier reviews.[3,6] Majority of the studies assessed Hb levels in the third trimester of pregnancy; therefore a full investigation across three trimesters was limited. Within the included studies, we observed marked variations in levels used to define
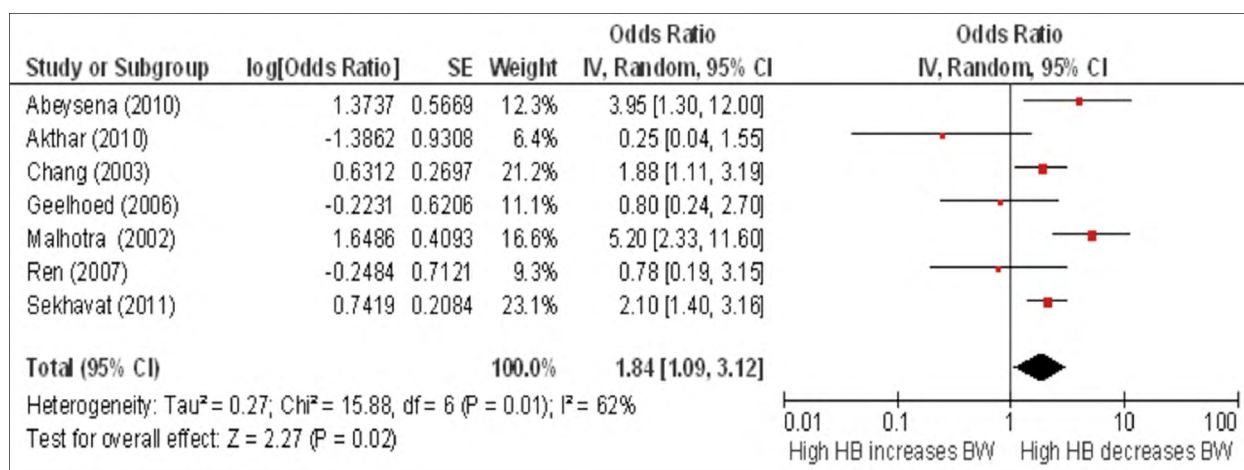
Figure 5: High hemoglobin levels and the risk of low birth weight.

anemia, which might be tailored based on study locations and populations. We understand that the varying Hb cutoff levels applied in different studies as well as different reference points is likely to be the primary reason of high levels of heterogeneity.[6] The analysis is based on summary data; however, there is limitation in the systematic review design that individual data cannot be obtained to calibrate Hb cutoff level to evaluate heterogeneity. On another aspect, we did not find much of heterogeneity with high Hb analysis, which may be due to the narrow cutoff range (observed between 11.5 and 12.0 g/dl) in all five studies. However, this could be an alternative explanation, but no confirmed validation was found for this variation, thus limiting the observations to explain heterogeneity between the studies. Included studies assessed Hb level during pregnancy; however, we found two studies[44,45] during electronic search measured body iron content based on packed cell volume and HYPO %; with their results presented through erythrocyte indices such as mean corpuscular volume (MCV), mean corpuscular Hb concentration (MCHC), and mean corpuscular Hb (MCH); thus, these studies were not included in the review. Finally, a Persian language study[46] could not be translated within available time frame. Author and publisher of the Persian study were contacted for English version, but informed about unavailability in English version, thus excluded.

Synthesis

This systematic review and meta-analysis based on observational epidemiological studies found that anemia during pregnancy (typically defined as Hb less than 10–11 g/dl in included studies) doubled the risk of having an LBW baby, and on an average reduces birth weight by 303 g. Furthermore, we found an unfavorable effect of high levels Hb during pregnancy (typically defined as more than 11.5 or 12 g/dl) related to a doubling in the risk of LBW. However, these findings need to be applied cautiously. Anemia is very common health issue in southeast Asia and sub-Saharan Africa among pregnant women, and therefore the apparent effect of anemia on birth weight is an important public health concern. The result of the meta-analysis is relevant to developing world, as in developed region more advanced systems are available for Hb measurement, iron deficiency evaluation, and general antenatal investigations.

Our findings showed that anemia in the first trimester had significantly larger effect compared to that in the second trimester; however, this subgroup analysis was based on small number of studies, therefore further research is required to confirm this finding. Pregnancy, Hb levels, and changes across trimesters are emphatically complex issues. During the first trimester of pregnancy, body iron requirement is doubled as iron is required for placenta formation.[37]. If Hb is lower in the first trimester then it is likely to reduce further, due to rapid iron use.[55] Previous research showed that poor placental formation and poor growth is a result of maternal anemia during pregnancy.[56,57] In case of third trimester, fetus grows rapidly and requires a high level of nutrition, thus majority of plasma expansion is observed in the third trimester.[55] Inadequate

expansion shows a high level of Hb, and this may mask the true Hb level.[55,57] Iron deficiency is a systematic condition in which immune response is likely to be altered due to proliferation of T and B lymphocytes.[47] Lymphocyte indices were noted lower during anemia, and hence women with anemia were found prone to infections, which could cause preterm delivery and thus LBW.[16] This could be supported with findings from a recent meta-analysis by Haider et al.[4] The meta-analysis of 26 cohort studies showed significant association of preterm deliveries in anemic group (crude OR: 1.28; 95% CI: 1.12–1.47; I 2 = 89%; 26 studies) and further the association remained significant with adjusted estimates (crude OR: 1.28; 95% CI: 1.11–1.48; I 2 = 83%; 13 studies).

Our results also showed significant effect on birth weight due to high Hb level. The exact mechanism is not confirmed, however based on published evidences, it appears that plasma expansion, blood viscosity, preeclampsia, or maternal smoking could be one of the etiological factors.[51-55] The alteration in blood viscosity reduces oxygen delivery to fetus and blood pressure changes.[55] Subsequently, the association between high Hb level and LBW could be due to preeclampsia as hypertension contributes to this phenomenon.[55,56] Importantly, with this review, meta-analyses of high and low Hb levels also suggested that there could be "U–shaped" relationship between maternal Hb and LBW. A recent study showed that birth weight decreases when maternal Hb is on lower or on higher side compared to normal range.[10] A very well-structured narrative review by Rasmussen[57] explained the association in an imperative way based on large databases such as National Collaborative Perinatal Project or Cardiff Births Survey. High Hb level (typically more than 12–14 g/dl) was found to be associated with small gestational age, thus causing LBW cases. Similarly, low levels of Hb are responsible for reduced fetal growth. It was observed that Hb levels, gestational age, and pregnancy-related changes are very crucial, which influence birth outcome at varying levels. Therefore, low and high Hb levels need to be closely monitored during pregnancy. We understand that birth outcomes changed with various Hb levels during pregnancy and this varied with the study populations. However, it is noteworthy that optimum level of Hb need to be defined and validated considering specific population characteristics, therefore a generalized cutoff level of Hb (11 g/dl during pregnancy) may not be relevant worldwide to diagnose anemia.

We observed that the studies with high-quality score showed threefold increase in the risk LBW with anemia whereas in studies with low-quality scores maternal anemia was associated with only 55% of increased risk of LBW. Normally low-quality studies produce larger effect sizes due to biases involved in the study designs[12]; however, we found it unusual, as low-quality studies showed smaller effect. We understand that this could be due to large number of studies involved in the low-score group.

We also explored recent published systematic reviews of clinical trials of iron supplementation, maternal anemia, and birth weight.[4,5] Recent review with meta-analysis of RCTs

by Haider et al.[4] showed that the use of iron with or without folic acid supplements reduces the iron deficiency and risks of LBW. Evidence from cohort studies in this review showed that prenatal anemia significantly increases the risk of LBW compared with no anemia (crude OR 1.25; 95% CI: 1.08–1.45; I^2 =90%; 25 studies), however association was nonsignificant with adjusted study estimates.[4] Results from our review are supporting findings obtained from recent two systematic reviews.

Conclusion and Scope for Future Research

We understand that only Hb level does not provide detailed information about iron content, and thus additional investigations appears useful.[1] The in-depth analysis based on MCV, MCHC, and MCH is required to analyze body iron content in detail.[44,45] Subsequently, erythrocyte protoporphyrin or transferrin receptor may contribute in general iron assessment.[57] However, these tests may not be affordable for large sample size particularly for research in low resource settings.[45] Maternal iron deficiency is a marker of nutritional status and could coexist with other risk factors, thus it could be challenging to treat anemia only with iron supplements without considering other essential micronutrient requirements. The accurate Hb analysis and pattern across trimesters is critical to understand, which has established challenges to isolate factors such as plasma expansion and Hb concentration to study the association and variation, across trimestral pattern.

We perceive that the future research in maternal anemia across three trimesters with advance technology, particularly in developing countries, with a suitable design would be valuable. There is also an urgent need to conduct research focusing on Hb cutoff levels considering individual population groups. This attempt to define Hb cutoff levels for individual population could reduce possible bias in the upcoming studies and would simultaneously help to specifically target public health interventions. Our results provide confirmatory evidence of a detrimental effect between maternal anemia (low Hb levels) and high Hb level, on birth weight based on observational studies. Results suggest that further studies are required to be continued specifically in southeast Asia and sub-Saharan Africa where iron-deficiency anemia is highly prevalent among pregnant women. This could be valuable to prevent adverse effects on neonatal health outcomes.

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