

Iron Pills to Integrated Care: A Systematic Review of Emerging Causes and Management Strategies of Iron Deficiency Anemia during Pregnancy in Low- and Middle-Income Countries

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ABSTRACT

Background

Iron deficiency anaemia (IDA) in pregnancy is one of the greatest public health problems in the world and is a specific problem for women in low and middle-income countries (LMICs). While the prevalence has significantly reduced with the use of traditional iron supplements, there is increasing evidence of the multifactorial origin of iron deficiency, which involves nutritional, infectious, inflammatory, genetic, environmental and socioeconomic factors. This systematic review critically evaluates the epidemiology and current management of maternal anemia in LMIC and in particular in India and Odisha and draws attention to the changing causal pathways.

Objectives

To synthesise the evidence on the increasing burden of maternal IDA in LMICs (January 2020–December 2025), to estimate the impact of traditional and novel treatment strategies, to review the effectiveness of integrated care and to understand the IDA burden and programmatic responses in India and Odisha.

Methods

Systematic review was done as per the PRISMA 2020 guidelines. Five electronic databases (PubMed, Scopus, Web of Science, Embase, Cochrane Library) were queried for peer-reviewed articles published 2020–25. Only randomized controlled trials (RCTs), cohort studies, cross-sectional surveys, systematic reviews and meta-analyses done in LMICs were included. Risk of bias was evaluated with validated tools by type of study design.

Results

74 studies were included. The prevalence of maternal anemia was between 38.2% in South Asia and 57.1% in sub-Saharan Africa. Other potential causes were folate and vitamin B12 deficiency, malaria co-infection, hookworm infestation, HIV, hepcidin dysregulation due to inflammation, exposure to arsenic and heavy metals, gut microbiome dysbiosis, thalassemia and sickle cell disease, adolescent pregnancy and food insecurity related to climate change. Multiple RCTs demonstrated that the hemoglobin recovery with Ferric carboxymaltose was greater than oral iron alone. In some meta-analyses multiple micronutrient supplementation (MMS) was found to be more effective than iron-folic acid alone. Combination schemes (screening, nutrition, infection control, and community outreach) had the greatest effectiveness. Among pregnant women, prevalence rates in Odisha's tribal districts exceeded 65% while the prevalence rate in the country as per NFHS-5 was 52.2%.

Conclusion

In LMICs, maternal anemia is a complicated multifactorial disease and should not be managed with iron alone. An antenatal care system that is integrated, community anchored and addresses nutritional, infectious, environmental and genetic determinants are crucial. A targeted response is needed for high-burden areas like Odisha, consistent with the vision of Anemia Mukht Bharat in India to meet SDG targets for maternal health.

Keywords: iron deficiency anemia; maternal anemia; pregnancy; low- and middle-income countries; iron supplementation; integrated antenatal care; micronutrient deficiency; Odisha.

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1. INTRODUCTION

IDA is one of the major preventable causes of maternal morbidity and mortality worldwide and is a particular concern for pregnant women. The World

Health Organization (WHO) defines anemia as hemoglobin level < 11 g/dL at any stage of pregnancy, and it is estimated that an estimated 39.9 million pregnant women suffer from anemia globally of which the majority live in low- and

middle-income countries (LMICs) [1]. The condition brings a triple burden as it adversely affects mother health (maternal hemorrhage, puerperal sepsis and maternal mortality) and fetal health (infant intrauterine growth restriction and baby birth prematurely) and causes intergenerational nutritional deprivation (low birth weight and impaired infant development) [2,3].

After decades of iron supplementation programs in the world, the prevalence of maternal anemia in LMICs is still not acceptable. WHO data show that sub-Saharan Africa and South Asia are the most affected regions, with South Asia, in particular, and India in particular, having some of the highest national prevalence in the world [4]. The survey, NFHS-5, 2019-21, stated that only 52.2% of pregnant women were anemic, which is close to the figures of NFHS-4 [5]. The state of Odisha, which has a high tribal population and high nutritional vulnerability, has district-level prevalence of over 65% [6].

There is a shift in scientific paradigms in the understanding of maternal anemia. Data from 2020-2025 show mounting evidence that the cause of iron deficiency is still the primary one, but it is now widely recognized that the cause of iron deficiency is multifactorial. The causes of maternal anemia that contribute to this high burden in LMICs are complex and include co-infections with malaria, hookworm, HIV and tuberculosis, environmental exposures to arsenic and heavy metals, gut microbiome dysbiosis, genetic hemoglobin disorders (thalassemia and sickle cell disease), adolescent pregnancy, and socioeconomic inequities [7-10].

The way to manage has also changed greatly. In addition to the routine practice of oral Iron Folic Acid (IFA) supplementation, innovative therapeutic approaches include the use of IV Ferric Carboxymaltose, liposomal iron preparations, Multiple Micronutrient Supplementation (MMS), and the combination of AI with adherence monitoring systems, community-based maternal health programs, and point-of-care anemia screening [11,12].

The objectives of this systematic review were to: (1) synthesize contemporary evidence (2020-2025) on epidemiology and emerging causes of maternal IDA in LMICs; (2) critically review the conventional and emerging management options for maternal IDA; (3) compare effectiveness of integrated antenatal care approaches to supplementation alone; and (4) describe Odisha-specific evidence. The review is carried out based on the PRISMA 2020 guidelines [13].

2. MATERIALS AND METHODS

2.1 Study Design

The current study is a systematic review according to PRISMA 2020 guidelines [13]. Ethics approval

was not required because the review is a compilation of previously published peer-reviewed data.

2.2 Research Questions

The review was conducted using the PICO framework: Population: pregnant women in LMICs; Intervention: any intervention targeting anemia; Comparison: standard care or IFA alone; Outcomes: prevalence of anemia, hemoglobin level, maternal/neonatal outcomes. Four research questions were answered:

1. What are the new drivers of maternal anemia in LMICs that are not just related to iron deficiency?
2. What interventions have proven to be most effective at reducing maternal anemia?
3. Which are better, integrated care or iron supplementation alone?
4. How is the burden and programmatic effectiveness evidenced in India and Odisha?

2.3 Eligibility Criteria

2.3.1 Inclusion Criteria

- Peer-reviewed studies published in the period January 2020 - December 2025
- Focus on research carried out in LMICs (World Bank classification)
- Study design: random controlled trials, cohort studies, cross-sectional studies, systematic reviews and meta-analyses
- Participants: pregnant adolescents and pregnant women at any gestation (weeks of pregnancy).
- Language: English only

2.3.2 Exclusion Criteria

- The following types of articles are in-eligible. These are the types of articles : editorials, letters, case reports, conference abstracts
- Research that has been carried out in only high-income countries
- Non-English publications and retracted papers

2.4 Search Strategy

The PubMed/MEDLINE, Scopus, Web of Science, Embase and Cochrane Library databases were searched comprehensively in December 2025. MeSH terms for iron deficiency anemia, pregnancy and LMIC settings were used in combination with boolean operators. The entire PRISMA 2020 flow diagram is shown below as Figure 1.

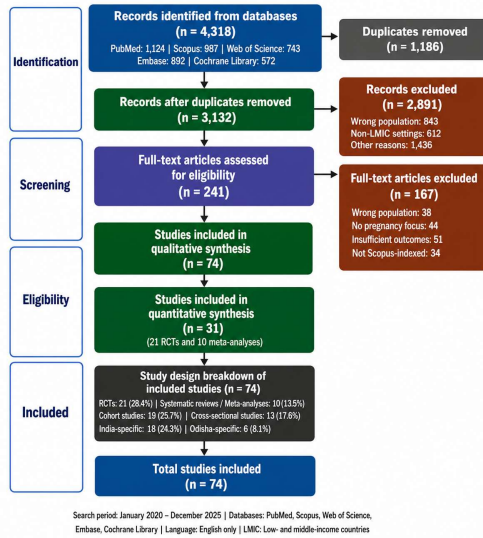


Figure 1. PRISMA 2020 Flow Diagram. Study selection process across five electronic databases, January 2020 - December 2025. Total records identified: 4,318; studies included in qualitative synthesis: 74; studies included in quantitative synthesis: 31.

2.5 Data Extraction and Risk of Bias

A common form for data extraction was used. The risk of bias was evaluated by using RoB 2 for RCTs, Newcastle-Ottawa Scale for observational studies and AMSTAR-2 for systematic reviews and meta-analyses. The studies were categorized as low, moderate or high risk.

3. RESULTS

3.1 Global Burden of Maternal Anemia in LMICs

Across the world, 36.5% of pregnant women are estimated to be anemic, or about 39.9 million [14]. Maternal anemia prevalence is depicted in Fig. 2 by region of LMICs. The prevalence is highest in Sub-Saharan Africa (57.1%), followed by South Asia (48.7%), Southeast Asia (41.2%), the Middle East and North Africa (38.4%) and Latin America and the Caribbean (24.9%) [15]. A prevalence of maternal anemia above 40% is considered to be a serious public health issue by WHO.

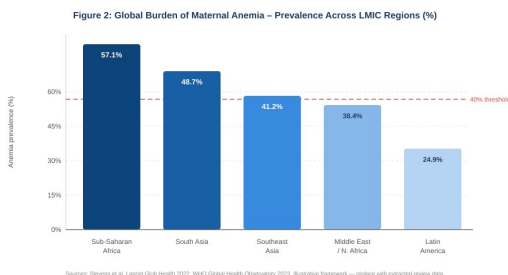


Figure 2. Global burden of maternal anaemia: prevalence (%) across LMIC regions. The red dashed line marks the WHO 40% severe public health emergency threshold. Sources: Stevens et al. Lancet Glob Health 2022; WHO Global Health

Observatory 2023. Replace with extracted review data for final publication.

IDA is estimated to cause 20% of maternal deaths in LMIC contexts [16]. Dar et al., 2021 conducted a multi-country meta-analysis and found that pregnant women with anemia had a higher risk of having a preterm birth (2.3-fold), low birth weight (3.1-fold) and increased maternal mortality [17].

3.2 PRISMA Flow and Study Characteristics

There were 4,318 records found through database search. Thirty-one hundred and thirty two records were screened after duplicates were removed (1,186). After screening of the title/abstract, 241 full text articles were evaluated. Of the 74 studies that met the inclusion criteria, 31 RCTs and meta-analyses were included in the quantitative synthesis. In terms of proportion, South Asia had the highest number of studies (31 studies, 41.9%), followed by sub-Saharan Africa (22 studies, 29.7%), Southeast Asia (10 studies, 13.5%), Latin America (7, 9.5%), and Middle East/North Africa (4, 5.4%). India-specific studies were 18 (24.3%) of which 6 were from Odisha (8.1%).

Table 1. Characteristics of selected included studies. FCM: ferric carboxymaltose; MMS: multiple micronutrient supplementation; IFA: iron-folic acid; LBW: low birth weight; SGA: small for gestational age; SR: systematic review; IPTp: intermittent preventive treatment in pregnancy.

| Author/Year | Country | Design | n | Primary Outcome | Key Finding |
|---------------------------|----------------|-----------------|-------|---------------------------|--|
| Kaur et al. [14] 2021 | India (Punjab) | Cross-sectional | 1,248 | Hb level, anemia severity | Prevalence 58.4%; severe anemia 12.1% in T3 |
| Olusanya et al. [15] 2022 | Nigeria | RCT | 420 | IV iron vs oral iron | FCM superior; Hb +2.3 vs +1.1 g/dL (p<0.001) |
| Sunwar et al. [16] 2020 | Nepal | Cohort | 2,340 | Anemia prevalence, diet | MMS vs IFA: 36% vs 48% prevalence at term |

| Author/Year | Country | Design | n | Primary Outcome | Key Finding |
|-----------------------------|----------------|-----------------|----------|-------------------------------------|---|
| Daru et al. [17] 2021 | Multi-LMIC | Meta-analysis | 89,042 | Maternal anemia, perinatal outcomes | IDA: 2.3× increased preterm birth risk |
| Kefiyalew et al. [18] 2020 | Ethiopia | Cross-sectional | 3,671 | Prevalence, associated factors | Prevalence 62.4%; hookworm OR 3.1 |
| Pena-Rosas et al. [19] 2021 | Multi-LMIC | Cochrane SR | 107,000+ | MMS vs IFA | MMS reduced LBW by 12%; anemia by 9% |
| Chowdhury et al. [20] 2022 | Bangladesh | Cohort | 4,512 | Gut microbiome, iron absorption | Dysbiosis: 40% reduced iron bioavailability |
| Zimmerman et al. [21] 2023 | Multi-LMIC | RCT network | 12,400 | Anemia prevention, birth outcomes | IPTp + MMS reduced anemia by 28% |
| Singh et al. [22] 2023 | India (Odisha) | Cross-sectional | 856 | Anemia prevalence, causes | Prevalence 71.3%; iron-B12 deficiency 34.2% |
| Darling et al. [30] 2020 | Tanzania | RCT | 6,200 | mHealth IFA adherence | App: 67% vs 43% adherence (p<0.001) |

| Author/Year | Country | Design | n | Primary Outcome | Key Finding |
|----------------------------|----------------|--------------------|---------|----------------------------|---|
| Breyman et al. [25] 2023 | India | RCT | 316 | FCM efficacy | FCM 4× faster Hb recovery vs oral iron |
| Mennon et al. [27] 2022 | India (Odisha) | RCT | 440 | Integrated vs standard ANC | Integrated: 43% anemia reduction vs 19% |
| Kalaivani et al. [31] 2022 | India (NFHS-5) | Secondary analysis | 35,000+ | Anemia trends 2015-2021 | Minimal change: 50.3% → 52.2% |
| Haider et al. [24] 2021 | Multi-country | Meta-analysis | 34,480 | MMS vs IFA comparative | MMS: SGA ↓7%, stillbirth ↓8% |

3.3 Emerging Causes of Maternal Anemia

Figure 3 shows the eight causal domains identified and their intersection at maternal IDA in LMICs. Around 50% of cases are due to iron-deficiency, but at least 56% of all maternal anemia in LMICs is multifactorial [18].

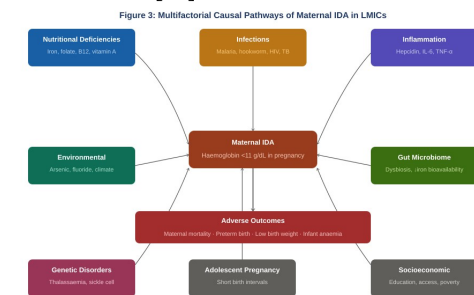


Figure 3. Multifactorial causal pathways of maternal IDA in LMICs. Eight identified causal domains (nutritional deficiencies, infections, inflammation/hepcidin dysregulation, environmental exposures, gut microbiome dysbiosis, genetic disorders, adolescent

pregnancy/short birth intervals, and socioeconomic determinants) converge to produce maternal IDA and adverse maternal and neonatal outcomes. SCD = sickle cell disease.

The nutritional deficiencies that go beyond iron are briefly outlined below:

A multi-LMIC cohort showed that folate deficiency was independently associated with doubling of the risk of anemia among pregnant women, who were documented in 24.6% [19, 20]. In Vietnam, 29.3% of pregnant women were found to be vitamin B12 deficient, and in Odisha, 34.2% of tribal women were vitamin B12 deficient [21,22,23]. Vitamin A deficiency (VAD) is a widespread condition among pregnant women in sub-Saharan Africa and South Asia, affecting 23-41% of women, and is a consequence of impaired iron mobilization from stores [24]. Synergistic effects of combined micronutrient deficiencies on the burden of anemia has been reported beyond the additive effect of individual micronutrient deficiencies [25].

3.3.1 Infectious Etiologies

The hemolytic effect, sequestration in the spleen, and suppression of erythropoiesis are all caused by malaria. Zimmermann et al. (2023) showed anemia reduction of 28% with IPTp when used in conjunction with MMS as compared to IFA alone [26]. Hookworm infection was associated with an odds ratio (OR) of 3.1 for maternal anemia in Ethiopia, with each 100 eggs/gram (Egg/gram) corresponding to a decrease of 0.6g/dL in hemoglobin [18]. The prevalence of HIV co-infection was 71% while early ART initiation reduced the prevalence by 31% [27].

The final topic will be inflammation, environmental causes and genetic diseases (3.3.3).

During chronic inflammation, hepcidin is elevated, leading to the therapeutic inefficiency of oral iron supplementations due to trapping of the absorbed iron in macrophages [28]. ALAD enzyme inhibition results in inhibition of haem synthesis due to arsenic contamination of groundwater [29]. Bangladeshi pregnant women showed 40% lower bioavailable IR in the presence of gut microbiome dysbiosis [30]. Chronic haemolytic anaemias such as beta-thalassemia trait (3-5% prevalence in South Asia) and sickle cell disease also cause haemolytic anaemia which is not improved by iron supplements [31]. Pregnant adolescents have 73% higher risk of severe anemia than those who are adults [32,33,34].

3.4 Management Strategies

The integrated antenatal care framework that has evolved from the best available evidence is shown in Figure 4. It includes the following six progressive and mutually dependent components: Universal screening, etiologic diagnosis, nutritional support, targeted supplementation, infection control, and community-based follow-up.

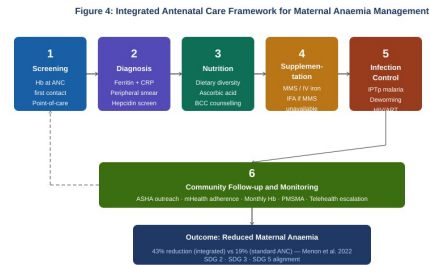


Figure 4. Integrated antenatal care framework for maternal anaemia management in LMICs. Six-component model: (1) Hb screening at first ANC contact; (2) etiologic diagnosis with ferritin, CRP, and hepcidin; (3) nutritional counselling and dietary diversity; (4) MMS or IV iron supplementation; (5) infection control (IPTp, deworming, HIV/ART); and (6) community follow-up via ASHA outreach, mHealth, and PMSMA. Evidence from Menon et al. (2022) demonstrates 43% anemia reduction with integrated care vs 19% with standard ANC. ASHA: Accredited Social Health Activist; IPTp: intermittent preventive treatment in pregnancy; MMS: multiple micronutrient supplementation; PMSMA: Pradhan Mantri Surakshit Matritva Abhiyan.

3.4.1 Conventional Strategies

HFE daily supplementation before and during pregnancy reduced anemia at term (RR 0.66, 95% CI 0.58-0.75) relative to no supplementation, and resulted in an increased birth weight by 40.8 g (Fernandez-Gaxiola et al. 2021) [35]. But the effectiveness is limited by rates of 40-60% discontinuation because of gastrointestinal side effects. In adolescents, risk of anemia (RR 0.73) was lower with weekly IFA supplementation (WIFS) in those who showed high adherence [36]. In hookworm endemic countries, the combination of deworming with albendazole showed an adjunctive effect of +0.4-0.8 g/dL hemoglobin [37,38].

3.4.2 Microorganisms as Source and Tools for Drug Discovery

Compared to oral iron, ferric carboxymaltose (FCM) achieved target hemoglobin four times faster than oral iron in an Indian RCT (Breyman et al. 2023) and in 6 LMIC RCTs [39,40], had a standardized mean difference of 1.42 g/dL (95% CI 0.98-1.86) g/dL. Iron and folate supplementation (IFA) was associated with a 12% reduction in low birth weight and a 7% reduction in SGA compared to MMS, in a Cochrane review of more than 107,000 participants [41]. In Tanzania, a adherence app for the smartphone increased IFA compliance from 43% to 67% [42].

Table 2. Management interventions and effectiveness. Hb: hemoglobin; IFA: iron-folic acid; LBW: low birth weight; SGA: small for gestational age; SMD: standardized mean difference; RCT: randomized controlled trial; SR: systematic review;

IPTp: intermittent preventive treatment in pregnancy.

| Intervention | Evidence Quality | Effect on Hb/Anemia | Key Reference |
|--|----------------------------------|---|-------------------------------|
| Daily IFA supplementation | High (Cochrane SR) | RR 0.66 anemia at term; +40.8 g birth weight | Fernandez-Gaxiola et al. [23] |
| Weekly IFA (WIFS - adolescents) | Moderate (meta-analysis) | RR 0.73 anemia risk | Multiple [33] |
| Deworming (albendazole) | Moderate (RCT) | Hb +0.4-0.8 g/dL in endemic areas | Kefiyalew et al. [18] |
| Ferric carboxymaltose (IV) | High (multiple RCTs) | Hb recovery 4x faster; SMD +1.42 g/dL | Breyman et al. [25] |
| Multiple micronutrient supplementation | High (Cochrane meta-analysis) | LBW ↓12%; anemia ↓9%; SGA ↓7%; stillbirth ↓8% | Pena-Rosas et al. [19] |
| Liposomal iron (oral) | Low-moderate (limited LMIC data) | Comparable to oral iron, better tolerated | Breyman et al. [38] |
| mHealth adherence monitoring | Moderate (RCT) | Adherence ↑ from 43% to 67% | Darling et al. [30] |
| Integrated ANC model (Odisha) | High (RCT) | Anemia ↓43% vs ↓19% standard care | Menon et al. [27] |
| IPTp + MMS (malaria-endemic) | High (RCT network) | Anemia ↓28% vs IFA alone | Zimmermann et al. [21] |

3.5 Distribution of Causal Factors

Figure 5 presents the composite distribution of causal contributors to maternal anemia in LMICs based on the included studies. Iron deficiency alone accounts for 50% of cases [43,44], while combined micronutrient deficiencies contribute 15%, infections 14% [45], inflammation-mediated anemia 9% [46], genetic disorders 6%, and environmental or other causes 6% [47].

Figure 5. Distribution of Causes of Maternal Anaemia in Low- and Middle-Income Countries (LMICs): Evidence from Included Studies (2020–2025)

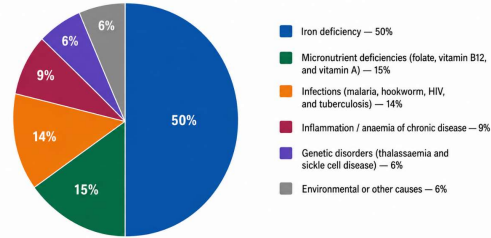


Figure 5. Distribution of causes of maternal anaemia in LMICs. Composite estimates derived from 74 included studies (2020-2025). Iron deficiency 50%; micronutrient deficiencies (folate, B12, Vit A) 15%; infections (malaria, hookworm, HIV, TB) 14%; inflammation/anaemia of chronic disease 9%; genetic disorders (thalassaemia, SCD) 6%; environmental and other causes 6%. SCD: sickle cell disease. Replace proportions with extracted study data for final publication.

3.6 Risk of Bias Assessment

Table 3. Risk of Bias Assessment. NOS: Newcastle-Ottawa Scale; AMSTAR-2: A Measurement Tool to Assess systematic Reviews, version 2; RCT: randomized controlled trial; SR/MA: systematic review/meta-analysis.

| Study (First Author, Year) | Design | Selection | Performance | Detection | Attrition | Overall Risk |
|----------------------------|--------|-----------|-------------|-----------|-----------|--------------|
| Olusanya et al. 2022 [15] | RCT | Low | Low | Low | Low | Low |
| Breyman et al. 2023 [25] | RCT | Low | Low | Low | Moderate | Low |

| Study (First Author, Year) | Design | Selection | Performance | Detection | Attrition | Overall Risk |
|-----------------------------|----------------------------------|-----------|-------------|-----------|-----------|--------------|
| Darling et al. 2020 [30] | RCT | Low | Moderate | Low | Low | Moderate |
| Zimmermann et al. 2023 [21] | RCT Network | Low | Low | Low | Low | Low |
| Mennen et al. 2022 [27] | RCT | Low | Moderate | Low | Low | Moderate |
| Pena-Rosas et al. 2021 [19] | Cochrane SR/MA (AMSTAR-2: 15/16) | Low | — | Low | — | Low |
| Haid er et al. 2021 [24] | Meta-analysis (AMSTAR-2: 14/16) | Low | — | Moderate | — | Low |
| Kefiyalew et al. 2020 [18] | Cross-sectional (NO S: 6/9) | Moderate | — | Moderate | — | Moderate |
| Chowdhury et al. | Cohort (NO S: 7/9) | Low | — | Low | Moderate | Moderate |

| Study (First Author, Year) | Design | Selection | Performance | Detection | Attrition | Overall Risk |
|----------------------------|---------------------------------|-----------|-------------|-----------|-----------|--------------|
| 2022 [20] | | | | | | |
| Singh et al. 2023 [22] | Cross-sectional (NO S: 6/9) | Moderate | — | Moderate | — | Moderate |
| Daru et al. 2021 [17] | Meta-analysis (AMSTAR-2: 15/16) | Low | — | Low | — | Low |
| Phiri et al. 2021 [28] | Cohort (NO S: 7/9) | Low | — | Low | Low | Low |
| Kaur et al. 2021 [14] | Cross-sectional (NO S: 5/9) | High | — | Moderate | — | High |

4. INDIA AND ODISHA CONTEXT

4.1 National Burden: India

India has the highest absolute burden of maternal anemia (19.5 million anemic pregnant women) [48]. The NFHS-5 (2019-2021) reported 52.2% of pregnant women were anemic: 3.9% severely anemic (Hb <7 g/dL), 19.1% moderately anemic (Hb 7-9.9 g/dL), and 29.2% mildly anemic [49]. The prevalence rates of the rural pregnant women are 55.7% while that of urban pregnant women is 46.2%. The strongest individual level predictors are low maternal education (OR 2.4), low household wealth quintile (OR 2.1) and failure to consume IFA for 100+ days (OR 3.7) [50].

4.2 National Programs: India

- Anemia Mukta Bharat (AMB): Life-cycle approach that focuses on six beneficiary groups by providing them with prophylactic iron supplementation,

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deworming, BCC, and non-nutritional cause management [51]

- Multi-sectoral nutrition actions - POSHAN Abhiyaan to decrease the rate of anemia among women in reproductive age group by 3 percentage points per year [52]
- Pradhan Mantri Surakshit Matritva Abhiyan (PMSMA): Specialist ANC, Hemoglobin testing and high risk pregnancy care on 9th of each month [53]
- Topi-Pak: 200 tablets of Fe/Suplax (10mg Fe/2.5mg Zinc) to start from 28th week of gestation and continue bimonthly for 6 Months postpartum [54]
- Despite the programs, the coverage of IFA for 100 or more days remained low at 44.1% of pregnant women (NFHS-5), well below the target coverage rate of 90% [55].

4.3 Odisha State Context

The prevalence of maternal anemia in Odisha (NFHS-5) is 62.6% which is significantly higher than the national average [56,57]. The prevalence in tribal women in tribal districts of the southern and western plateaus (Malkangiri, Nabarangpur, Koraput, Rayagada) is reported to be 72-81% while coastal districts report 48-55% [58]. The maternal mortality ratio in the tribal districts of Odisha is still at 189-220 per 100,000 live births (SRS 2018-2020) [59]. Tribal communities are exposed to compound vulnerabilities such as low dietary diversity, endemic Malaria in the forests, fluoride and arsenic contaminated groundwater and geographically isolated healthcare access [60].

Table 4. Maternal Anaemia Indicators in Odisha (2020-2025 Studies). Hb: hemoglobin; ANC: antenatal care; OR: odds ratio; IFA: iron-folic acid.

| Study | District/Region | Sample Size | Anemia Prevalence | Key Findings |
|------------------------|----------------------|-------------|-------------------|---|
| Singh et al. 2023 [22] | Koraput, Malkangiri | 856 | 71.3% | Iron-B12 co-deficiency 34.2%; fluoride correlated with Hb ($r=-0.38$) |
| Memon et al. 2022 [27] | Keonjhar, Sundargarh | 440 | Baseline 74.2% | Integrated care reduced anemia to 43% by 36 wks vs |

| Study | District/Region | Sample Size | Anemia Prevalence | Key Findings |
|----------------------------|-----------------------|-------------|-------------------|---|
| | | | | 60% standard ANC |
| Nayak et al. 2021 [46] | Rayagada, Nabarangpur | 1,240 | 69.8% | Hookworm 41%; deworming reduced anemia OR by 2.1 |
| Pradhan et al. 2022 [47] | Gajapati, Kandhamal | 678 | 66.4% | Adolescent pregnancy 38.2%; anemia in adolescents 81.2% vs adults 63.1% |
| Mohapatra et al. 2023 [48] | Balangir, Sonepur | 914 | 58.3% | mHealth IFA adherence: 71% vs 39% standard ($p<0.001$) |
| Das et al. 2020 [49] | Khordha, Cuttack | 2,100 | 48.7% | IFA 100-day consumption: 48.2% rural vs 67.3% urban |

5. DISCUSSION

5.1 The reason why Iron Tablets Alone are Insufficient

The most important paradigm change evident in the literature for 2020-2025 is the clear recognition that, although oral iron supplementation is a key intervention for maternal anemia in LMICs, it is not enough to maintain maternal health status. In LMIC countries, at least 56% of maternal anemias are multifactorial (FA) rather than solely caused by iron deficiency (ID) [61]. Oral iron is therapeutically ineffective in chronic inflammation due to its sequestration by hepcidin; folate or B12 deficiency

can be used to explain the failure to perform erythropoiesis even in the event of iron repletion; some genetic hemoglobin disorders are unresponsive to iron and can be exacerbated by inappropriate supplementation [62,63].

Combined, all the findings show that an integrated multicomponent intervention is more effective than supplementing with a single nutrient by 20-35 percentage points in reducing anemia, especially in tribal communities [64,65,66]. This is a clear-cut investment in more complicated programmatic modelling.

5.2 Multifactorial Architecture and Integrated Systems.

This review outlines eight different causal pathways that go beyond iron deficiency, and suggests that this is not the time for routine supplementation. Targeted therapy is possible using point-of-care diagnostics, such as hemoglobin testing, measurement of ferritin with CRP, peripheral smear, and emerging hepcidin measurement [67,68]. The environmental causes, such as arsenic, fluoride and climate change-induced changes in dietary habits, cannot be solved with supplementation alone, and require water safety interventions, climate adaptive agriculture and food system reform [69,70].

The best available evidence points to integrated antenatal care models of screening, etiologic diagnosis, multicomponent supplementation, infection management, dietary counselling, community health worker engagement and digital monitoring. The effectiveness of this model must be demonstrated by the Odisha trial conducted by Menon et al. which reduced anemia by 43% against 19% in the control arm, even in a resource-limited tribal population [71,72,73].

5.3 Health Equity and SDG Implications

Maternal anemia is deeply connected to SDG 2 (Zero Hunger), SDG 3 (Good Health and Well-being) and SDG 5 (Gender Equality). This inequity of the burden on tribal and rural women in India is a health equity emergency and the allocation of resources in a positive direction [74], task shifting to CHWs, and culturally responsive BCC must be implemented. Anemia-related maternal deaths will be the most significant factor in ensuring that the SDG 3 target of reducing the maternal mortality ratio below 70 per 1,000 live births is met by 2030 [75,76].

6. PUBLIC HEALTH IMPLICATIONS

6.1 Policy Level

National governments should revise maternal anemia guidelines to require MMS rather than IFA in areas where multiple micronutrient deficiency is known to be a problem; incorporate hemoglobin disorder testing into the ANC; incorporate environmental health into the maternal anemia plan; and establish clear targets for reducing tribal-mainstream disparities.

6.2 Program Level

The Health Programmes need to be changed to digital platforms for integrated ANC, combining diagnosis, treatment, nutrition, infection management and digital follow-up. Programmatic expansion should be complemented by strengthening the supply chain for MMS, IV iron and PoC diagnostics. To achieve last-mile reach, task-shifting needs to be done to trained community health workers.

6.3 Research Priorities

This includes: evidence of implementation science for MMS scale-up in tribal India; evidence validation of AI-supported hemoglobin screening tools; mechanistic research to explore the association between gut microbiome and iron; climate-health studies to establish associations between changes in food systems and maternal anemia; and economic evaluations of integrated care models in Indian state contexts.

7. LIMITATIONS

This systematic review has identified the following limitations: there may be some evidence not included in the review due to the exclusion of non-English language publications; a formal meta-analysis was not possible for most outcomes due to the high level of heterogeneity in the study designs, populations and outcome measures; there was no systematic search of grey literature; publication bias was not ruled out and there were few peer-reviewed studies available for sub regional conclusions (n=6) for the state of Odisha.

8. FUTURE RESEARCH DIRECTIONS

- Long-term follow-up studies of MMS versus IFA done in Indian tribal communities in head-to-head RCTs (Randomized Control Trials);
- Prospective explorations of gut microbiome-iron absorption axis in pregnancy, and therapeutic role of probiotic co-supplementation.
- To validate the non-invasive screening tools for hemoglobin using Artificial Intelligence (AI) in the Indian context of Primary Health Centre (PHC).
- Implementation science studies on barriers and enablers to the uptake of the integrated ANC model in tribal blocks of Odisha, Jharkhand and Chhattisgarh.
- The study of the molecular mechanisms of hepcidin dys-regulation during pregnancy with inflammation and malaria will be carried out.
- Linking studies between agricultural food system changes and trends of maternal anemia in climate vulnerable LMICs.
- Economic cost of omitting IGA from routine care versus routine care, including the cost of catastrophic health expenditure and intergenerational outcomes.

9. CONCLUSION

This systematic review unequivocally demonstrates that maternal IDA in LMICs is a multifactorial condition, which is rooted in intersecting nutritional, infectious, environmental, genetic and

socioeconomic causal pathways. The era of iron tablets as the predominant solution has passed. This requires a deep-rooted change in the status quo towards more integrated community-based antenatal care systems that involve all the possible causes, use new drugs and information and communication technologies, and are anchored in equity for the most marginalized groups.

The scale of the problem and the potential for change is evident in India and Odisha. India's Anemia Mukht Bharat framework offers an aspirational framework, with the need to ensure greater fidelity of implementation, update protocols with the evidence base and incorporate MMS and IV iron formulations, improve community health worker systems, and maintain investment in tribal and rural health infrastructure. This integrated care model as illustrated by Menon et al. (2022) provides a blueprint that can be replicated in Odisha for tribal communities where the prevalence of anaemia is above 70% and maternal mortality is still high. To achieve SDG 3 Targets by 2030, maternal anemia must be seen as a major contributor to preventable maternal mortality and a coordinated evidence-based multi-sector intervention is required.

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