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Review Article

Maternal micronutrition beyond iron-folic acid: global evidence and Indian perspectives from preconception to lactation: an expert consensus

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ABSTRACT

Maternal undernutrition contributes substantially to adverse pregnancy outcomes in low- and middle-income countries. In India, anemia and deficiencies of vitamin B12, vitamin D, zinc, and folate remain widespread. Although iron-folic acid (IFA) supplementation is central to antenatal care, evidence suggests that multiple micronutrient supplementation (MMS) reduces low birth weight and small-for-gestational-age births compared with IFA alone. This review examined how global MMS evidence can inform context-specific strategies for Indian women. Published evidence on maternal micronutrient deficiencies, MMS, and international guidelines was synthesized with thematic analysis of seven regional advisory board meetings involving >90 Indian clinicians. Findings confirmed a high burden of micronutrient deficiencies and supported MMS over IFA alone. Expert panels favored a phased approach aligned with gestational physiology, beginning with folate, vitamin B12, and pyridoxine during preconception and early pregnancy, followed by iron, calcium, vitamin D, and DHA. Key barriers included gastrointestinal intolerance, complex dosing, and dietary insufficiency. These findings support transitioning from IFA-based supplementation toward a comprehensive, context-adapted strategy spanning preconception through lactation.

Keywords: Multiple micronutrient supplementation, Maternal nutrition, Iron-folic acid supplementation, Preconception to lactation, Expert consensus

INTRODUCTION

Maternal nutrition is a critical determinant of fetal growth, birth outcomes, and long-term offspring health,

influencing placental development, birth weight, neurodevelopment, and metabolic risk.¹

Nearly 2 billion people globally suffer from "hidden hunger": subclinical micronutrient deficiencies arising

from monotonous diets, increased pregnancy demands, infections, and socioeconomic constraints.^{1,2} In India, 50-70% of pregnant women have multiple deficiencies, including iron, vitamin B12, vitamin D, and folate.^{2,3} NFHS-5 shows persistent anemia (52.2% of pregnant women) despite Anemia Mukh Bharat, along with B12 deficiency (37-47% in vegetarians) and vitamin D inadequacy despite sunlight exposure.^{3,4} Micronutrients support cellular proliferation, placental function, immune modulation, and fetal organogenesis, and their deficiencies are linked to low birth weight, small-for-gestational-age births, and impaired neurodevelopment.² These deficiencies coexist and interact, limiting single-nutrient interventions.

IFA supplementation remains the cornerstone of antenatal nutrition and is globally recommended for preventing and treating anemia in pregnancy.⁵ However, persistent anemia and widespread multiple deficiencies suggest IFA alone is insufficient in India.^{3,4} WHO conditionally recommends MMS where IFA supply is adequate, urging contextual pilots.⁶

Translating MMS into routine Indian practice is complex, given heterogeneous diets, high deficiency prevalence, no universal fortification, and distinctive prescribing behaviors such as higher folate dosing and phased supplementation.^{3,4} Real-world antenatal care often follows stepwise, trimester-specific regimens balancing physiological needs, tolerability, pill burden, and adherence, diverging from global MMS recommendations.

Global MMS evidence therefore needs contextualizing within Indian healthcare by integrating epidemiology, practice patterns, behavioral determinants, and policy; identifying barriers and enablers; optimizing formulations (iron content, folate dosing, calcium separation, acceptability); and building evidence and consensus.^{3,6}

This narrative review bridges global MMS evidence with Indian clinical practice to inform context-specific strategies, proposing a pragmatic, phased MMS approach aligned with gestational physiology, patient-centered care, and existing public health programs.

In our view, this coexistence of deficiencies is the central reason IFA-only strategies plateau in India: correcting hemoglobin without correcting the underlying one-carbon and vitamin D pathways treats a symptom rather than the physiological deficit.

LITERATURE RESEARCH

This narrative review synthesizes evidence from systematic searches of PubMed and Scopus (2015-2026), covering randomized controlled trials, meta-analyses, and international and national guidelines (WHO, ICMR, FOGSI). Studies on maternal supplementation during pregnancy and lactation, relevant to India and other low-

and middle-income countries (LMICs), were selected using predefined criteria.

Qualitative insights came from verbatim minutes of seven regional advisory board meetings (26 October-2 December 2025), each with 10-15 key opinion leaders (total n >90) from across India. Data were analyzed using Braun and Clarke's thematic analysis (2006) with inductive coding, focusing on: (i) supplementation practices (phased versus comprehensive), (ii) barriers to implementation (adherence, tolerability), (iii) micronutrient classification (core versus add-on), and (iv) feasibility of moving toward MMS-based strategies.

Published evidence and expert consensus were triangulated.

This review did not follow a formal PRISMA-guided systematic or scoping framework; it uses a structured narrative approach to generate actionable, India-specific insights for clinical practice and policy, with transparent synthesis and interpretation.

As the study involved expert discussions without patient-level data, ethical approval was not required; discussions followed standard professional and confidentiality norms.

BIOLOGICAL RATIONALE FOR MMS

During pregnancy, the body's need for essential micronutrients increases considerably, with requirements for key nutrients rising by around 20-100%. In particular, iron needs increase by approximately 50% to about 27 mg/day, while folate requirements nearly double to around 600 µg/day, along with increased requirements for calcium and vitamin D.⁷ These increased requirements reflect the physiological demands of placental development, fetal growth, and maternal tissue expansion.

Micronutrients function through interdependent pathways, requiring coordinated rather than isolated supplementation. Folate and vitamin B12 synergistically support one-carbon metabolism, DNA synthesis, and methylation essential for fetal development. The MTHFR C677T polymorphism, reported in 10-20% of North Indians, may impair folate metabolism, elevate homocysteine, and increase neural tube defect risk.⁸

Similarly, zinc plays a catalytic role in over 300 enzymatic reactions, including DNA polymerase activity and cellular proliferation, and its deficiency has been associated with impaired fetal growth independent of iron status.⁹ Magnesium contributes to vascular regulation and is involved in vitamin D metabolism, with potential implications in reducing the risk of hypertensive disorders such as preeclampsia.¹⁰

While IFA supplementation effectively addresses hemoglobin levels and anemia, it does not account for the broader spectrum of micronutrients required for optimal

metabolic and developmental processes. In contrast, MMS aims to restore this biological balance by addressing interconnected deficiencies. Evidence from individual participant data meta-analyses suggests modest but consistent improvements in biomarkers such as hemoglobin and inflammatory markers with MMS compared with IFA alone.¹¹

Furthermore, maternal micronutrient demands extend beyond pregnancy into the lactation period, during which nutrients such as vitamin B12 are actively transferred into breast milk, potentially leading to depletion of maternal stores within the first 3-6 months postpartum if not adequately replenished.⁷

This gene–nutrient interaction, in our reading, is a stronger argument for India-specific dosing than for adoption of a fixed international formulation, since a uniform folic acid dose calibrated to Western polymorphism frequencies would systematically under-treat a meaningful subset of Indian women.

Collectively, these biological considerations support the need for a multi-micronutrient approach to maternal supplementation, reflecting the complex and interdependent nature of maternal–fetal nutrient physiology.

GLOBAL EVIDENCE AND GUIDELINE LANDSCAPE FOR ANTENATAL MICRONUTRIENT SUPPLEMENTATION

Micronutrient supplementation has long been part of global antenatal care, traditionally using IFA to prevent anemia. Iron deficiency remains the most common nutritional deficiency worldwide, and IFA reduces maternal anemia, improves hemoglobin, and lowers the risk of low birth weight and preterm birth.^{1,5}

However, emerging evidence over the past two decades has highlighted that maternal undernutrition is not limited to iron deficiency alone but represents a multi-micronutrient deficiency state, particularly in LMICs, where dietary diversity is limited and nutritional demands during pregnancy are substantially increased.^{2,11}

Deficiencies in micronutrients such as vitamins A, B-complex, D, zinc, iodine, and calcium have been independently associated with adverse maternal and neonatal outcomes, including impaired fetal growth, increased risk of preterm birth, and compromised immune function.²

MMS, typically 13-15 vitamins and minerals as in UNIMMAP, has been studied as a comprehensive response to multifactorial maternal malnutrition. Randomized trials and meta-analyses, including a Cochrane review of over 140,000 women, show MMS significantly reduces low birth weight and small-for-gestational-age births versus

IFA alone, with modest effects on preterm birth and limited impact on mortality.¹²

Further analyses suggest that the benefits of MMS are not uniform across populations but are more pronounced among nutritionally vulnerable groups, including anaemic and underweight women, and when supplementation is initiated early in pregnancy and maintained with high adherence.¹¹

These findings underscore the importance of contextual and population-specific approaches to MMS implementation.

Reflecting emerging evidence, WHO's 2020 recommendations conditionally support MMS in populations with high micronutrient deficiency, with rigorous monitoring and evaluation.⁶ This marked a shift from earlier guidance that did not routinely recommend MMS, recognizing its potential benefits and need for context-specific adaptation.

Similarly, the International Federation of Gynecology and Obstetrics (FIGO) now recommends considering MMS over IFA supplementation alone for pregnant women in low- and middle-income countries and populations with a high prevalence of nutritional deficiencies.⁵

This recommendation reflects growing evidence that comprehensive supplementation improves maternal nutritional status and reduces low birth weight and small-for-gestational-age births. FIGO's updated guidance reinforces the consensus that MMS better addresses undernutrition where multiple deficiencies coexist.

Despite growing evidence supporting MMS, uncertainties remain about universal implementation: variable baseline nutritional status, differing dietary patterns, potential nutrient interactions, and challenges in adherence, cost, and delivery. Global recommendations therefore favor contextual adaptation over uniform adoption.

Recent expert discussions and policies, particularly in LMICs, stress developing country-specific MMS formulations that reflect local diets, prevalent deficiencies, and recommended dietary allowances rather than adopting standardized ones such as UNIMMAP.¹³

Taken together, global evidence supports MMS for improving birth outcomes, but its implementation must account for local epidemiology, clinical practices, and health-system capabilities.

This highlights the need to translate global recommendations into country-specific contexts, particularly India, where nutritional deficiencies are widespread and clinical practices differ from trial settings (Table 1).

Table 1: Global evidence and guideline landscape for antenatal micronutrient supplementation.

Domain	Key source	Key findings	Implication for practice
Biological basis	Gernand et al 2016 ²	Multiple micronutrients regulate placental function, fetal growth, and immune pathways	Maternal nutrition is multi-dimensional; single-nutrient strategies are insufficient
Global burden	Black et al 2013 ¹	High burden of maternal undernutrition contributing to adverse neonatal outcomes	Need for comprehensive nutritional interventions
MMS efficacy	Keats et al 2019 ¹² (Cochrane)	MMS reduces low birth weight (RR ~0.85-0.88) and SGA births	MMS provides broader benefits beyond IFA
MMS subgroup benefit	Smith et al 2017 ¹¹ (Lancet)	Greater benefit in anaemic, underweight women and early initiation	Targeted and phased MMS strategies may be more effective
WHO guideline	WHO 2020 ⁶	Conditional recommendation for MMS in high-burden settings	Context-specific implementation required
FIGO guidance	FIGO 2025 ⁵	Recommends considering MMS over IFA alone in low- and middle-income countries and populations with a high prevalence of micronutrient deficiencies	Supports broader maternal micronutrient supplementation strategies and strengthens the rationale for context-specific MMS implementation in high-burden settings.
Policy evolution	Mukherjee et al 2024 ¹³ (ICMR) ¹⁵	Need for country-specific MMS formulation	Adaptation required for local context

Global MMS policy has evolved with growing evidence of benefits in populations with high maternal micronutrient deficiency. WHO's 2020 guidance conditionally recommends MMS in high-deficiency settings, reporting an approximately 12% reduction in low birth weight versus IFA alone and emphasizing context-specific implementation and evaluation.⁶

Similarly, the United Nations Children's Fund (UNICEF) supports MMS as a programmatic intervention in LMICs, particularly where multiple micronutrient deficiencies coexist and dietary diversity is limited, recognizing its potential as a scalable and cost-effective enhancement to existing antenatal nutrition programs.¹⁴

Recent guidance from the International FIGO further acknowledges the broader role of micronutrients in improving maternal and neonatal outcomes. While continuing to support iron and folic acid as foundational components of antenatal care, FIGO highlights emerging evidence supporting MMS in reducing risks of adverse outcomes such as low birth weight and preterm birth, particularly in high-burden settings.⁵ Collectively, these global positions indicate a transition toward more comprehensive micronutrient strategies, while consistently emphasizing the importance of contextual adaptation, feasibility, and integration within existing health systems, rather than universal replacement of IFA-based approaches (Table 2).

Table 2: Global guideline perspectives on MMS.

Organization	Position on MMS	Key Evidence/Justification	Implementation Perspective
WHO (2020)⁶	Conditional recommendation for MMS in high-deficiency populations	~12% reduction in low-birth-weight vs IFA	Context-specific implementation with monitoring and evaluation
UNICEF¹⁴	Supports MMS in LMIC programs	Addresses coexisting micronutrient deficiencies; improves fetal growth and neonatal outcomes	Scalable, cost-effective integration into maternal health programs
FIGO (2025)⁵	Recognizes role of MMS alongside IFA	Evidence for reduction in low birth weight and preterm birth	Encourages consideration in high-burden settings; not full replacement of IFA

The United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) formulation represents the most widely studied and standardized composition for MMS in pregnancy. Developed through

collaboration between global agencies including the WHO and UNICEF, UNIMMAP comprises 15 essential vitamins and minerals designed to address common micronutrient deficiencies in low-and middle-income settings.^{6,14}

Although UNIMMAP provides a global reference formulation, its applicability varies with dietary patterns, baseline deficiencies, and recommended dietary allowances. Thus, context-specific MMS formulations are particularly relevant in India, where deficiencies and clinical practices differ from trial settings.

Population-specific evidence is also emerging. A BMGF-funded, ICMR-led six-site randomized controlled trial (2023-2026) is evaluating an India-specific MMS formulation, reflecting a shift toward locally relevant clinical evidence.³⁹

INDIAN NUTRITIONAL EPIDEMIOLOGY AND POLICY CONTEXT

India has a complex nutritional profile, with persistent anemia and multiple micronutrient deficiencies despite national supplementation programs. NFHS-5 (2019-21) found that more than half of women of reproductive age were anaemic, highlighting ongoing nutritional challenges despite widespread IFA supplementation.^{4,7}

Beyond iron deficiency, emerging evidence highlights a substantial burden of coexisting micronutrient deficiencies among Indian women. A systematic review and meta-analysis reported high prevalence rates of deficiencies in vitamin B12 (~50%), vitamin D (~60%), and folate (~30-40%), underscoring the multi-dimensional nature of maternal undernutrition in India.³ These findings align with broader global evidence suggesting that micronutrient deficiencies rarely occur in isolation and often interact to influence maternal and fetal outcomes.

NFHS-5 documents 52.2% anemia in pregnancy (rural 54%, urban 50%), stagnant from NFHS-4 despite AMB's 100 mg iron daily.⁴ Complementary deficiencies persist: vitamin B12 <150 pmol/L in 47% vegetarians, folate insufficiency 41%, vitamin D <50 nmol/L in 70-90% despite sunlight.³

In the absence of mandatory folate fortification (unlike the United States mandate introduced in 1998), combined with genetic factors such as MTHFR polymorphisms and the impact of urbanization on reducing traditional dietary folate intake, the risk of folate insufficiency is likely to be increased in the Indian population.

Dietary patterns in India further contribute to this burden. Predominantly cereal-based diets with limited dietary diversity, combined with socio-economic constraints, cultural practices, and limited intake of animal-source foods, contribute to deficiencies in key micronutrients such as vitamin B12, iron, and zinc.²

In addition, the absence of widespread food fortification strategies, particularly for folate, differentiates India from several high-income settings and necessitates greater reliance on supplementation.

Recent national and regional studies further highlight the substantial and overlapping burden of micronutrient deficiencies among pregnant women in India, extending beyond iron deficiency alone. As summarized in Table 3, anemia remains common, affecting approximately 45-54% of pregnant women, with some studies reporting prevalence as high as 70% despite routine IFA supplementation.⁴ Deficiencies in other essential micronutrients are also widespread, including vitamin B12 (32-70%), vitamin D (85-93%), and zinc (19-50%), while inadequate calcium intake has been reported in up to 60-66% of women. These findings reflect both insufficient dietary intake and the increased nutritional demands associated with pregnancy.^{3,15}

Folate deficiency remains an important concern, with studies indicating 24-29% deficiency and a larger proportion of women having insufficient levels for optimal neural tube defect prevention, particularly in the absence of mandatory food fortification.³ Similarly, emerging evidence highlights deficiencies in micronutrients such as magnesium and copper, which have been associated with adverse outcomes including preterm birth and fetal growth restriction, although data remain relatively limited.

Global MMS formulations may not directly translate to India due to higher folate dosing practices, folate-metabolism polymorphisms, limited biochemical screening, and established clinical practices. Pill burden, iron-related gastrointestinal intolerance, cost, and adherence further influence real-world effectiveness.

Recent Indian expert and policy discussions therefore emphasize context-specific MMS formulations reflecting local dietary patterns, recommended dietary allowances, and prevalent deficiencies rather than direct adoption of standardized formulations such as UNIMMAP.¹³ This evolving perspective highlights a transition toward more integrated nutritional strategies while maintaining alignment with existing public health programs.

These findings support MMS in India but highlight the need to adapt implementation to local clinical practices, patient behavior, and health-system realities, bridging global evidence with real-world feasibility through India-specific supplementation models.

Notably, iodine status appears relatively adequate at the population level due to successful salt iodization programs, with over 90% household coverage of iodized salt, highlighting the impact of targeted public health interventions.⁴

Collectively, these findings underscore that maternal undernutrition in India is multi-micronutrient in nature, with several deficiencies coexisting and interacting, thereby strengthening the rationale for more comprehensive supplementation strategies beyond single-nutrient approaches.

Table 3: Micronutrient deficiency status among Indian pregnant women based on national and regional studies.

Micronutrients	Deficiency range / findings	Study period/ publication range	References
Iron	45.7% in urban and 54.3% in rural pregnant women; anemia prevalence up to 70% despite routine IFA use	2019-2024	Locks et al 2024, Verma et al 2024 ^{16,17}
Folate	24-29% deficiency; up to 78% insufficiency for neural tube defect prevention	2019-2024	Bhide et al 2019, Das et al 2024 ^{18,19}
Vitamin B12	32-70% deficiency; marginal deficiency in an additional 23-30% of women	2024-2025	Das et al 2024, Behere et al 2021 ^{19,20}
Vitamin B6	Up to 29% prevalence; associated with anemia and glucose intolerance in pregnancy	2007-2020 (limited Indian data)	Sivaprasad et al 2019 ²¹
Zinc	19-50% deficiency; associated with preterm birth and fetal growth restriction	2024-2025	Sairoz et al 2024, Gohari et al 2023 ^{22,23}
Copper	10-22% deficiency; low intake associated with spontaneous preterm birth in Asian populations	2020-2025	Gohari H et al 2023 ²³
Calcium	60-66% intake below RDA (<1000 mg/day); linked to hypertensive disorders and preeclampsia	2021-2025	Harinarayan et al 2021 ²⁴
Vitamin D	85-93% deficiency; 35-68% severely deficient (<20 ng/mL serum 25(OH)D); prevalent despite sunlight exposure	2019-2025	Sharma et al 2016, Yadav et al 2023, Dwarkanath et al, 2019 ²⁵⁻²⁷
Magnesium	4.6-44% deficiency; associated with preterm labor, low birth weight, and preeclampsia risk	2023-2025	Pathak et al, 2003, Boda et al, 2025 ^{28,29}
Iodine	Population-level adequacy due to iodized salt; ~93% households covered	2019-2021	Jauhari et al 2020 ³⁰

Adapted from NFHS-5, Venkatesh et al and recent Indian studies.

INDIAN GUIDELINE ON IFA SUPPLEMENTATION

IFA supplementation continues to be a key component of antenatal care in India. National guidelines from the Ministry of Health and Family Welfare, ICMR, and FOGSI recommend daily supplementation with approximately 60-100 mg of elemental iron and 400-500 µg of folic acid during pregnancy. Supplementation is generally started in the second trimester and continued through the postpartum period.^{4,14,31} However, clinical practice in India often diverges from these baseline recommendations, with many obstetricians prescribing higher doses of folic acid, particularly in early pregnancy. This divergence is driven by a combination of epidemiological burden, genetic factors, and pragmatic clinical considerations.

India continues to face a high prevalence of folate insufficiency, with studies reporting 17.5-29.4% deficiency among pregnant women and up to 78% insufficiency for optimal neural tube defect (NTD) prevention, indicating inadequate baseline folate reserves in a significant proportion of women.³ This concern is compounded by the absence of mandatory folate fortification policies and by dietary transitions associated with urbanization, which reduce intake of folate-rich foods. Additionally, genetic polymorphisms such as MTHFR variants (e.g., C677T and A1298C), which are

relatively prevalent in Indian populations, may impair folate metabolism and increase physiological requirements, further contributing to deficiency risk.³²

Indian clinicians may use higher folic acid doses (1.5-5 mg/day) or alternatives such as 5-MTHF or folinic acid, particularly during the periconceptional and early pregnancy periods. This approach aims to rapidly replenish folate stores and reduce NTD risk, although such dosing is not consistently specified in formal guidelines and reflects clinical considerations related to nutritional and genetic factors.

Emerging evidence also highlights the interaction between folate and vitamin B12. Indian studies report high maternal B12 deficiency and suggest that low B12, particularly with high folate status, may be associated with increased insulin resistance and gestational diabetes risk.³³ Recent evidence further indicates that while standard periconceptional folic acid supplementation remains essential for neural tube defect prevention, prolonged use of high-dose folic acid may warrant careful consideration, especially in populations with prevalent vitamin B12 deficiency.³⁴ These findings support a more individualized approach to maternal micronutrient supplementation that emphasizes adequate vitamin B12 status alongside folate optimization, particularly in the Indian setting where vitamin B12 deficiency remains common.^{33,35}

Thus, while global recommendations often advocate lower minimum doses, Indian clinical practice represents a context-specific adaptation that integrates epidemiological evidence, genetic considerations, and preventive intent to optimize maternal and fetal outcomes.^{5,6}

CALCIUM AND VITAMIN D3 SUPPLEMENT AS PER INDIAN GUIDELINE

Calcium and vitamin D supplementation constitute an essential component of antenatal care in India, with national and professional guidelines recommending 1-1.5 g elemental calcium daily, along with vitamin D supplementation (400-600 IU/day), initiated from the second trimester and continued into the postpartum period to reduce the risk of hypertensive disorders such as preeclampsia.^{14,31,36} Importantly, these guidelines emphasize separate administration of calcium and iron-folic acid (IFA) supplements, with a minimum gap of 2 hours to avoid interference with iron absorption, a recommendation reinforced through national programs such as Anemia Mukht Bharat, which also targets adequate coverage through provision of 180 IFA and 360 calcium tablets during pregnancy and lactation.^{36,37}

Despite standardized recommendations, real-world implementation requires careful sequencing, adherence strategies, and counseling to balance pill burden and nutrient absorption. Concerns about higher-dose folic acid and autism spectrum disorder (ASD) have not been supported consistently.

Large-scale analyses, including a US Preventive Services Task Force review, found no consistent association between recommended folic acid supplementation and adverse maternal or fetal outcomes, supporting its continued preconceptional use for neural tube defect prevention.³⁸

REAL-WORLD CLINICAL PRACTICE IN INDIA: INSIGHTS FROM EXPERT ADVISORY BOARDS

Expert advisory panels across India showed strong consensus for sequential, trimester-specific supplementation rather than a single comprehensive formulation. Approximately 95-98% of clinicians initiated folic acid in the first trimester, commonly using ~5 mg preconception and 1-1.5 mg during early pregnancy, with vitamin B12 and pyridoxine as adjuncts.

During the second trimester, supplementation typically expanded to iron (~100 mg elemental), calcium (1-1.5 g/day), DHA (~200 mg), and vitamin D (1000-2000 IU/day), reflecting guidelines and clinical practice. During lactation, this core regimen was generally continued, with magnesium and trace elements added selectively according to symptoms or risk.

Clinical practices showed near-uniformity across regions, with experts noting converging nutritional patterns and anemia prevalence. Less than 5% routinely used standardized formulations such as UNIMMAP, while ~90% favored phased supplementation, citing tolerability, pill burden, and familiarity. Separating iron and calcium by ≥ 2 hours was widely endorsed.

Higher folate dosing was consistently reported across Indian advisory discussions, attributed to MTHFR polymorphisms, lack of mandatory folate fortification, dietary insufficiency, and limited biochemical monitoring. Unlike global recommendations of 400-800 $\mu\text{g/day}$, Indian clinicians commonly prescribe ~5 mg preconception and 1-1.5 mg during pregnancy, reflecting a precautionary, context-adapted approach.

PATIENT-CENTRIC DETERMINANTS OF ADHERENCE TO ANTENATAL SUPPLEMENTATION

Adherence is a critical determinant of antenatal supplementation, cited as a key barrier by about 90% of clinicians. Gastrointestinal intolerance to iron, especially ferrous salts, reportedly causes discontinuation in about 20-30% of patients, undermining anemia prevention. Ferric pyrophosphate iron, a patented micronized, micro-encapsulated form, is designed to improve absorption and reduce gastrointestinal side effects.

A variety of oral iron formulations are used in clinical practice in India, including ferrous sulfate, ferrous fumarate, ferrous gluconate, ferrous ascorbate, and newer formulations such as ferrous bisglycinate and ferric salts. Among these, ferrous salts remain the most widely prescribed due to availability and cost-effectiveness, although gastrointestinal intolerance-manifesting as nausea, constipation, or metallic taste-has been reported in up to 20-30% of patients, contributing to reduced adherence.

BRIDGING THE GAP BETWEEN GLOBAL EVIDENCE AND INDIAN CLINICAL PRACTICE

Despite robust global evidence for MMS, routine uptake in India remains limited, reflecting clinical, behavioral, and system-level factors beyond evidence alone.

A key gap

trial-tested MMS regimens such as UNIMMAP are fixed combinations given uniformly throughout pregnancy, whereas Indian clinicians typically use trimester-specific, stepwise supplementation tailored to physiological needs, tolerability, and adherence.

Patient-centric challenges, including gastrointestinal intolerance to iron, pill burden, and complex dosing, undermine adherence, so clinicians often favor simplified, flexible regimens, particularly in low-risk pregnancies.

System and policy factors add to the gap

Continued emphasis on IFA-based national programs, no standardized MMS formulations for Indian populations, and no widespread food fortification. These limit the scalability of global MMS recommendations.

Indian women's heterogeneous profile, with coexisting iron, vitamin B12, vitamin D, and other deficiencies, calls for context-specific adaptation rather than direct transplantation of global models.

Clinicians are not resistant to MMS per se, but to rigid formulations misaligned with real-world practice and patient behavior. The gap is thus implementation-driven, not scientific, reflecting differences in workflows, patient expectations, and system constraints.

Bridging it requires pragmatic, flexible frameworks that combine MMS strengths with Indian clinical realities, enabling a gradual, context-sensitive transition toward comprehensive nutrition.

DISCUSSION

Implementation science perspective

Although trials show MMS is efficacious, real-world adherence in LMICs is suboptimal (50-70%) without structured behavioral support. In India, supply constraints, cost (₹10-20 per course in pilots), and low awareness call for well-designed demand-generation pilots. ICMR modeling finds MMS cost-effective at about \$62 per disability-adjusted life year (DALY) averted. Reminder systems and peer counseling raise adherence to the 70-90%.¹²

Modular supplementation lowers dropout by about 25% compared with blanket regimens. ICMR projects program costs of ₹150-300 per course, while preventing low birth weight can avert substantial downstream costs, including neonatal intensive care at about ₹50,000 per neonate. Planned pilots aim for at least 70% adherence through ASHA-led community engagement before scale-up.

However, the higher iron doses recommended by ICMR for national anemia-control programs, together with the preference for higher folate in practice, may make a single MMS formulation pharmaceutically unfeasible. An India-

specific, modified MMS approach may therefore be most appropriate.

Together with the dropout data, this suggests the economic case for MMS in India is strongest for a phased delivery model rather than a single fixed-dose product, as cost-effectiveness and adherence move together.

Proposed India-adapted MMS framework

Global evidence and Indian clinical practice support a context-adapted MMS approach rather than direct adoption of standardized formulations. Although UNIMMAP provides a validated foundation, its fixed-dose design does not fully align with India's phased, patient-centric prescribing patterns.^{6,12,30}

Accordingly, we propose a pragmatic, phased MMS framework tailored to the Indian context, integrating the strengths of multi-micronutrient strategies with real-world clinical practices. This model is designed to optimize maternal and fetal outcomes while maintaining adherence, tolerability, and feasibility within existing healthcare systems.⁴

Conceptual framework

The proposed model is based on three key principles:

Physiological alignment

Nutrient requirements vary across gestation and should be addressed sequentially.²

Patient-centricity

Regimens should minimize pill burden and maximize tolerability.³⁰

Contextual flexibility

Supplementation should reflect local deficiencies, dietary patterns, and clinical practices.^{3,12}

Phased supplementation model

The framework adopts a trimester-specific supplementation strategy, reflecting both biological needs and real-world prescribing patterns (Table 4).

Table 4: Proposed phased MMS model for India.

Phases	Clinical stage	Core nutrients	Add-on/ conditional nutrients	Rationale
Phase 1	Preconception /1 st trimester	Folic acid (1-5 mg), Vitamin B12, pyridoxine, low dose of iron in the first trimester to support anemia later in the pregnancy	±Iodine, ±vitamin D	Neural tube development, correction of baseline deficiencies (WHO, Venkatesh et al ^{3,6})

Continued.

Phases	Clinical stage	Core nutrients	Add-on/ conditional nutrients	Rationale
Phase 2	2 nd trimester	Iron (60-100 mg), calcium, vitamin D, folic acid, vitamin B12, pyridoxine	DHA (~200 mg), Zinc	Rapid fetal growth, anemia prevention, bone health (FOGSI, Keats et al ^{12,31})
Phase 3	3 rd trimester	Continue iron, calcium, vitamin D	Magnesium, DHA, ±zinc	Increased fetal demand, prevention of preeclampsia and preterm birth (Gernand et al ²)
Phase 4	Lactation	Iron, calcium, vitamin D	DHA, Magnesium	Maternal recovery, nutrient transfer through breast milk (WHO ⁶)

Core vs add-on nutrient strategy

Successful implementation of this framework requires attention to clinical, behavioral, and system-level factors, including:

Adherence optimization

Simplified regimens and improved tolerability.

Counseling strategies

Patient education and behavioral reinforcement (advisory data).

Dosing coordination

Iron and calcium are both recommended in the second and third trimesters, but calcium inhibits iron absorption. They can therefore be part of the same supplementation strategy yet taken at separate times of day to optimize bioavailability and adherence, consistent with FOGSI recommendations.³⁰

Cost and accessibility

Alignment with national programs.³⁴

Gradual integration

Transition from IFA to broader strategies.^{6,12}

Synthesis and implications

The proposed framework represents a hybrid model that bridges global evidence with local clinical realities, enabling a transition from single-nutrient supplementation toward more comprehensive strategies without compromising adherence or feasibility.^{2,12}

Importantly, this approach does not seek to replace existing IFA-based programs abruptly but rather to evolve them into a more integrated, context-sensitive nutritional strategy, aligned with both patient needs and healthcare system capabilities.^{6,12,30}

Implications for policy, practice, and research

The proposed India-adapted MMS framework has important implications for policy development, clinical practice, and future research, particularly in the context of evolving national nutrition strategies. While global evidence supports the benefits of MMS, its translation into large-scale programs in India requires phased, evidence-informed integration within existing public health initiatives, such as the Anemia Mukh Bharat (AMB) program.

Policy implications

A key policy priority is gradual transition from IFA-based programs toward comprehensive micronutrient strategies. ICMR-led pilot initiatives, including Maharashtra studies (2025-2026), can assess feasibility, adherence, and clinical outcomes of adapted MMS approaches before wider implementation.¹³

Such phased integration allows policymakers to assess real-world effectiveness, supply chain feasibility, cost implications, and acceptability among both providers and patients, thereby reducing the risks associated with premature national adoption. Importantly, alignment with existing AMB infrastructure can facilitate smoother implementation and minimize disruption to established supplementation programs.⁴

Clinical practice implications

The findings of this review highlight the need for greater alignment between clinical guidelines and real-world practice, particularly through structured communication and capacity-building initiatives. Professional bodies such as FOGSI and ICMR can play a pivotal role in developing standardized clinical guidance, patient education materials, and training programs for healthcare providers, emphasizing the rationale for phased, patient-centric supplementation strategies.³⁰

Stepwise supplementation frameworks may improve adherence and outcomes by aligning recommendations with patient preferences and tolerability. Patient leaflets,

simplified dosing algorithms, and digital adherence tools may further support compliance in routine antenatal care.

Research implications

MMS efficacy is supported, but India-specific data on implementation and long-term outcomes are limited. Advisory panel consensus (>90%) favored real-world evidence and meta-analyses over large new randomized trials, deemed less feasible due to cost, logistics, and ethics.

Future research priorities

Implementation

Adherence, tolerability, and effectiveness of phased MMS.

Health economics

Cost-effectiveness of IFA-versus MMS-based approaches.

Biomarker-guided strategies

Ferritin-guided or individualized iron dosing to optimize benefit and limit adverse effects.

Long-term outcomes

Maternal micronutrient status and offspring neurodevelopment, growth, and cardiometabolic health.

Strategic integration

Coordination among policymakers, professional societies, and clinicians is essential to ensure MMS strategies are scientifically sound, feasible, and culturally appropriate. India's transition toward comprehensive maternal nutrition should follow a stepwise, evidence-based approach integrating global recommendations with local evidence, clinical experience, and health-system realities.

Limitations

This narrative review has several limitations. Its structured narrative approach, rather than a systematic or scoping framework, may introduce selection bias and limits reproducibility despite efforts to include high-quality sources. Expert advisory input may also introduce interpretative bias and does not fully represent India's regional diversity; findings therefore reflect qualitative insights rather than generalizable epidemiological data.

The proposed India-adapted MMS framework is based on existing evidence and expert consensus and requires prospective validation of clinical outcomes, adherence, and cost-effectiveness. Heterogeneity across studies may limit comparability, while India-specific evidence for nutrients such as magnesium and selenium remains

limited. Publication bias and uneven regional data may further affect interpretation.

CONCLUSION

Maternal undernutrition in India remains a multidimensional challenge, with high anemia prevalence and coexisting folate, vitamin B12, vitamin D, and zinc deficiencies that IFA alone cannot address. Although global evidence supports MMS, Indian practice already reflects a phased, patient-centric approach shaped by tolerability and health-system realities.

Drawing on narrative synthesis and input from >90 Indian clinicians, this review proposes a trimester-specific framework: folate, vitamin B12, and pyridoxine from preconception through the first trimester, followed by iron, calcium, vitamin D, and DHA through lactation. This scalable model can inform programs such as Anemia Mukh Bharat and guide implementation, cost-effectiveness, and long-term outcome research, shifting the focus from whether to adopt MMS to how to operationalize it.

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