Micronutrient deficiency during pregnancy leads to adverse maternal and child outcomes. Multiple micronutrient deficiencies are common among pregnant women from low and middle income countries like India. The available scientific evidence on use of multiple micronutrient supplementation (MMS) during pregnancy shows overall improved birth outcomes, reduction in small for gestational age and low birth weight as compared to iron and folic acid supplementation (IFA). There is no increased risk of still births and early neonatal mortality due to MMS. Based on the findings of future field trials in India, MMS during pregnancy may be considered as an option for IFA. The programmatic issues including cost of shift from IFA to MMS should be factored in when introducing MMS.

Background

India has achieved impressive improvements in reduction of maternal and infant mortality. The strong leadership by Ministry of Health and Family Welfare (MoHFW), Government of India (GoI), with collaborative efforts from the state governments and non-governmental organizations has helped in reducing maternal mortality ratio (MMR) from 254 (in 2005) to 130 (in 2016) per 100,000 live births and infant mortality rate from 58 (in 2005) to 33 (in 2017). MoHFW, GoI has implemented number of programs and schemes to improve the health and nutrition of both mother and children. In March 2018, Prime Minister’s Overarching Scheme for Holistic Nourishment (POSHAN) Abhiyaan was launched to improve the nutrition outcomes of children, adolescents, pregnant and lactating women.

The magnitude of multiple micronutrient deficiencies among pregnant women from low middle income countries is high.
Pregnant women from low and middle income countries (LMIC) are at increased risk of micronutrient deficiency (Figure 1). The inadequate intake of nutritious food among the women of reproductive age group, issues with availability and consumption of iron folic acid tablets and existing infections are the major reasons for micronutrient deficiency. Micronutrient deficiency during pregnancy can affect the growth of the fetus irreversibly with increased risk for neonatal and infant mortality and morbidity. Global estimates report that one third of the pregnant women are anemic, 15% are vitamin A deficient, 17 to 40% are iodine deficient. The magnitude of micronutrient deficiency among pregnant women from LMICs is high. In India the National Surveys and individual studies have reported the deficiencies of iron (anemia – 50%), Zinc (73.5%), magnesium (43.6%), folic acid (26.3%) and iodine (6.5-13.5%) in pregnant women. The National Nutrition Monitoring Bureau survey in 2011-2012 showed that most pregnant woman in India consumed less than half of their increased daily needs of iron (78%), and vitamins A (83.2%), B2 (52.5%), C (50.6%), folate (72%) (Figure 2). Hence, to address the huge burden of micronutrient deficiencies during pregnancy, interventions such as dietary diversity, food fortification and multiple micronutrient supplementation (MMS) are the possible options. MMS might be relatively easy and feasible to implement as system for delivering IFA and calcium supplementation during pregnancy already exist.
Most of the studies had used more than three micronutrients in MMS. To standardize the MMS formulation internationally, UNICEF developed UNIMMAP or United Nations Multiple Micronutrient Antenatal Preparation in collaboration with WHO and the United Nations University. UNIMMAP, which contains 15 micronutrients, was used by most of the studies with or without minor modifications in the content of the UNIMMAP (Table 1).

Meta-analysis of individual patient data (n=112,953) from 14 LMIC, comparing the effect of MMS vs IFA reported that MMS resulted in improved birth outcomes—reduction in very low birth weight by 21%, low birthweight by 14%, early preterm by 13%, preterm by 7%, and small-for-gestational-age births by 6% compared to IFA alone. MMS resulted in improved survival of female neonates and infants. Women initiating MMS before 20 weeks of gestation had greater reductions (11%) in the risk of preterm birth. MMS significantly reduced the risk of infant mortality even among the deliveries without access to skilled birth attendant (18%). Multiple micronutrient supplements did not significantly increase the risk of stillbirth or neonatal, 6-month, or infant mortality; neither overall nor in any of the 26 examined subgroups. MMS with iron content less than 30mg of elemental iron was associated with increased risk of stillbirth and early neonatal mortality.

**Figure 2.** Micronutrient consumptions among pregnant from India – Proportion of pregnant women consuming less than 50% of Recommended Dietary Allowance

**Formulation of multiple micronutrient supplements**

UNICEF developed United Nations Multiple Micronutrient Antenatal Preparation (UNIMMAP) which contains 15 micronutrients.
Table 1. Composition of United Nations Multiple Micronutrient Antenatal Preparation (UNIMMAP):

<table>
<thead>
<tr>
<th>S.no</th>
<th>Nutrient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vitamin A</td>
<td>800 µg</td>
</tr>
<tr>
<td>2</td>
<td>Vitamin B1</td>
<td>1.4 mg</td>
</tr>
<tr>
<td>3</td>
<td>Vitamin B2</td>
<td>1.4 mg</td>
</tr>
<tr>
<td>4</td>
<td>Niacin</td>
<td>18 mg</td>
</tr>
<tr>
<td>5</td>
<td>Vitamin B6</td>
<td>1.9 mg</td>
</tr>
<tr>
<td>6</td>
<td>Folic acid</td>
<td>400 µg</td>
</tr>
<tr>
<td>7</td>
<td>Vitamin B12</td>
<td>2.6 µg</td>
</tr>
<tr>
<td>8</td>
<td>Vitamin C</td>
<td>70 mg</td>
</tr>
<tr>
<td>9</td>
<td>Vitamin D</td>
<td>5 µg</td>
</tr>
<tr>
<td>10</td>
<td>Vitamin E</td>
<td>10 mg</td>
</tr>
<tr>
<td>11</td>
<td>Copper</td>
<td>2 mg</td>
</tr>
<tr>
<td>12</td>
<td>Iodine</td>
<td>150 µg</td>
</tr>
<tr>
<td>13</td>
<td>Iron</td>
<td>30 mg</td>
</tr>
<tr>
<td>14</td>
<td>Selenium</td>
<td>65 µg</td>
</tr>
<tr>
<td>15</td>
<td>Zinc</td>
<td>15 mg</td>
</tr>
</tbody>
</table>

MMS resulted in improved birth outcomes - reduction in very low birth weight by 21%, low birthweight by 14%, early preterm by 13%, preterm by 7%, and small-for-gestational-age births by 6% compared to IFA alone.

Available literature on impact of use MMS in pregnancy on birth outcomes:

A meta-analysis of trials done on daily iron supplementation in pregnant women reported that every 10 mg increase in the elemental iron linearly decreased the risk for low birth weight by 3% (95%CI: 2 to 5). This effect was observed up to 66 mg of total elemental iron dose.⁸

Cochrane review updated in 2019, included 20 trials of MMS compared to IFA or iron alone or placebo reported that MMS resulted in significant reduction in small-for-gestational age (RR 0.92, 95% CI 0.88 to 0.97; 17 trials), low birthweight (RR 0.88, 95% CI 0.85 to 0.91; 18 trials) and very preterm births (RR 0.81, 95% CI 0.71 to 0.93; 4 trials). There was no significant difference in preterm birth, neonatal mortality, perinatal mortality, still birth, congenital anomalies, maternal anemia, maternal mortality, miscarriage or caesarean section between MMS or iron (with or without folic acid) groups.⁹
WHO antenatal guidelines 2016 state that “There is some evidence of additional benefit of MMS containing 13–15 different micronutrients (including iron and folic acid) over iron and folic acid supplements alone, but there is also some evidence of risk, and some important gaps in the evidence.”

WHO recommends that “Though overall there was insufficient evidence to warrant a recommendation, the policymakers in populations with a high prevalence of micronutrient deficiencies might consider the benefits of MMS on maternal health to outweigh the disadvantages, and may choose to give MMS that include iron and folic acid”.

WHO’s recommendation on MMS in antenatal period is based on the Cochrane systematic review (MMS Vs Iron with or without folic acid) published in 2015. The review reported that MMS resulted in significant reduction in low birth weight (12%) and small for gestation age (8%) (Table 2). There was no significantly different effect of MMS on maternal mortality, preterm birth, still birth, neonatal or perinatal mortality over IFA. In sub group analysis, the review reported increased risk of neonatal mortality (in MMS group) in settings where home deliveries without supervision of skilled birth attendant were common. Such observations were not observed in deliveries at health facilities or when conducted by skilled birth attendant. Hence the author recommended use of MMS primarily in settings where skilled maternal care and facility-based births can be provided. There was no significant difference in the maternal anemia (in 3rd trimester) between the MMS and IFA groups. There was also no significant difference in outcome based on different iron content or time of initiation of MMS between the groups.

Evidence from India

Gupta et al (2007) assessed the effect MMS (29 vitamins and minerals) compared to placebo among undernourished pregnant women (BMI < 18.5 and/or a hemoglobin level of 7 to 9 g/dL). The birth weight of newborn in MMS group was 98 g (95% CI: −16 to 213 g) more compared to placebo group. Low birth weight was 43.1% in placebo group and 16.2% in MMS group. Early neonatal morbidity was 28.0% in placebo group compared to 14.8% in MMS group. The authors concluded that administration of MMS to undernourished pregnant women may reduce the prevalence of low birth weight and early neonatal morbidity.
Cost-effectiveness of MMS

Svefors et al reported that transition from 60 mg elemental iron (IFA tablet) at 14 weeks to early MMS at 9 weeks, one Disability-Adjusted Life Year (DALY) was saved at a cost of US$24. Shaheen et al reported use of MMS averted one infant death at a cost of US$ 797 to 907 and one additional life year was saved at US$ 27 to 30.

Kashi et al reported the cost-effectiveness of MMS in 3 high burden Asian countries based on modelling. MMS would avert 4,391 (Pakistan), 5,769 (India), and 8,578 (Bangladesh) more DALYs than IFA per 100,000 pregnancies. The Incremental Cost Effectiveness Ratio of transitioning from IFA to MMS was USD 41.5 in Pakistan, USD 31.6 in India, and USD 21.3 Bangladesh.

WHO guideline on antenatal care states that UNIMMAP supplements cost about US$ 3 per woman per pregnancy while IFA costs less than US$ 1. Similar differential between MMS and IFA are likely to operate in India also, albeit at overall lower costs as supplements are overall cheaper in India.

Recommendation

The available efficacy trials comparing multiple micronutrients with iron and folic acid supplementation during pregnancy have reported improved birth outcomes such as reduction in small for gestational age and low birth weight. There is no increased risk of still births or early neonatal mortality due to MMS. The meta-analysis included studies majorly from low and middle income countries including India. However, food habits are culturally driven and we do not have information from India regarding acceptability and compliance to MMS among pregnant women. Based on the findings of future field trials in India, MMS during pregnancy may be considered as an option for IFA.

MMS would avert more DALYs than IFA among pregnant women and is more cost effective.
References


Acknowledgments

Lead: Prof. Shashi Kant, Head, CCM, AIIMS;
Nodal person: Dr. Kapil Yadav, Additional Professor, CCM, AIIMS;
Members: Prof. Renu Saxena, Head, Department of Hematology, AIIMS;
Prof. Vatsla Dadhwal, Department of Obs. and Gynae., AIIMS;
Prof. Puneet Misra, CCM, AIIMS; Prof. Sanjay K. Rai, CCM, AIIMS;
Dr. Sumit Malhotra, CCM, AIIMS; Dr. Partha Haldar, CCM, AIIMS;
Dr. Ravneet Kaur, CCM, AIIMS; Dr. Jagdish Prasad Meena, Department of Pediatrics, AIIMS; Dr. Archana Singh, Department of Biochemistry, AIIMS;
Research Staff: Dr. Gomathi Ramaswamy; Ms. Kashish Vohra, NCEAR-A.

National Centre of Excellence and Advanced Research on Anemia (NCEAR-A) is established in All India Institute of Medical Sciences (AIIMS), New Delhi with the support of Ministry of Health and Family Welfare (MOHFW), GoI, and UNICEF. The mandate of NCEAR-A is to develop and provide technical support to the Ministry of Health and Family Welfare, Government of India, for incorporating scientific, policy and community perspective in policy and programmatic decisions for control of anemia.

Suggested Citation:

Contact Details:
National Centre of Excellence and Advanced Research on Anemia Control
Room no. 38, Centre for Community Medicine,
All India Institute of Medical Sciences (AIIMS),
Ansari Nagar, New Delhi -110029
Email Id: nceara.aiims@gmail.com
Phone No.: +91-1126593848