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REVIEW

# Micronutrients Deficiency and Their Associations with Pregnancy Outcomes: A Review

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**Abstract:** Micronutrients are vitamins, minerals and trace elements that are used in minute doses as cofactors, antioxidants and modulators of gene transcription homeostasis. MMNs may have a role in averting or treating adverse pregnancy outcomes and maternal complications. In 2016, WHO suggested the use of iron-folic acid (IFA) rather than multiple micronutrients (MMNs) during pregnancy owing to some feared adverse outcomes like perinatal mortalities. However, this effect is debatable as such complications could be also due to genetic or environmental factors. Therefore, this appraisal should provide appropriate information and guidance to health workers, scholars and policymakers. This review includes large sample-sized studies with a special focus on developing countries like Ethiopia. The articles were selected using systematic searching with Boolean operators, advanced search techniques, snowballing and search limits. Mendeley was used as a reference management tool where the source of databases and references were PubMed, AJOL, Google Scholar, IRIS, Summon, DOAJ, Cochrane Library, Oxford Medicine Online, WHO reproductive health libraries majorly from the Hinari program. Articles from BMC, American Society for Nutrition, Lancet, Elsevier, John Wiley and Sons LTD, PLoS One, Springer and Nature Publishing Groups were also used. The results showed that there are no variations in adverse effects between MMNs and IFA. Moreover, MMNs are valuable in anemic pregnant women with lower preconception weight as it increases maternal weight and reduces low birth weight and anemia more than IFA. Therefore, MMNs may have greater health benefits than IFA for the offspring by minimizing fetal complications and the cost of their treatment, resulting from the MMN deficiency state.

**Keywords:** multiple micronutrients, IFA, adverse birth outcomes, pregnancy, mortalities

## Introduction

During pregnancy, there is an increment in the demand of macronutrients, caloric requirements and supplementation of minerals and vitamins; (iron, folate, iodine, calcium and vitamin D (VIT. D)) which are considered as micronutrients to ensure optimal quality and quantity of diet for the mother and the fetus. Micronutrients (MNs) are deficient both in developing and developed countries owing to malnutrition and inappropriate dietary habits respectively.[1,2] MN supplementation has been saving millions of lives in developing countries although the coverage is minimal.[3] Multiple micronutrients (MMN) are minerals, vitamins and trace elements that are needed in small doses daily for physiological functions outside the calorific value.[4] WHO stated that these substances are the 'magic wands' that enable the body to produce enzymes, hormones and other substances essential for proper growth and development. As tiny as the amounts are, however, the consequences of their absence are severe. (WHO, 2020)

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MMN is also defined as a single tablet containing more than three different MN, excluding MN-fortified powders, foods and beverages.[5,6] The most common of them include iron, zinc, iodine, magnesium, copper, selenium, calcium, Vitamins A, $B_1$, $B_2$, $B_3$, $B_6$, $B_{12}$, folic acid, C, D and E. Maternal nutrient stores (during preconception, conception and lactation) and diet provide all the macro and micronutrients to sustain most favorable fetal, infant and child development.[7,8] MNs like, zinc, folate, niacin, riboflavin, and vitamins B6 and B12 are considered principally significant as they are implicated in one-carbon metabolism, which is necessary for cell proliferation, growth, and protein synthesis in the earliest stages of gestation.[9] Consequently, maternal deficiencies in key MN can have severe effects on fetal development and maternal health resulting in adverse outcomes and maternal health complications.

## Adverse Birth Outcomes

These undesirable outcomes and complications include preeclampsia (PE), preterm delivery (PTD), gestational diabetes mellitus (GDM), intrauterine growth restriction (IUGR), small for gestational age (SGA), low weight (LBW), stillbirth, perinatal, neonatal and maternal mortality. The first four outcomes listed above together affect 25% of first pregnancies and have associations with MN deficiencies[10] predicting lifelong morbidity and mortality of the mother and offspring with their prevalence being higher in developing countries.[11] The prevalence of PTD, SGA, LBW, maternal mortality, stillbirth and neonatal mortality in Sub-Saharan Africa (SSA) are 12, 16.5, 13, 546, 28.7 and 27.7% respectively.[9] MMN supplementation in pregnant women may be a promising approach for reducing these adverse outcomes as so many findings are supporting their potential use despite some disputes which could be resolved via further investigations.[12,13]

## MMNs and IFA Supplementation Health Benefits

Nowadays, MMN appears preferable over individual MN in either kinetics or dynamics in the body. For example, a lower dose of iron was recommended as the absorption of iron was expected to be enhanced due to vitamin C, vitamin A, and riboflavin in an MMN formulation, which is helpful for anemic pregnant women as both Vitamin A and iron have uses and the side-effects associated with higher doses of iron minimized.[14]. While many developing countries have adopted the use of iron and folic acid (IFA), MMNs could also be provided as the adverse pregnancy outcomes and their treatment costs, (due to MMNs deficiency), are enormous compared to the use of IFA alone. So, MMN can be recommended provided that their significance is confirmed through serious investigations than IFA only.[9,15] In Ethiopia, there is a loss of 450 million USD in GDP to MMN deficiencies than the cost of MMN interventions which is less than 51million USD.[16] Besides, some developed countries often do not recommend IFA at all in non-anemic pregnant women, rather they use MMN containing IFA. Therefore, suggesting MMN supplementation for pregnant women could be a wise recommendation in Low and Middle-Income Countries (LMICs) where malnutrition is common[17]. Supplementation rates reported in developed countries are more than LMICs but still 14–36% during the three-months pre-conception and 40–91% during the antenatal period. Besides, iron, folate and vitamin D intake are below the national average in Europe, USA, UK, Japan, Australia and New Zealand as pointed in a meta-analysis from sixty-two articles. Therefore, the issue of MN deficiency is a worldwide encumbrance that needs to be addressed at this level[18]. In a cohort study from Norway, there was also too much saturated fat consumption with limited intake of MMN during pregnancy which could raise the risk for adverse pregnancy outcomes.[19] Therefore, dietary supplementation (if possible) or MMN supplementation should be a global issue of attention and its use during the preconception and pregnancy periods may prevent morbidities and mortalities starting from fetal life to even adulthood. Current meta-analysis indicated that MMN supplementation led to a reduction of LBW and SGA over IFA. Besides, MMN reduced LBW, SGA and six-month infant mortality on anemic while reducing PTB in underweight pregnancies. Moreover, MMN reduced neonatal, six months and infant mortality than IFA alone.[9,20] Besides, the low cost of MMN than IFA (taking into consideration the cost due to disabilities incurred upon failure to take MMN) and the absence of significant side effects over IFA will make MMN preferable in LMICs with comparable or even better adherence to treatment.[9] Besides, it was also indicated that adverse outcomes like LBW, PTD, IUGR and SGA, treatment expenses are higher than the cost of MMN provision[15,21] which may once more justify the substitution of IFA with MMN during pregnancy worldwide in the future.

## WHO and UN Nutritional Recommendations: The Role of MMN or IFA

As part of the nutritional intervention balanced protein, energy and MN supplements are recommended by WHO with and without context-specific situations. While IFA is recommended unconditionally, others like zinc, vitamin A (VA), and calcium are recommended under a specific context. WHO also recommends MN especially IFA to reduce the risk of iron deficiency anemia and those with neural tube defects (NTD) among pregnant women respectively.[22] Moreover, there is also a plan to reduce LBW by 30% and anemia by 50% globally to curtail morbidities and mortalities by 2025.[23] Also, a high nutritional burden in women has been recognized by the UN sustainable development goal (SDG) with a target to address the nutritional needs of adolescent girls as well as pregnant and lactating women by 2030.[24] However, MMNs supplementation is not recommended by WHO for pregnant women to improve maternal and perinatal outcomes.[25]

## Significance

This review discusses the current knowledge on multiple and individual micronutrients with their benefits in ensuring positive pregnancy outcomes through a reduction in morbidities and mortalities. It also describes the effect of micronutrient deficiency with adverse pregnancy outcomes, which helps to understand their roles for the normal development of the fetus and the health of the mother. Also, it described the effects of the selected MNs and associated factors on adverse pregnancy outcomes. In addition, it presents equivocal findings that require further investigations. It recommends that organizations working in nutrition to consider MMNs rather than IFA supplementation during pregnancy as there seems to be a little reduction in the adverse pregnancy outcomes with supplementation of MMNs based on the findings of this review.

# Methodology

The articles included in this review consist of large sample-sized studies, including reviews majorly on MMN and birth outcomes at a global level (both from high and low-income countries) with a special focus on developing countries of Sub-Saharan Africa (SSA) like Ethiopia, where the deficiency is enormous. Moreover, individual micronutrient and birth outcome studies were also included for comparison. Furthermore, the types of articles selected included at least twenty randomized control trials (RCTs) most of which were double-blind. Others were twenty reviews, including major meta-analysis, twenty cohort studies, twenty cross-sectional and case-control studies. The articles were selected using systematic searching with Boolean operators, advanced search techniques, snowballing and search limits. Moreover, Mendeley was used as a reference management tool and the source of databases and references were PubMed, AJOL, Google Scholar, IRIS, Summon, DOAJ, Cochrane Library, Oxford Medicine Online, WHO reproductive health libraries majorly from the Hinari program. Besides, published articles that were accessible to LMICs were also utilized from BMC, American Society for Nutrition (ASN), Lancet, Elsevier, John Wiley and Sons LTD, PLoS One, Springer and Nature Publishing Groups. Moreover, few books related to the topic were also used especially while defining few concepts used in the review.

# Literature Review

## Introduction

Globally, twenty million infants are born with LBW per year and over three million infants die during the neonatal period where one-third of these deaths are attributable to maternal and child undernutrition.[6] There are also over two billion people who are at risk for vitamin A, iodine, and/or iron deficiencies,[26] although efforts are being made to prevent and control it. The prevalence is particularly high in Southeast Asia and SSA where pregnant women and young children are at an increased risk.[27] Even though MN deficiencies of public health concern include zinc, folate, and B vitamins, there is limited data on the actual prevalence of these deficiencies and their association with pregnancy outcomes.[26] Studies that were majorly conducted in developed countries, where MN deficiencies and adverse outcomes are less common, have diverse explanations about the effects of MN on pregnancy outcomes.[18,27,28] Investigations about MMN rather than single MN deficiency is recommended as MMN deficiencies are common in low socioeconomic populations.[13,29] Furthermore, in many locations, more than one MN deficiency exists, suggesting the need for simple approaches that can evaluate and justify the measurement of MMN levels during pregnancy and their association with the pregnancy outcomes.[26,30] So many studies have been conducted that have equivocal outcomes on the relationship between MMN level, associated factors and pregnancy outcomes.[31] In most of the studies, the direct or indirect effect of MMN and associated factors on reducing anemia, NTD, PE, VAD (Vitamin A Deficiency), LBW, PTD and SGA has been.[13] Further studies on stillbirth, perinatal, neonatal, infant and maternal mortality have been recommended.

There is a scarcity of investigations on individual MN deficiencies and their effects on pregnancy outcomes in SSA countries like Ethiopia. The few available studies reported that MN deficiency in Ethiopia was highly elevated as reported in the EDHS of 2016. This exercise is aimed to thoroughly review MN associated factors and pregnancy outcomes globally with a particular emphasis on LMICs in SSA. Also, systematic reviews with large sample-sized studies conducted in Asian countries like China, Bangladesh, Nepal, India, and some developed countries were included.

## Micronutrients (MMNs, IFA, Trace Elements) and Adverse Pregnancy Outcomes

Pregnant women in SSA are at particular nutritional risk because of poverty, food insecurity, political and economic instabilities, frequent infections and pregnancies.[32] These nutritional deficiencies of MMN in SSA include iron, folate, calcium, VIT. D and VA which will result in poor obstetric outcomes, such as anemia, NTD, rickets, LBW, SGA, PTD, stillbirth, maternal and neonatal mortality. Women (especially pregnant and lactating), infants and young children are among the most nutritionally vulnerable groups.[9] This is due to their high physiological nutrition requirements, which are usually not adequate. Moreover, with women and children from SSA, environmental and economic factors place the extra burden on their dietary status. The vulnerability of women is also worsened by the heavy workload, frequent and short reproductive cycles with the absence of adequate replacement of the body's depleted stores.[14] One of the adverse health outcomes during pregnancy are stillbirth and neonatal death. About 3 million stillbirths and three million early neonatal deaths occurred worldwide in 2004; 98% of which were in less developed countries.[9] Potentially preventable causes of stillbirth and early neonatal deaths had been associated with maternal anemia and related MN deficiencies.[33] Besides, periconceptional nutritional (folic acid) supplementation or fortification, prevention of malaria and improved detection and management of syphilis during pregnancy in endemic areas also reduce stillbirths.[34] Moreover, prophylactic use of antimalarial drugs during pregnancy increased mean weight and gestational age in a cross-sectional study in Nigeria.[35] Associated factors like rural residence and poor quality and the number of deliveries in health institutions contributed to raised adverse pregnancy outcomes like stillbirth.[36] A huge review from about twenty-one RCTs also reported a reduction of the incidence of stillbirth (by 9–11%) because of MMN supplementation.[37] The need for further studies on this topic therefore arises. Moreover, studying MMN in concert is necessary as their deficiencies are generally common in low socioeconomic populations, where the exposure is to multiple rather than single MN deficit is familiar.[17,38]

Diverse maternal factors like obesity, knowledge of the mother about gestational age and ethnicity are also related to adverse pregnancy outcomes; these include GDM, PE, macrosomia, NTDs, IUGR, and genetic malformation and Cesarean section.[39,40] Also, obese pregnant women were at a higher risk of MN deficiencies due to poor eating habits and reliance on energy-dense and MN-deprived foods[41] leading to pre-eclampsia and DM which resulted in PTD.[42] Intrauterine MN status also has links with the potential risk of chronic diseases although the root causes were largely unknown.[43]

Different studies have been conducted on the effect of MMN versus IFA on pregnancy outcomes taking into consideration common adverse outcomes like LBW, SGA, PTD, weight, stillbirth, perinatal, neonatal or infant mortality. MMN consumption failed to reduce the incidence of LBW and other pregnancy outcomes in India.[44] This is supported by another RCT study in Hungary which reported that antenatal multivitamin supplementation increased PTB and fertility with no significant effect on fetal death and LBW in singletons.[44] On the other hand, supplementing pregnant mothers with MMN highly benefited a growing fetus by improving birth weight and reducing the number of infants born with LBW.[45] Besides, a meta-analysis on prenatal MMN supplementation is associated with a 19% reduction on the risk of LBW with improved weight when compared with IFA but not on the risk of PTB and SGA[46], unlike an RCT where MMN supplemented group had less number of SGA infants than the placebo.[47] A prospective cohort study in rural Tibet of China also indicated the benefits of MMN over folic acid in reducing LBW, PTD, maternal third-trimester anemia and perinatal mortality but not SGA.[48] However, in a double-blind RCT in Nepal, MMN supplementation reported no additional benefits over IFA in reducing the risks of LBW although it reduced LBW and led to an increased weight more than the control.[49] In a similar study, it reduced LBW and stunting, protecting the future generation from adverse pregnancy outcomes.[50] In another meta-analysis study, mothers supplied with MMN had an average rise in weight (by 22gm) and reduction in the prevalence of LBW (by about 10%) and SGA with a great impact on women of high BMI.[51] However, there was no change in length and head circumference. Besides, a prospective cohort study indicated an increased risk of SGA due to poor MN intake or status.[11] A recent meta-analysis indicated a reduction in LBW, SGA, PTD, diarrhea incidence and retinol concentration compared to IFA supplementation with little to no effect on mortality (maternal, neonatal, perinatal, and infant) outcomes.[13] Besides, MMN supplementation during pregnancy reduced SGA compared to IFA, in the absence of risk on neonatal mortality, on women with BMI of twenty-two and above, where a trained attendant was available and most of the births took place in health facilities.[52] Moreover, MMN supplementation had resulted in a reduction in the number of LBW babies than placebo or two and less MN taking groups with a reduction in SGA babies and maternal anemia but not with IFA supplemented once in a Cochrane review of RCT articles. There was also no significant difference between MMN versus IFA supplementation on perinatal mortality and PTB.[53] Furthermore, a double-blind RCT in China indicated that IFA reduced PTD and early neonatal mortality more than folic acid alone and better than MMN. Also, MMN has been observed to increase weight than the folic acid group[54] and an increase in hemoglobin levels by both MMN and IFA supplementation than folic acid alone. On the other hand, MMN supplementation in another double-blind RCT study reduced the incidence of LBW and early neonatal morbidity.[55] This indicates the absence of a consensus on the benefits of MMN over IFA[54] or on the effects such as PTD, SGA and perinatal mortality.

Moreover, some challenges remain unrequited including the risk of neonatal mortality in some populations, absence of sufficient MMN and cost of MMN. Hence, these results suggested that it could not supply some basis to recommend the substitution of IFA with MMN for pregnant women living in LMICs.[14] On the other hand, MMN supplementation containing IFA provided greater reductions in neonatal mortality (by 15%) for female than male neonates when compared with IFA alone. It generally indicated that MMN improved survival for female neonates and provided greater birth-outcome benefits for infants born to undernourished and anemic pregnant women. Early initiation in pregnancy and high adherence to MMN supplements also provided greater overall benefits.[20] Besides, long-term intermittent MMN supplementation enhanced hemoglobin and MN status more than IFA although MMN contains lower amounts of iron than IFA in a study conducted in Bangladesh.[56] In another double-blind RCT conducted in Indonesia, women talking MMN from the time of enrolment to 90 days postnatal had an 18% reduction in early infant mortality than IFA. There was also a reduction in the infant mortality rate of mothers who are undernourished or anemic by 25% and 38%, respectively. Moreover fetal and neonatal death was reduced by 11% and LBW by 14% due to MMN rather than IFA supplementation with a vast benefit to undernourished and anemic pregnant women.[12] Moreover, the provision of MMN supplementation has improved mean weight and reduced the risk of LBW but not the length, head circumference or duration of gestation over IFA.[57] Likewise, in a non-randomized trial in Vietnam, MMN supplementation improved the mean weight and reduced LBW in pregnant women than those who received IFA alone.[50] However, the effect of MMN supplement on fetal and infant deaths was inconsistent on a double-blind RCT conducted in Guinea-Bissau as prenatal MMN increased weight but there was no difference with IFA on perinatal mortality.[58] Another study also reported that effective MN interventions for pregnant women should include supplementation with IFA and noted a reduced risk of LBW at term by 16% with MMN.[5]

On the CNS, little evidence exists to retain the general uses of iron, zinc or MMN in motor or cognitive development.[59] A review, in general, has indicated birth defects of the CNS due to mineral deficiencies during pregnancy.[60] MMN complement had modestly improved changes in cognitive outcomes but not the psychomotor development compared with IFA in a double-blind RCT study in China[61] unlike another study in Nepal where intellectual and motor functioning development was positively associated with IFA only.[43] Moreover, in Bangladesh, MMN supplementation of low BMI mothers had infants with significant but small improvement observed in motor scores and activity ratings compared with mothers of low BMI that received IFA.[62] A systematic review also indicated prenatal MMN and n-3 fatty acid but not individual MN supplementation for child mental development thus demanding further studies.[63]

In other systems, MN status in fetal and early life span can change metabolism, vasculature, organ growth and function, where their deficiency could result in cardiometabolic disorders, adiposity, altered kidney function, leading finally to type 2 DM and CVD[43,64] which can be linked to early days MN deficiency and late-life development of chronic diseases. On the other hand, a cohort study from Australia also reported a low copper and zinc status associated with a reduced risk of any pregnancy complication as compared with high copper and zinc status[10] while prenatal Zn and Se statuses were associated with child psychomotor skills within the first years of life.[65] Moreover, low serum levels of Mg, Co and folate increased birth defect risks while Cd, Pb and Al do the opposite in an exploratory study in Poland.[66]

MN is crucial for the maintenance of cell proliferation and function as cofactors to enzymes in the oxidant defense system, and mediating inflammation and immune response. The complications like PE and IUGR had been associated with increased oxidative stress and circulatory markers of inflammation which could indicate the connection between MN deficiencies and their outcomes.[43,64,67] An association has been also described between low levels of trace elements having antioxidant functions, (Fe, Zn, Mn, Cu and Se) with an increased risk of developing PE.[60]

Pre- and periconceptional understanding of MN on the mother and embryo has a huge role in comprehending MN's position on maternal-placental and fetal communication, placentation and embryogenesis. This makes the preconception and first-trimester era a recommended time to propose that most interventional studies be conducted especially at this period.[59] The association between trace minerals and pregnancy has been described previously, however many of these studies have been conducted in late pregnancy or at term. As many of these pregnancy complications occur in early gestation[10], it is important also to understand how MN status in the first trimester is associated with adverse pregnancy outcomes. Marginal MN deficiencies early in pregnancy may lead to more severe deficiencies later in pregnancy due to increased metabolic demands from the rapidly growing placenta and fetus.[68] For the case in point, the initiation of MMN supplements before 20 weeks gestation also provided greater reductions in PTD (by 11%) as reported in previous studies.[20]

Therefore, there is still a need for further investigations as the number of studies are small with non-homogenous findings on the use and exploration of latent adverse effects on MMN supplementation. Moreover, with future enriched studies on MMN and solving the current heterogeneous findings, the supplementation programs could usher in a largely beneficial improvement in ANC services accompanied by increased contact, improved nutrition, deworming and access to clinical care delivery.

Even though it is essential to address issues like perinatal mortality and interaction between individual micronutrients that are available within MMN, it appears that MMN can engender positive health outcomes in pregnancy. Moreover, to address the issue of multiple and parallel MN deficiencies, UNICEF, United Nations University, and the WHO have developed an MMN tablet that provides the daily recommended intakes of the following MN: vitamins A (800µg), B1 (1.4mg), B2 (1.4mg), B6 (1.9mg), B12 (2.6mg), C (70 mg), D (200IU) and E (10mg), and niacin (18mg), folic acid (400µg), copper (2mg), selenium (65µg), and iodine (150µg) with 30mg of iron and 15mg of zinc, for pregnant women. More recently, lipid-based nutrient supplements (LNS) have been used to address the adverse effects of MN deficiencies in mothers. These supplements typically contain the same vitamins and minerals found in MMN supplements, plus components of protein, essential fatty acids, and energy in the form of fats (such as vegetable fat, peanut/groundnut paste, milk powder and sugar).[13]

## Factors Associated with Micronutrients and Adverse Pregnancy Outcomes

In general, maternal MMN levels could be affected by factors such as diet qualities[69], fertility rates, parity, interpregnancy intervals, repeated pregnancies, increased physiological demands and diversity of the food taken by pregnant women,[70] gestational weight gain,[71] quality of health care, poverty, inequalities, socio-cultural factors (like early marriage, adolescent pregnancies and traditional dietary practices), country's economy, poor bioavailability and/or presence of infections[32,72,73] and female fetus, which is associated with LBW.[74,75] Preconception nutritional and health status is also a factor, indicating also where parenting has to begin.[76]

Dietary diversity helps to obtain the required micro and macronutrients in a balanced manner and measuring tools have been developed for evaluating the quality of diet in this regard. A total of ten food clusters were used and respondents who consumed less than five were classified as having insufficient others that those consumed greater than five were classified as having sufficient dietary diversity practice.[70] Studies had reported the inadequacy of dietary diversity in pregnant women who participated in a study that was conducted in North-East

Ethiopia (69%) and East Gojjam (55%) in the Amhara region, Ethiopia, showing MN inadequacy in more than half of the pregnant women.[69,77] Practically, diet is usually not easy or expensive to manage and it is more effective to prevent MN deficiencies through supplementation[59] as recommended by the nutrition guidelines of health institutions like WHO.

MMN deficiencies have not been addressed adequately and further studies are necessary to investigate the direct association between individual components of an MN and pregnancy outcomes. Most plant foods have complex matrix containing many bioactive compounds, known as phytochemicals, in addition to multiple vitamins and minerals. There is growing evidence of additive and synergistic relationships between phytochemicals and MN enabling absorption, bioavailability and utilization.[78] Additionally, pieces of evidence suggest that many phytochemicals found in fruit, vegetable and whole grains have antioxidant, anti-inflammatory, anti-obesity and chemo-protective properties which will have synergy with MMN.[79] Likewise, fortified foods are one of the enhanced approaches used for modifying the diet at the population level, the others being nutritional education and dietary supplements.[80] However, care should be taken to suggest dietary changes ensuring the requirements of specific populations concerning sub-optimal, excess or claimed but not aimed intakes.[81] Therefore, the above factors can be associated with MN levels and pregnancy outcomes in one way or another.

A retrospective cohort study reported an association between teenage pregnancy (11% worldwide contributing 23% of the disease burden of pregnancy) with increased risks for PTD, LBW, neonatal mortality and low Apgar score at 5 minutes.[82] Adolescent (teenage) pregnancy, where there is a higher than usual requirement for nutrients, is associated with LBW, SGA,[83] anemia, poor maternal nutrition, raised neonatal morbidity and mortality, IUGR, PTD, ANC miss outs and poor nutritional knowledge.[11,84] Moreover, adolescent pregnancies[84] were reported to affect young mothers' growth and nutritional status and this was related to at least a 50% rise in the risk of stillbirth, PTD, LBW, SGA, asphyxia and neonatal deaths.[11] Besides, adolescent pregnancy and preeclampsia were associated with LBW and PTD but not with Apgar score value at the first and 5th minute, ICU admission and severe neonatal conditions in Ethiopia.[83] Inter-pregnancy intervals (less than six months) were also associated with PTD, LBW, stillbirth and early neonatal death[76] while long inter-pregnancy intervals (higher than forty-eight months) were related to an increased risk of PE.[85,86]

Factors such as nulliparous women, multiple pregnancies, advanced maternal age (≥40 years), history of PTD, and maternal medical disorders have also been identified as main predictive factors for the risk of preterm babies.[87] Studies also indicated that obese women (BMI≥30kg/m$^2$)[41]; underweight women (BMI≤18.5kg/m$^2$),[40] some ethnic minorities, vegetarians and vegans to be at risk of MN deficiencies[74] which made the women more prone to adverse pregnancy outcomes. Studies reported also that markers of maternal pre-pregnancy status like short stature, low and high BMI are linked to increased risks of PTD and SGA.[68] There was also a better response to MMN in underweight women (18.5kg/m2) where the MMN group had offspring with heavier weight (by 98gm), longer (0.8cm), and large (0.2cm) in mid-arm circumference compared with the placebo group. Moreover, the incidence of LBW declined from 43.1 to 16.2% with MMN supplement than the placebo.[55] It was also reported that women who developed pregnancy complications had a higher BMI in early pregnancy with no significant difference in maternal age, smoking status or use of supplement at 15±1 weeks of gestation. On the other hand, underweight or low BMI (≤18.5kg/m$^2$) is associated with weakened fertility[88] and the underweight women who conceived had a 72% increased risk of miscarriage during the first trimester than normal-weight pregnancy women.[74,89] A prospective study established that preconception maternal health status and health-related behaviors can affect weight and fetal growth. In particular, maternal BMI and vegetable consumption significantly predict weight and fetal growth, after controlling for possible prenatal mediators and sociodemographic variables.[90] Besides, pregestational and gestational underweight was also shown to impact neonatal morbidities like increased risk of LBW, SGA and PTD[91] and low gestational weight gain below the recommendations was associated with a higher risk of SGA and PTD and lower risk of large for gestational age and macrosomia as indicated by a review.[71] Moreover, reduced language skills at 12 months, cognitive and motor growth at 24 months was related to the offspring of women with low BMI (≤18.5kg/m$^2$).[65] Besides, in a meta-analysis from seventeen RCTs with MMN supplementation versus IFA, a greater effect has been observed on PTD among low BMI pregnant women (RR reduction by 16%) and starting supplementation before 20 weeks of gestation provided greater reductions in PTD (RR=0.89; 95% CI: 0.85–0.93; P<0.04). This is accompanied by a general increase (>95%) in survival and pregnancy outcome up on MMN supplementation.[20,92] It is not only the availability of MN that has an impact on pregnancy outcome, other factors such as adherence to treatment for example IFA (where 41.38% of the pregnant women are adherent to treatment) are important.[93]

Gestational weight gain of about 8kg is obligatory and accounts for the fetus, the placenta, amniotic fluid volume and adaptation to maternal tissues (eg uterus, breast, blood volume). A weight loss could result in ketonemia, ketonuria and pregnancy-induced insulin resistance which may result in abnormal fetal growth or later neurocognitive development. The recommended weight gain of the mother and fetus during pregnancy depends on the BMI of the pregnant woman.[94] Inadequate pregnancy weight gain is reflected in the high prevalence of LBW among 14% of infants in Sub-Saharan Africa. On the other hand, about 40% of women aged 20–24yrs in Sub-Saharan Africa marry early (age less than 18 years) with many years of childbearing ahead, pregnancies occurring frequently, and at short intervals, giving the mother insufficient time to replace her nutrient stores before the next pregnancy.[32,95] Moreover, the poor quality of the diet in SSA contributes to the widespread energy and MN deficiencies resulting in adverse pregnancy outcomes which are exacerbated by a smaller number of skilled medical attendants.[96] On the other hand, studies in urban US women indicated twice reduction in risk of PTD and overall risk of LBW up on nutritional supplements. Nonetheless, vitamin supplementation before pregnancy did not prevent women from experiencing miscarriage or stillbirth and multiple pregnancies and less likely to develop pre-eclampsia. Likewise, another cohort study in the United Kingdom[97] indicated regular MMN supplementation association with reduced PTD but not with size at birth. Besides, the risk of PTD, LBW, SGA and Apgar score at the 5th minute was associated with the educational level while PTB and Apgar score are associated with the residence of the mother.[98] On the other hand, while some studies had shown an association of unemployment with PTD, LBW, SGA and higher perinatal mortality, others have shown no relation.[99,100]

Epigenetic influences, characterized by heritable long-term changes in gene expression which are not caused by changes in gene sequences, have shown to also cause a significant role in long-term pregnancy outcomes.[17] MN improved also immune function, energy metabolism and anabolic process that help in reducing IUGR and maternal stress. However, there is no sufficient confirmation on the effect of individual MN on adverse pregnancy outcomes.[46] During the use of MMN for the intended purposes, it should be with due caution as there could be adverse outcomes in a specific population, and there is still a challenge on the recommendations as overconsumption may result in adverse outcomes; further studies are recommended to fill the gaps of knowledge on the consumable requirement and the purpose of individual MN in mitigating adverse pregnancy outcomes.

Concerning the onset of measurement of MN status, it is better to conduct this during the first trimester as many pregnancy complications originate in early gestation. This MN deficiency will occur later in pregnancy due to raised metabolic demands from the rapidly growing placenta and fetus. Hence, determining the plasma level of copper, zinc, selenium or iron at 15±1weeks of gestation could be related to several pregnancy outcomes which could ease possible interventions as well.[10] Even though women's nutrition before and during the first trimester of pregnancy is important, there is a need for well-designed prospective studies and controlled trials in developing country settings that examine relationships with low weight, SGA, PTD, stillbirth and maternal and neonatal mortality.[68] Adherence to IFA or MMN supplementation is also a factor that could affect the MN level and the corresponding pregnancy outcomes. Factors like educational level, onset and number of ANC follow-ups, knowledge about IFA and anemia and nutritional education are associated with adherence to supplementation.[93]

Apart from the daily requirement of MN, the recommended calorie intake during the first, second and third trimesters should be 300, 340 and 452 kcal/day, respectively with an estimated calorie level of 80,000 kcal during the mean pregnancy period of 250 days though it is affected by BMI and age of the pregnancy. Moreover, the recommended protein intake should be 60g/day; carbohydrates 45–64% of daily calories and 20–35% daily calories of fat.[94]

The other important thing is the presence of physiological change during pregnancy in the normal ranges of several laboratory values. Both total RBC mass and plasma volume raise with a greater proportion to the plasma volume resulting in hemodilution and anemia during pregnancy. Therefore, anemia refers to low hemoglobin (Hb) (<11,10.5, and 11gm/dl) or low Hematocrit (Hct) value (<33%, <32% and 33%) during the first, second and third trimesters respectively.[94,101] There is also a decrease of about 30% serum total albumin compared to non-pregnant values. Besides, estrogen raises the liver production of proteins resulting in greater protein binding of corticosteroids, sex steroids, thyroid hormones and VIT. D during pregnancy leading to reduced free plasma levels.

## Individual Micronutrients Deficiency and Adverse Pregnancy Outcomes

MN intake levels in women living in resource-poor environments except for vitamin A (29%), C (34%), and niacin (34%) were reported to be below the mean or median estimated average requirements in over 50% of the studies in a systematic review from fifty-two articles[102], including urban settings.[103] This makes the morbidities and mortalities associated with MMN deficiency more severe in developing countries. Systematic reviews from Ethiopia, Kenya, Nigeria and South Africa also indicated the prevalence of anemia in pregnant women, ranging from 32–62%, 19–61%, and 9–47%, with the prevalence of vitamin A, iodine, zinc and folate deficiencies ranging from 21–48%, 87%, 46–76% and 3–12% respectively[29] amid a great public health concern demanding dietary diversity and fortification of commonly consumed and affordable food products or MN supplementation.

There is scientific data that some MN such as iron, iodine, zinc, folate, vitamin A and vitamin D are significantly involved in pre-and postnatal brain development. Moreover, the subsequent MN deficiencies are associated with adverse neonatal and maternal outcomes. The effect of MMN with IFA is therefore helpful than IFA alone in mitigating adverse outcomes.[104] A review on reducing preterm incidence indicated that docosahexaenoic acid (DHA), zinc together with vitamin D, vitamin A, calcium, iron, folic acid, combined iron-folate, magnesium, MMN, and probiotics showed a lower risk of PTB although further studies with a larger sample size are essential.[105]

The common clinical signs of Iodine deficiency disorders (IDD) are endemic goiter (accounting 740 million estimated numbers globally) and cretinism.[106] The prevalence of IDD is higher in the Eastern Mediterranean region (32%), followed by Africa (20%), Europe (15%), and Southeast Asia (12%) based on the clinical signs observed during severe conditions. Virtually one-third of the world's population is at risk of iodine deficiency. Nearly 90% of the salt is adequately iodized in Latin America and the Caribbean but Asia, Sub-Saharan Africa and North East and North Africa had been shown to have iodized salt coverage rates of 65–75%, 50–74%, and around 50% respectively.[26] Studies on reproductive outcomes of iodine indicated an association between iodine deficiency (ID) and cretinism, stillbirths, abortions and congenital abnormalities.[31] Likewise, in a prospective cohort study in Bangladesh, increased maternal urinary iodine was positively associated with birth weight, length and head circumference in male offspring with a well-recognized impact on the offspring's cognitive impairment.[107]

Calcium with VIT. D deficiency was estimated to affect about one billion people globally and was increasingly documented as being common during pregnancy. Despite the important role of calcium in neurotransmission, hormone release, blood clotting, bone marrow homeostasis, brain development and modulation of the immune system, the impact of antenatal VIT. D is still under investigation.[108] A systematic review with fifteen RCT articles also explained the association of calcium and VIT. D supplementation with regards to the reduction of pre-eclampsia, LBW and PTD.[109,111] Besides, supplementation during pregnancy has reduced the incidence of gestational hypertension by 35%, pre-eclampsia by 52–55% and PTD by 24%.[6,112] On the contrary, a review of twenty-five RCT studies indicated no clear additional benefits to calcium supplementation in the prevention of PTD or LBW.[111] Maternal MN intake was also associated with neonatal weight even in women that are not at risk of malnutrition. In a study on the association of maternal MN intake and neonatal outcomes, a negative association between weight and maternal third-trimester VIT. D intake was observed.[113] Moreover, cultural dress codes limiting exposure to sunlight, skin pigmentation and lack of VIT. D rich foods are also associated with VIT. D deficiency[74] indicating that cultural and dietary habits influence the VIT. D level and contribute to adverse outcomes like pre-eclampsia.

There is very limited nationally represented data on the magnitude and severity of zinc deficiency (ZD) and it is estimated that 82% of all pregnant women in the world suffer from zinc deficiency. Zinc deficiency in a mother is associated with growth retardation, poor congenital development, LBW, spontaneous abortion, abnormalities in gene replication, protein and DNA synthesis and also in translation and transcription of DNA[114] with also poor immune functions.[31] Zn is found in over 200 metalloenzymes throughout the body and its plasma level is used as an indicator though influenced by infections and diurnal variations.[26] In Ethiopia, nearly 38% of under-five children are stunted which indirectly implicates lower zinc nutritional status.[115,116] Moreover, an institution-based cross-sectional study conducted in Gondar, Ethiopia reported a 57.4% prevalence of ZD in pregnant women with higher associations occurring in those living in rural areas, with short inter-pregnancy interval, poor consumption of food from animal origin, poor dietary diversity, lack of nutritional education, low serum albumin level and parasitic infestations[117,118]. In terms of dietary intake, the bioavailability of zinc has been inhibited by phytate which inhibits zinc absorption present in cereal-based diets of many developing countries.[118] Reviews of twenty RCTs on zinc supplementation during pregnancy found a reduction in PTB (by 14%) and labor duration in women of low incomes[119,120] but not accompanied by a similar reduction in stillbirths, neonatal death, SGA or LBW which may explain the presence of other nutritional deficiencies along with Zn. This created difficulties in recommending single MN like Zn supplementation as the pieces of evidence are not sufficient to associate Zn plasma level with adverse outcomes in a double-blind RCT study in low-income African-American women in the USA.[121] However, findings from Malawi indicated a PTD association with higher maternal serum concentrations of copper and zinc.[122] While a systematic review explained a weak association of Zn supplementation with reduced PTD[119], another indicated that Zn supplementation, compared to placebo, showed no impact on the risk of having an LBW, little to no effect on reducing the risk of pre-eclampsia or eclampsia, PTD and SGA though there was an improvement in the serum zinc level[13] indicating that these heterogeneous findings may demystify potential studies. Besides, women who are vegetarian or with dietary control also could have MN deficiencies (like iron and zinc from animal sources) which can be solved with careful inclusion of some fortified foods.[88] However, care should be taken during the use of fish as a rich source of omega-three-fatty acids as some form of fish could contain large deposits of mercury resulting in damage to memory, learning and behavior of infants.[94]

The consumption of Folic acid or multivitamins containing folate is helpful in the primary prevention of NTDs and some other inherited abnormalities (cardiovascular defects), as their use in the periconceptional period can reduce about one-third of these abnormalities and offer a better choice than termination of pregnancy.[21,123] It is involved in one-carbon metabolism (together with other vitamins like VB12) supporting rapid cell growth, cell replication, cell division and nucleotide synthesis for fetal and placental maturity. Besides, lower serum folate is associated with higher maternal plasma homocysteine concentrations, resulting in pre-eclampsia and abnormal placental function, ultimately leading to PTD. Folic acid deficiency can lead to hematological abnormalities, pregnancy complications and congenital malformation although the association with other outcomes is controversial. Though folic acid has many defined effects on pregnancy, studies about its effect on LBW, PTD, and perinatal mortality were indistinct.[31] Folic acid deficiency-induced megaloblastic anemia is the most common cause of anemia during pregnancy next to IDA.[17] In rural Ethiopia, 46% of women are said to have folate deficiency based on a cross-sectional study.[124] In another cohort study on adolescent pregnancy, folic acid intervention showed significant reductions in the rates of both pre-eclampsia in mothers and SGA in newborns. Besides, the incidence of SGA was higher in subjects with poor folate status (both RBC and serum folate).[11] On the other hand, in a double-blinded RCT study in China, IFA with or without other MNs prevented anemia in pregnancy than folic acid alone without affecting perinatal mortality and other fetal outcomes like PTD and weight. Besides, stillbirth, perinatal, neonatal and infant mortality were not different between MMNs and IFA groups.[125] However, a recent cross-sectional study in China indicated the association of periconceptional FA supplementation with increased weight and reduced risk of SGA and LBW in both singletons and twins; being more prominent on the twins.[126] Moreover, a cohort study in China indicated that preconception folic acid supplementation is associated with the reduction of PTD and its protective effect is greater on women with normal BMI than low or high BMI[42] confirming some qualm on folic acid effect on weight, SGA and PTD unlike NTD.

Iron is essential in the production of hemoglobin and in the synthesis of enzymes that are required to use oxygen for the production of cellular energy. It is suggested for the mother during pregnancy and the rapidly growing fetus. Anemia (low hemoglobin levels) and IDA sometimes serve as indicators of overall poor maternal nutritional status during pregnancy; though anemia could also arise from auxiliary causes like $VB_2$, $VB_{12}$, folic acid, abnormal hemoglobin, malaria, HIV, TB and helminths.[127–129] During the third trimester, high levels of hemoglobin are associated with a bigger risk of PTD. High hemoglobin levels usually associate clinically with an increased risk of pre-eclampsia and suggest the failure of the plasma volume to expand. Various studies indicated a "U-shaped" relationship between low and high maternal hemoglobin or hematocrit and PTD.[21] WHO indicated that on average 56% of pregnant women in developing and 30 to 40% in developed countries, respectively, were anemic.[128] In Ethiopia, a retrospective cohort study in Bahir dar indicated at least 41% overall anemia excluding the anemic HIV seropositive pregnant women.[130] Hemoglobin levels can be helpful to define anemia which depends on age, race, physiological status, smoking and altitude. The population at most risks for ID and IDA are young children and women of reproductive age (WRA), particularly during pregnancy. This is due to bigger physiological demands, combined with increased losses and poor dietary intakes. The global prevalence of anemia among children and WRA in different regions of the globe indicated that more than half of the pregnant women and young children are anemic in South East Asia, West Pacific and Africa.[26,131] In developed countries, pregnant women and young children are at risk of iron deficiency and widespread enrichment of common foods such as cereals and wheat flour have been identified as successful control of ID. A systematic review had found that pregnant women who received MMN had fewer LBW and SGA than those who received only iron, with or without folic acid;[28] with also decreased six-month infant mortality than IFA alone with the effect being great in low BMI pregnant and anemic women[20]; while another study indicated a reduction of infant death than the IFA group with the effect more pronounced in anemic-low BMI women.[12] In a double-blind RCT study in Mexico, MMN supplementation had no additional effect on improving the size, LBW, IUGR and PTD over iron-only supplemented group[132] and the risk was also higher in subjects with low food iron intake in pregnant adolescents.[11] Another study has shown a significant association between anemic women and fetal head circumferences ie maternal hemoglobin has a positive relationship with the neonatal measurements of weight, length and head circumference,[133] and also between anemic pregnant women and PTD or LBW (<37weeks) than non-anemic pregnant women.[133] In a prospective cohort study, ID and anemia are associated with more weight in the third trimester.[134] In contrary to others, this study also concluded that neither maternal iron status nor anemia was related to weight.[135] Most recently, a meta-analysis from LMICs compared to placebo or no treatment, iron supplementation reduced the risk of maternal anemia by 47% and reduced the risk of having an LBW by 12%. However, no effect of iron was found on the risk of perinatal mortality in the existence of raised maternal serum ferritin concentrations. It also has little effect on increasing maternal transferrin receptor concentration, on reducing the risk of pre-eclampsia, neonatal mortality, infant mortality, PTB and SGA.[13] Besides, it also identified the lack of impact of MMN supplementation on maternal mortality, perinatal mortality, maternal anemia, and iron deficiency anemia. However, in a meta-analysis of 17 RCTs, MMN supplementation showed a 15% reduction on the risk of delivering an LBW, 9% reduction on the risk of stillbirths, a 7% reduction on the risk of SGA infants, 16% reduction on the risk of diarrhea among children ages 6 months to under-five and a raised serum retinol level when compared to iron with or without folic acid.[20,134] Similarly in a meta-analysis study, MMNs reduced the risk of LBW but has no overall effect on perinatal mortality in developing countries.[136] Though further studies are mandatory, the presumed absence of usefulness of MMNs in reducing perinatal mortality remained as one of the challenges in replacing IFA with MMN.[22] However, these results depicted the absence of a consensus as genetic and environmental factors that contribute to the early death of the fetus by the natural process (via abortion and stillbirth) could be temporarily prevented upon MMNs supplementation resulting in later neonatal or perinatal mortality. Moreover, the level of education, place of residence and quality of health care are also the major associated factors that could result in neonatal mortality. The WHO guidelines for ANC recommend IFA rather than MMN during pregnancy to prevent the risk of neonatal mortality since 2016.[22] Currently, findings are in favor of MMN supplementation than IFA as it reduces LBW, SGA and reduced risk of neonatal mortality. Especially in LMICs where there is a generalized deficiency of MMNs, WHO should revise the ANC recommendations in favor of MMNs as it will ensure positive pregnancy outcomes which minimize adverse effects accompanied by lower treatment costs.[13,14] However, the current WHO guideline does not interdict MMNs as it advises their use on condition.

Calcium supplementation is associated with a significant protective benefit over pre-eclampsia compared to placebo but did not impact the risk of having LBW, stillbirths, PTD, or Caesarean section as a mode of delivery[13] and it also improved mean infant weight without the prevention of PTD or LBW.[111] On the other hand, a review indicated that calcium supplementation during pregnancy reduces the incidence of gestational hypertension by 35%, pre-eclampsia by 52%–55%, and PTD by 24%.[17] Likewise, vitamin D supplementation therapy in pregnancy could help in reducing the incidence of pre-eclampsia on an RCT in Iraq.[112] This could make also calcium and vitamin D very essential as hemorrhage, hypertension, sepsis, abortion and embolism are the leading causes of maternal death where hypertension (pre-eclampsia) accounts for 14%.[137] Findings also showed that vitamin D supplementation might have reduced the risk of PTD by 36%. It was noted in studies that vitamin D had a greater reduction in PTB risk compared to studies that provided additional supplements such as iron and folic acid. Vitamin D supplementation made no difference in the risk of infants born as SGA, the risk of having a Caesarean section as a mode of delivery, or maternal serum calcium concentrations, but did significantly increase the vitamin D concentrations in pregnant mothers.[13] However, many studies have conflicting results on vitamin D deficiency and adverse pregnancy outcomes like preeclampsia, GDM, LBW, PTB, and Cesarean delivery necessitating further studies.[112] Although global estimates of other deficiencies are unavailable, population-based studies in South Asia including India, Bangladesh, and Nepal have reported those for zinc (15–74%), VB12 (19–74%), VE (as α-tocopherol,50–70%) and folate (0–26%) in pregnant women. In Ivory Coast, the prevalence of deficiencies among women of reproductive age varied widely for VA (1%), iron (17%), VB12 (18%) and folate (86%). In the plains of Southern Nepal, the prevalence of MN deficiencies in pregnant women include VA (7%), VIT. D (14%), VE (25%), B12 (28%), B2 (33%), B6 (40%), folate (12%), iron (40%) and zinc (61%) which are even severe in rural areas while 4% have normal MN status.[59] Moreover, a study on serum zinc, copper, selenium, calcium and magnesium levels in pregnant and non-pregnant women in Gondar, Northwest Ethiopia reported that deficiency in one, two, three, or four mineral elements were observed in 44.8%, 14.4%, 9.9%, and 5.1% of the pregnant women, respectively.[29] Another study also indicated that trace elements like copper, magnesium, selenium and zinc have an association with complications of pregnancy.[31] Besides, a recent meta-analysis conducted from 2005 up to 2015 in Ethiopia, Nigeria, Kenya and South Africa reported that 19–61% had ID (9% in Ethiopia and 47% in Nigeria), VAD ranged from 31–48%; folate deficiency was 12% to 4% and zinc deficiency from 56% to 46% in Ethiopia and Nigeria, respectively with Iodine deficiency reported in Ethiopia only as 87%.[29]

## Vitamins Deficiency and Adverse Pregnancy Outcomes

The global prevalence of vitamin deficiencies is unidentified due to limited national representative data.[26] For instance, riboflavin deficiencies (RD) are quite common in many parts of the developing world and there is sparse data on the extent of this deficiency though it can be measured easily on urinary or serum levels with day to day variation. Studies conducted in India, China, Guatemala and Gambia, have found that 50% of pregnant and lactating women had subclinical RD. VA and riboflavin play a role in iron metabolism and there is significantly improved iron status and reduced anemia in young children and pregnant women compared with those taking only one nutrient promoting MMN.[55]

Vitamin A is required for vision, maintaining cell function for growth, immune function, hematopoietic system, epithelial integrity, red blood cell production, immunity and reproduction, especially during pregnancy. Vitamins A and E deficiencies were associated with very LBW infants.[138] Vitamin A deficiency (VAD) typically resulted in xerophthalmia with serum levels of VA<0.35μmol/dl with serum retinol level considered the most widely used biochemical indicator of VA status. Studies estimated 3.3million young children with clinical VAD with the larger proportions in South East Asia, Africa and America[139] where deficiencies during pregnancy could also be contributing factors. Besides, studies in pregnant women from Nepal, Philippines, Zambia, Ghana and Mali have reported prevalence values for VAD (serum retinol level<20μg/dl) from 19–38%. Studies also indicated that VAD was related to PTD, IUGR, LBW and embryonic development.[140,141] Weekly vitamin A or ß-carotene supplement during pregnancy also reduced maternal mortality by 50% in a controlled trial in Nepal.[31] However, a recent review indicated that Vitamin A supplementation, compared to placebo, showed no impact on maternal mortality, nor any effect on the risk of stillbirths or maternal hemoglobin concentration but an increase in serum retinol level.[13] VAD is also considered to cause anemia through multiple mechanisms, including the role of retinoids in erythropoiesis and vitamin A importance for immune function and iron metabolism.[127] Another cross-sectional study in India reported an association of PTD and maternal anemia with VAD[140] also indicates the role of VA in minimizing anemia. Besides, a case-control-cross sectional study in India associated VAD with IUGR.[141]

During pregnancy, a placenta is a place of dynamic oxygen metabolism that constantly releases oxidizing species that obliterate normal placental functions. Therefore, the fetoplacental unit should generate abundant antioxidants like glutathione peroxidases (selenium) and superoxide dismutases (copper, zinc and manganese) as well as vitamin C and E.[59,67] Vitamin E is used for maintaining the metabolic function of the body and it possesses antioxidant and scavenging free radical activities.[142] However, another meta-analysis found that supplementation with vitamins C and E during pregnancy does not prevent pre-eclampsia.[143] Besides, supplementation with three or more MN was associated with a 39% reduction in maternal anemia compared with placebo or with two MN or fewer.[5] On the other hand, deficiencies of VB6, VB12 and folate might contribute to disturbances in gametogenesis, fertilization and development of embryo before implantation, which was associated with systemic and follicular homocysteine level. Although VE, Selenium, zinc, copper and iodine deficiencies have also been associated with miscarriages, specific MN functions that support these outcomes are rare. The other striking feature of individual MN is their availability in antioxidant enzymes like glutathione peroxidases (selenium), superoxide dismutase (copper, zinc and manganese), which are essential for protecting the embryo and placenta from pre-eclampsia and poor fetal growth. Iron-containing MMN supplementation also was associated with a reduced risk of pregnancy-induced hypertension compared with folic acid only supplements in a recent RCT study in China. Dietary antioxidant supplements, such as Vitamin C, E copper, zinc, selenium and Vitamin B12 have been associated with reduced oxidative stress and improved endothelial function reducing hypertension in pregnancy.[144] Moreover, poor selenium status had an association with increased risk of spontaneous miscarriage, pre-eclampsia, PTD and gestational diabetes.[145] Besides, Iron, zinc, B vitamins and iodine are helpful for neural development and gestational iron deficiency conferred risk chiefly to the development of the hippocampus and altered brain energy metabolism, neurotransmitter system and myelination.[59] In 2016, WHO reviewed its ANC recommendation and acknowledged that policymakers in a population with a high prevalence of nutritional deficiencies might wish to provide MMN supplements containing IFA. However, WHO did not universally recommend MMN supplements, observing that there was evidence of benefit but also harm.[22] Interestingly, recent researches are emerging which pushes for the recommendation of using MMN than IFA.[146] Similarly, MMN supplementation is advisable than IFA alone for the maternal, fetal and children healthy outcomes.[6]

## Conclusion

In conclusion, MN including vitamins, minerals and trace elements are very essential for the health of the mother, fetus, infant, the developing child and prospective generation development along with macronutrients. Though MMNs are needed in smaller amounts, their deficiencies especially during the periconceptional period resulted in adverse birth outcomes such as anemia, visual problems, pre-eclampsia, NTDs, metabolic and cardiovascular disorders (CVD), LBW, PTD, SGA, stillbirth, perinatal, neonatal and child mortalities. Many studies on MMN and individual MN tried to depict the effect of MMN in reducing pre-eclampsia, NTDs, LBW and anemia. Though equivocal, MMN has also been found in several studies to reduce the risk of PTD, SGA, stillbirth, perinatal, infant and child mortality. Interestingly, pregnant women with low body weight or anemia can also benefit from MMN supplementation as it protects adverse pregnancy outcomes. Besides, many studies are recommending MMN-IFA than IFA alone which may also reinforce the decision of WHO to revise the ANC guidelines which allow the antenatal use of IFA than MMN supplementation. These MMN can be also helpful both in the developed and developing countries as the MMN deficiencies are present in both, with varying degrees. Although MMN has been shown to have greater health benefits, mortalities associated with them are the challenges that should be addressed and investigated. This could be either related to MMN consumption or due to other factors like inherent genetic abnormalities, level of education of the woman, place of residence, utilization of health services during preconception, antenatal and postnatal periods and preconception BMI of the woman as it was also observed in the articles reviewed in this paper. Especially, the future genetic fetal diagnosis could identify the root causes of mortalities as early deaths of the fetus due to inherent abnormalities (which could cause abortion) may be prolonged, upon the use of MMN, to cause late stillbirth or perinatal mortality. Hence, over-assessment of mortalities during MMN researches may be curtailed, enabling one step ahead on its benefit over IFA during pregnancy. Moreover, recent studies also are recommending MMN as they have benefits over IFA with no significant difference in the risk of stillbirth, perinatal and infant mortalities. In those mothers with MN deficiencies, which are prevailing in SSA countries like Ethiopia, fortification of the diet (if possible) or MMN supplementation than IFA will have a principal effect on reducing adverse pregnancy outcomes accompanied by a major drop of disability treatment costs.

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