Multiple micronutrient supplement

Essential medicine status

Section: 22. Medicines for reproductive health and perinatal care > 22.5. Other medicines administered to the mother

ATC codes: A11AA01

Indication	Maternal care for other specified conditions predominantly related to pregnancy ICD11 code: JA65.Y
Medicine type	Chemical agent
List type	Core
Additional notes	For use in specific contexts. Refer to current WHO recommendations.
Formulations	Tablet containing: Vit A: 800 mcg retinol activity equivalent Vit C: 70 mg Vit D: 5 mcg (200 IU) Vit E: 10 mg alpha tocopherol equivalent Vit B1: 1.4 mg Vit B2: 1.4 mg Vit B3: 18 mg niacin equivalent Vit B6: 1.9 mg Folic acid: 400 mcg Vit B12: 2.6 mcg Iron: 30 mg Iodine: 150 mcg Zinc: 15 mg Selenium: 65 mcg Copper: 2 mg
EML status history	First added in 2021 (TRS 1035)
Sex	Female
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Multiple micronutrient supplement

Expert Committee recommendation

The Expert Committee noted the high prevalence of nutritional deficiencies in low- and middle-income countries where many women enter pregnancy already malnourished. Deficiencies of multiple essential vitamins and minerals result in potentially severe health consequences for pregnant women and their infants, including increased maternal and perinatal mortality. The Committee noted that evidence from over 20 randomized trials conducted across multiple countries, often at low risk of bias, demonstrates that daily supplementation with multiple micronutrient supplements in pregnancy compared with supplementation with iron and folic acid alone improves pregnancy outcomes. While the evidence does not show benefits in terms of neonatal and maternal mortality, it does show a relevant reduction in the risk of small for gestational age births, low birth weight and preterm and very preterm births. Data on mortality are affected by the high heterogeneity among studies. The evidence also shows that multiple micronutrient supplements are safe and cost-effective compared with iron and folic acid supplements, particularly where the prevalence of undernourished women is high. The Committee noted recommendations about use of multiple micronutrient supplements in pregnant women included in WHO guidelines, and joint WHO, UNICEF and World Food Programme guidelines. All recommendations agree on the direction of the recommendation (i.e. recommending multiple micronutrient supplements in certain situations), despite differences in terms of the strength and scope of the recommendations at the population level (e.g. restriction to emergency settings, use in women with tuberculosis or use in the context of research). The Committee agreed that more research is needed on the effects of switching from daily iron and folic acid supplements containing a 60 mg dose of elemental iron to daily multiple micronutrient supplements containing a lower dose (30 mg) of elemental iron in populations with a high prevalence of iron deficiency anaemia, but also recognized that there is no evidence of harm in this group. The Committee considered, however, that listing multiple micronutrient supplements as an essential medicine would not prevent answering this important question and similar questions (e.g. the potential interactions between different micronutrients) and may facilitate research. The Committee also expressed reservations about the probability that new trials will be started and completed in the short term to further explore the benefits and harms of multiple micronutrient supplements or their acceptability compared with tablets with a smaller number of micronutrients. Implementation research on the adoption of multiple micronutrient supplements will be informative, but it is unlikely that this evidence will change the cumulative evidence reached so far, with a benefit-to-harm ratio clearly in favour of multiple micronutrient supplements. The Committee therefore recommended listing multiple micronutrient supplements on the core list of the EML for the use as an antenatal supplement in pregnant women. The Committee considered that further evidence on the adequacy of the daily elemental iron dose in multiple micronutrient supplements is desirable.

Background

Multiple micronutrient supplements for use as an antenatal supplement for pregnant women have not previously been considered for inclusion on the EML.

Public health relevance

Sufficient intake of micronutrients are required during pregnancy to support maternal health and normal fetal development (2). Globally, many pregnant women do not meet these requirements, which has negative consequences for their own health as well as for the health, growth and development of their infants. Insufficient nutrient intake before and during pregnancy, combined with increased metabolic demands during pregnancy, results in severe nutritional deficiencies, particularly in low- and middle-income countries where many women enter pregnancy already malnourished. Maternal anaemia is the most common micronutrient deficiency, affecting 40% of pregnant women globally. In the WHO regions, South-East Asia (49%), Africa (46%) and the Eastern Mediterranean (41%) have the highest prevalence followed by Western Pacific (33%), the Americas (26%) and Europe (27%) (3). While anaemia is not always due to iron deficiency, a 2013 analysis suggested that 19.2% of pregnant women in low- and middle-income countries had iron deficiency anaemia (4). A literature review of micronutrient deficiencies found that vitamin D, iodine and zinc deficiencies were widespread in women of reproductive age. On average in low- and middle-income countries, 63.2% of women of reproductive age were vitamin D deficient, 41.4% were zinc deficient, 31.2% were anaemic, 22.7% were folate deficient and 15.9% were vitamin A deficient, using WHO cut-off criteria for each indicator (5). Adverse pregnancy outcomes, including low birth weight (LBW), small for gestational age, preterm birth and perinatal mortality, are relatively common in low- and middle-income countries, and are associated with micronutrient deficiencies. Overall, 14.6% of all live births in low- and middle-income countries in 2015 were LBW (< 2500 g) with South Asia having the greatest burden (26.4%) (6). Babies that are preterm or small for gestational age have an increased mortality risk (7). On the basis of secondary analyses of data from the 2012 Child Health Epidemiology Reference Group in low- and middle-income countries, an estimated 23.3 million infants, or 19.3% of all live births, were small for gestational age, and an estimated 606 500 neonatal deaths (21.9% of all neonatal deaths) were attributable to being small for gestational age. Infants that are small for gestational age are defined as those weighing < 10th centile of birth weight-for-gestational age and sex according to the multiethnic, INTERGROWTH-21st birth weight standard (8). South Asia also had the highest prevalence of infants born small for gestational age (34% of all live births). A 2018 review assessing data from national registries, reproductive health surveys and published studies estimated that 14.84 million children, or 10.6% of live births, were born preterm worldwide in 2014. More than 80% of preterm babies were born in Asia (7.8 million or 10.4% of live births) and sub-Saharan Africa (4.2 million or 12.0% of live births) (9). Global estimates for stillbirths and neonatal mortality are 18.4 per 1000 total births and 18.6 per 1000 live births, respectively, with regionally higher prevalence in sub-Saharan Africa and South Asia (10, 11).

Benefits

To date, 21 clinical trials have compared the use of multiple micronutrient supplements with iron and folic acid supplements in pregnant women in low- and middle-income countries, and 10 of these trials used the UNIMMAP formulation. Two meta-analyses compared multiple micronutrient supplements with iron and folic acid supplements from trial data, including a 2019 Cochrane review that included 19 trials (12) and a 2017 individual patient data meta-analysis of 17 trials (13). The Cochrane review showed that, overall, multiple micronutrient supplements resulted in a 12% reduction in low birth weight (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.85 to 0.91) and an 8% reduction in births of babies that were small for gestational age (RR 0.92, 95% CI 0.88 to 0.97) compared with iron and folic acid supplementation, with high and moderate quality evidence (based on GRADE criteria), respectively (12). No significant differences were found for other maternal or pregnancy outcomes assessed, including preterm birth, stillbirth, maternal anaemia in the third trimester, miscarriage, maternal mortality, perinatal mortality, neonatal mortality or risk of delivery by caesarean section, when multiple micronutrient supplements were compared with supplementation with iron with or without folic acid. The Cochrane review included several population-level subgroup analyses, including analyses that stratified based on the study-specific averages of maternal body mass index, maternal height, timing of supplementation and iron dose (12). Based on the 10 trials in which the average maternal body mass index was ≥ 20 kg/m2, there was evidence of a lower incidence of babies born small for gestational age among women who received multiple micronutrient supplements compared with those who received iron and folic acid supplementation ($P = 0.001$). However, there was no evidence of a difference based on the three trials where the mean body mass index was < 20 kg/m2. Similarly, based on the six trials in which the average maternal height was ≥ 154.9 cm, multiple micronutrient supplementation was associated with a reduction in babies born small for gestational age compared with those who received iron and folic acid supplementation ($P < 0.001$), while no effect was seen in the eight trials in which the average maternal height was < 154.9 cm. Thus, while the review suggests that multiple micronutrient supplements reduce the risk of babies born small for gestational age, this effect was only seen in women with better nutritional status, as defined by a height of at least 154.9 cm or a body mass index of at least 20 kg/m2. Based on trials in which the average maternal body mass index was < 20 kg/m2, women receiving multiple micronutrient supplements had a lower rate of preterm birth compared with those who received iron and folic acid supplementation ($P < 0.001$), whereas no difference for preterm birth was observed among trials in which the average body mass index was ≥ 20 kg/m2. No statistically significant subgroup differences were found by the dose of iron for preterm birth, small for gestational age birth or perinatal mortality based on 15 studies included in this subgroup analysis. The 2017 individual patient data meta-analysis found that multiple micronutrient supplements reduce the risk of stillbirth (on the basis of fixed-effects analysis), very low birth weight, low birth weight, early preterm birth, preterm birth and small for gestational age birth (by the standards of the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) and Oken reference) compared with iron and folic acid supplementation (13). This analysis also found an increased risk of being born large for gestational age (by INTERGROWTH-21st standards but not by Oken reference) in women taking multiple micronutrient supplements. While this finding may raise concerns about increased risk of obstructed labour and/or asphyxiation, the authors noted that multiple micronutrient supplementation was not associated with increased risk of stillbirth or mortality at any time point, including among women with short stature (< 150 cm), who are more likely to be at risk of obstructed labour. Twenty-six subgroup analyses were conducted with numerous outcomes to identify individual characteristics that may modify the effect of multiple micronutrient supplementation compared with iron and folic acid supplementation alone. Subgroup analyses found that the beneficial effects of multiple micronutrient supplementation compared with iron and folic acid supplementation were greater in anaemic pregnant women than non-anaemic pregnant women for low birth weight (19% reduction versus 9% reduction), small for gestational age births (8% reduction versus 1%) and 6-month infant mortality (29% reduction versus 7% reduction). The effects of multiple micronutrient supplementation compared with iron and folic acid supplementation in reducing the risk of preterm birth were greater in underweight pregnant women than non-underweight women (16% reduction versus 6% reduction). The effects of maternal multiple micronutrient supplementation compared with iron and folic acid supplementation in reducing mortality were greater in female infants than male infants for neonatal mortality (15% reduction versus 6% increase), 6-month mortality (15% reduction versus 2% reduction) and infant mortality (13% reduction versus 5% increase). The effects of multiple micronutrient supplementation compared with iron and folic acid supplementation in reducing the risk of preterm birth were greater in women who started supplementation before 20 weeks of gestation than those who started after 20 weeks (11% reduction versus no change after 20 weeks). However, the effects of multiple micronutrient supplementation compared with iron and folic acid supplementation in reducing the risk of stillbirth were greater in women who started supplementation after 20 weeks of gestation than those who started before 20 weeks (19% reduction versus 3% reduction). The effects of multiple micronutrient supplementation compared with iron and folic acid supplementation in reducing mortality were greater when adherence was ≥ 95% versus < 95% for neonatal mortality (12% reduction versus 5% increase) and infant mortality (15% reduction versus 6% increase). Multiple micronutrient supplementation did not have any significant effect on the risk of stillbirth, or neonatal, 6-month or infant mortality in any of the 26 subgroups analysed compared with iron and folic acid supplementation.

Harms

The Cochrane review found no harms for multiple micronutrient supplementation in terms of mortality outcomes (stillbirths, perinatal and neonatal mortality) (12). This conclusion was supported by two trials that were statistically powered to analyse the effect on early infant mortality. A large trial in Bangladesh did not find an increase in neonatal or early infant mortality risk in the multiple micronutrient supplementation group versus the control (iron and folic acid supplementation). In a posthoc analysis, however, higher neonatal mortality was reported in male infants due to birth asphyxia (14). The Cochrane review authors concluded that these findings should be interpreted with caution due to potential misclassification of the underlying cause of death, which was ascertained by verbal autopsy with parents (12). A recent analysis examined the risk of exceeding the upper intake level, as set by the United States National Academy of Medicine, of any micronutrient in the UNIMMAP formulation if it is consumed with a nutritionally adequate diet (15). In this case, most of the micronutrient intakes remain well below the upper level and only iron, folic acid and niacin would meet or slightly exceed the upper level. For niacin, the upper level is based on the side-effect of flushing and only occurs with the synthetic form nicotinic acid, which is not used in dietary supplements. UNIMMAP contains 18 mg of nicotinamide (not nicotinic acid) so this does not contribute to the upper intake level. If niacin were present in the form of nicotinic acid, it would still be well below the upper intake level of 35 mg/day (15). For folic acid, there are no known side-effects for reaching the upper level. Rather, the upper level is set based on the risk of masking the diagnosis of pernicious anaemia, which can occur with high folate intake in the presence of vitamin B12 deficiency. However, multiple micronutrient supplementation contains vitamin B12, which reduces this risk (15). The National Academy of Medicine gives the upper level for iron as 45 mg/day based on gastrointestinal side-effects which are most commonly reported when a supplement is taken on an empty stomach and would be a concern for both multiple micronutrient supplementation and iron and folic acid supplementation. WHO recommends pregnant women receive between 30 mg and 60 mg of iron a day (16), which is met by the UNIMMAP formulation. Importantly, the upper levels are set for the healthy population and do not apply to the treatment of iron deficiency anaemia in which case the daily iron intake may need to exceed the upper level (15).

Cost / cost effectiveness

The current listed price of the multiple micronutrient supplements provided by the UNICEF Supply Catalogue website is US$ 1.79 for 100 tablets (product no. S1580101) (20). To provide 6-month coverage per individual, the unit cost adjusted to 180 tablets is US$ 3.22. Depending on the packaging and other variables, the price can vary considerably, but based on information from global manufacturers and UNICEF, the median price for a 180-tablet bottle is US$ 2.50 for a purchase at scale. The cost of the supplements is important to know as well as the programme implementation costs, including national-level administration, training, nutrition education programmes and supervision. The estimated programmatic roll-out cost is US$ 0.42 per patient, using a published calculation methodology (21). Several recent studies have shown the cost–effectiveness of multiple micronutrient supplementation compared to iron and folic acid supplementation. A 2019 analysis modelled the cost–effectiveness of the two interventions in Pakistan, India and Bangladesh (22). The analysis found that multiple micronutrient supplementation would avert 4391, 5769 and 8578 more disability-adjusted life years (DALYs) than iron and folic acid supplementation per 100 000 pregnancies in Pakistan, India and Bangladesh, respectively (62.6%, 76.8%, and 82.6% certainty). The incremental cost–effectiveness ratio of transitioning from iron and folic acid supplementation to multiple micronutrient supplementation was US$ 41.54, US$ 31.62 and US$ 21.26 per DALY averted, for Pakistan, India and Bangladesh, respectively. This study concluded that multiple micronutrient supplementation was cost-effective and resulted in positive health outcomes for both infants and pregnant women, and supports the transition from iron and folic acid supplementation to multiple micronutrient supplementation in Pakistan, India, and Bangladesh. This modelling was subsequently done for 29 additional countries, which found multiple micronutrient supplementation was highly cost-effective in all scenarios modelled (23). Another 2019 modelling analysis that evaluated the cost–effectiveness of transitioning from iron and folic acid supplementation to multiple micronutrient supplementation focused on Bangladesh and Burkina Faso (24). The analysis found that transitioning to multiple micronutrient supplementation could avert more than 15 000 deaths and 30 000 cases of preterm birth annually in Bangladesh (compared with iron and folic acid supplementation) and more than 5000 deaths and 5000 cases of preterm births in Burkina Faso. The cost per death averted was US$ 175–185 in Bangladesh and US$ 112–125 in Burkina Faso.

WHO guidelines

The 2020 WHO antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: multiple micronutrient supplements during pregnancy (16), recommend antenatal multiple micronutrient supplementation only "in the context of rigorous research". This recommendation updates the 2016 guidelines (17), when antenatal multiple micronutrient supplementation was not recommended. The recommendation was changed because, while the evidence suggests that there may be a limited benefit and little harm in replacing iron and folic acid supplements with multiple micronutrient supplements, the evidence on low birth weight and its component parts (preterm birth and small for gestational age birth) was difficult to interpret. Gestational age accurately assessed by ultrasound emerged as an important feature of future trials. In addition, the sustainability of changing to the higher-cost multiple micronutrient supplements is not known and more evidence is needed on the effects of changing to a 30 mg dose of iron from a higher dose of iron (e.g. 60 mg), particularly in settings where higher doses of iron are routinely used due to a high prevalence of anaemia or other reasons. The 2013 WHO guidelines for nutritional care and support for patients with tuberculosis (18) recommend that all pregnant women with active tuberculosis receive multiple micronutrient supplements that contain iron and folic acid and other vitamins and minerals, according to the UNIMMAP, to complement their maternal micronutrient needs (conditional recommendation, very low quality evidence). Multiple micronutrient supplementation has also been recommended by WHO, UNICEF and the World Food Programme for pregnant women affected by an emergency (19).

Availability

Antenatal micronutrient supplements, with similar formulations to UNIMMAP, which provide about 1 recommended dietary allowance (RDA) a day of approximately 15 micronutrients, are widely available in pharmacies and other market places globally. A market assessment of 32 low- and middle-income countries found that every country had either locally manufactured or imported maternal multiple micronutrient supplementation products containing at least 10 micronutrients (25). While none of the multiple micronutrient supplementation products matched the UNIMMAP formulation, the wide availability of multiple micronutrient formulations indicates that there is global manufacturing capacity that could meet the global need for a UNIMMAP-multiple micronutrient supplementation product. As with most nutrition supplements, no global consensus exists on the regulatory status of the multiple micronutrient supplementation product for pregnant women. At the individual country-level, this product can be considered either as a dietary supplement and regulated as a food, or as a therapeutic product that is regulated as a drug. In some countries, including the India, Japan, USA, and European Union countries, multiple micronutrient supplements are regulated as a dietary supplement, while in other countries, such as Australia, Bangladesh, Mexico and New Zealand, multiple micronutrient supplements are regulated as a drug. The regulatory classification of multiple micronutrient supplements can have implications for how the product is manufactured, imported, packaged, distributed and/or promoted. To help establish a product that conforms to internationally recognized good manufacturing practice (GMP) requirements and pharmacopoeial standards, the Expert consensus UNIMMAP – MMS product specification was created by an expert panel hosted jointly by the New York Academy of Sciences and the Micronutrient Forum (26). Manufacturers of supplements must be registered entities and certified as adhering to GMP requirements. For GMP, these include the requirements of the Australian Therapeutics Goods Administration, Health Canada, US Food and Drug Administration, or the WHO for the manufacture of nutritional products. For pharmacopoeias, these include quality standards for nutritional supplements as set by the British Pharmacopeia, European Pharmacopeia, International Pharmacopeia, Japanese Pharmacopeia and US Pharmacopeia. Currently, four companies manufacture a UNIMMAP-formulated product for global distribution: Contract Pharmacal Corporation, DSM Nutritional Products, Lekapharm and Lomapharm. In addition, there are companies manufacturing a multiple micronutrient supplementation product for local distribution, such as Beximco and Renata in Bangladesh. The Renata product will conform to the Expert consensus UNIMMAP – MMS product specification.

Other considerations

The Committee noted the many letters of support received in relation to this application.

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