Prevention of intrauterine growth retardation by multiple micronutrient supplements during pregnancy in Burkina Faso

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Summary

Chapter 1: General introduction and study objectives
Intra Uterine Growth Retardation (IUGR) exerts vital consequences for the infant in the short term, but will also impact the individual’s health trajectory throughout the life course. Moreover, women born with a low birth weight (LBW; birth weight<2500 g) are more likely to give birth to infants with LBW, contributing to the trans-generational cycle of malnutrition and poverty. Therefore, improving foetal growth may confer both short- and long-term benefits for the offspring. IUGR is highly prevalent in Africa and Asia, and multiple micronutrient deficiencies during pregnancy are considered an important risk factor. This is why we tested the health benefits of a prenatal supplement containing 1 RDA of 15 micronutrients (UNIMMAP) on pregnancy outcomes in comparison with the usual WHO recommended iron+folic acid supplements (IFA).

Composition of the UNIMMAP and IFA supplement

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Form</th>
<th>IFA</th>
<th>UNIMMAP</th>
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<tbody>
<tr>
<td>Vitamin A, µg</td>
<td>Retinol</td>
<td>-</td>
<td>800</td>
</tr>
<tr>
<td>Vitamin B-1, mg</td>
<td>Thiamine HCL</td>
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<tr>
<td>Vitamin B-2, mg</td>
<td>Riboflavin</td>
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<td>Vitamin B-3, mg</td>
<td>Nicotinamide</td>
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<td>Vitamin B-6, mg</td>
<td>Pyrodoxine</td>
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<td>Vitamin B-9, µg</td>
<td>Folic acid</td>
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<td>Vitamin B-12, µg</td>
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<td>Vitamin C, mg</td>
<td>Ascorbic acid</td>
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<tr>
<td>Vitamin D, µg</td>
<td>Cholecalciferol</td>
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<td>Zinc sulfate</td>
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<tr>
<td>Copper, mg</td>
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<tr>
<td>Selenium, µg</td>
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</tr>
<tr>
<td>Iodine, µg</td>
<td>Potassium iodide</td>
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<td>150</td>
</tr>
</tbody>
</table>

IFA: Iron and Folic Acid; UNIMMAP: UNICEF/WHO/UNU Multiple Micronutrient supplement for pregnancy and lactating women

For this purpose we set up a double-blind randomized controlled trial (registered at Clinicaltrials.gov as NCT00642408) in the catchment area of two health centres in Houndé district, Burkina Faso. Participating women (n=1426) were recruited as early as possible during pregnancy and randomized to receive either UNIMMAP or IFA until delivery. The intake of both supplements was directly observed by home visitors. After delivery, infants were followed up to their first birthday for health and growth monitoring.

Chapter 2: Dietary behaviour, food and nutrient intake of pregnant women in a rural community in Burkina Faso
We assessed dietary habits during pregnancy in the study population through an interactive 24-h recall survey (n=218) and in-depth interviews (n=37). To contrast the results, we also assessed the diet of non-pregnant women (n=176).

The cereal-based diet of pregnant women was globally deficient in several micronutrients such as zinc, iron, thiamine, riboflavin, niacin, vitamin B6, acid folic, vitamin A and vitamin C. The majority of interviewees reported dietary restrictions during pregnancy, but we found no consistent pattern of avoided food types, except two which were recurrently cited: ‘sweet’ food items, like honey and sugar, particularly among Mossi people, and ‘cold’ or ‘cooled down’ meals. Such restrictions were meaningful within the cultural framework of the
interviewees. In contrast, the term ‘vitamin’, which referred to the iron and folic acid tablets, was strikingly widespread in this rural, mostly illiterate, community. Between traditions and modern recommendations, pregnant women displayed pragmatism in adapting their food intake to their individual needs.

Consistently, no quantitative differences were observed in food intake, food choice and nutrient intake between pregnant and non-pregnant women. During the third trimester of gestation women did not show any major differences in food and nutrient intake compared with women in their first/second gestational trimester. The mean nutrient intakes were found to be insufficient compared with the recommended daily allowances, especially for pregnant women.

In conclusion, pregnant women in this rural area of Burkina Faso do not seem to restrict their diet significantly during pregnancy. The additional nutritional requirements of pregnancy are not accounted for in their dietary practices.

Chapter 3: Effects of maternal multiple micronutrient supplements on fetal growth.

Pregnancy outcome was known in 96.3% of the 1426 trial participants. Overall, 15.1% of singleton newborns had a low birth weight (birth weight<2 500 g) and 39.7% were small for their gestational age (birth weight below the 10th percentile of a reference population with same gestational age). After adjustment for gestational age at delivery, birth weight [52 g; (95% CI: 4, 100); p=0.035], birth length [3.6 mm; (95% CI: 0.8, 6.3); p=0.012], arm circumference [1.2 mm; (95% CI: 0.2, 2.3); p=0.020], and chest circumference [2.8 mm; (95% CI: 0.1, 5.6); p=0.041] were all significantly higher in the UNIMMAP group . There was no difference between trial arms in the Rohrer index or head circumference.

UNIMMAP had a differential effect by percentiles of birth weight and length distributions. The risk of large-for-gestational-age infants was higher in the UNIMMAP group [OR: 1.58; (95% CI: 1.04, 2.38); p=0.03], although the risk of low birth weight remained unchanged. The effect of UNIMMAP on birth size was modified by maternal body mass index at enrolment, the effect of UNIMMAP being the highest in newborns whose mother had the highest BMI, and could be more important in multiparous than in primiparous women and in women taking sulfadoxine-pyrimethamine instead of chloroquine for malaria prevention. Primigravidity was also associated with lower maternal height, arm circumference, and haemoglobin concentration, and the own nutritional needs of the mother might have competed with those of the fetus, resulting in no benefit of UNIMMAP on newborn outcomes.

Unexpectedly, the risk of perinatal death was increased in the UNIMMAP group with marginal statistical significance [OR: 1.78; (95% CI: 0.95, 3.32); p=0.07], and this seemed to affect mainly primiparous women [OR: 3.44; (95% CI: 1.1, 10.7); p for interaction=0.11]. We were unable to assess the association of this excess mortality with cephalopelvic disproportion for large babies as stillbirths were not measured. However, this explanation was unlikely in our case because half (20 of 40) of the perinatal deaths were premature. That UNIMMAP improved the survival of frail fetuses unable to survive the trauma of birth was an implausible alternative explanation, as the risk of miscarriage was not reduced in the UNIMMAP group.

The question of potential harms linked to UNIMMAP utilization is discussed in details in Chapter 8.

Chapter 4: Effect of maternal multiple micronutrient supplements on cord blood hormones

We assessed whether the effect of UNIMMAP on foetal growth was mediated by hormonal changes in cord blood. For this purpose we measured the concentration of insulin-like growth factor I (IGF-I), leptin, insulin, free thyroxine (T4), and cortisol in cord serum in a sub-sample of 294 live singleton newborns. As expected, IGF-I and leptin were two independent
predictors of birth weight. Growth-retarded infants had 41.2% lower IGF-I (p < 0.0001) and 27.3% lower leptin (p = 0.04) than did infants with normal growth. However, we detected no overall effect of UNIMMAP supplementation on cord hormone concentrations, comparatively to the IFA group. UNIMMAP significantly affected concentrations of IGF-I [+30%, (95% CI: 8%, 52%); p = 0.009] and leptin in male newborns. In these infants, 51.1% (p = 0.08) of the effect of UNIMMAP supplementation on birth weight was mediated through IGF-I, whereas for female newborns, this proportion was negligible. We found that primiparae presented a specific hormonal pattern, with lower IGF-I, insulin, and fT4, and higher cortisol, than in samples from multiparous women. UNIMMAP supplementation increased cortisol cord concentration by 36% (p = 0.009) in these individuals (p for interaction = 0.02).

In conclusion, it does not seem that the effect of UNIMMAP on foetal growth was mediated through clear-cut hormonal changes in cord blood. This could be due to the relatively small sample size, to a mediation of UNIMMAP effect through other hormones which were not measured, such as placental lactogen, or to IFA being also active on cord hormone concentrations.

Chapter 5: Assessment of a dose-response relation between prenatal iron intake and maternal hemoglobin?

Prenatal micronutrients may affect foetal growth through a change in maternal haemoglobin. As UNIMMAP contains half the amount of iron of IFA, the dynamic of the physiologic responses may have varied. For instance, the effect on maternal haemoglobin might have been achieved more rapidly with IFA than with UNIMMAP given the higher iron dose in IFA. Also, in both supplementation groups the optimal effect on maternal haemoglobin could have been reached with a limited number of tablets. This chapter therefore presents a dose-response analysis of maternal haemoglobin concentration in both UNIMMAP and IFA groups.

At inclusion in the trial, 43.2% (548/1268) of the participants whose haemoglobin was tested were anaemic. The prevalence of anaemia was 26.9% (102/379) in participants included during the first trimester, 45.5% (267/587) and 59.3% (179/302) in the second and third trimesters.

On average, the haemoglobin concentration decreased over gestation by 0.019 g/dL (95% CI: 0.012, 0.025 g/dL; p<0.0001) per week in the IFA and UNIMMAP groups. An increment in haemoglobin concentration per micronutrient tablet [β (±SE) = 0.006± 0.001 g/dL; p<0.0001] was observed only in women who were anaemic at inclusion, whereas a decrease was observed in the other mothers (-0.003±0.001 g/dL; P = 0.002, p for interaction<0.0001); the finding was similar in both the IFA and UNIMMAP groups. The haemoglobin concentration of women with baseline anaemia reached the haemoglobin concentration of their non-anaemic counterparts (11.1±0.64 g/dL) at ≅180 tablets, independently of the type of micronutrient received. Despite this, micronutrient intake did not significantly prevent anaemia (51.0% in the third trimester). Even in women without anaemia at baseline, 42.1% (214/508) became anaemic despite receiving the micronutrient supplements. Supplements were a risk factor for haemoconcentration [odds ratio per tertile of tablet intake= 2.10; (95% CI: 1.12, 3.94), p<0.001] independently of supplement type or initial haemoglobin concentration.

In conclusion, UNIMMAP triggered the same haemoglobin dose response with half the amount of iron as provided by IFA treatment. The effect of UNIMMAP on foetal growth is thus unlikely to be mediated through changes in maternal haemoglobin. The benefit of iron supplements in non-anaemic women is unclear. Despite micronutrient supplementation, anaemia remained highly prevalent during gestation, partly because of physiologic haemodilution.
Chapter 6: Prenatal Micronutrient Supplements Cumulatively Increase Fetal Growth

We saw in Chapter 3 that UNIMMAP improved foetal growth only moderately in comparison to IFA, as also reported in other similar trials. This might be due to insufficient amounts of UNIMMAP or to IFA being in reality an active control. We therefore assessed the association between cumulative micronutrient intake (CMI) and foetal growth in both groups.

The odds of delivering a small-for-gestational-age baby was reduced by 21% (95%CI: 5, 35; p=0.013) for each additional tertile of CMI. The association between CMI and birth weight was modified by gestational age at start of the supplementation (p-interaction=0.001). Each unit of CMI was associated with a 1.6g (95%CI: 0.3, 3.1; p=0.019) higher birth weight at a mean-centered gestational age at enrolment, whereas the gradient was 2.4g (95%CI: 0.7, 4.2; p=0.006) later in pregnancy. In spite of this greater increment in birth weight per tablet, entering the study at a later gestational age was significantly associated with a lower birth weight [-9g per week (95%CI: -19, 1), p=0.07]. Maternal BMI at enrolment was also a positive modifying factor (p-interaction=0.02), with no association between CMI and birth weight for low maternal BMI.

There was no evidence of an effect modification by group allocation, i.e. we observed the same change in birth weight per unit of CMI with either IFA or UNIMMAP. This is an important finding, as IFA has mainly been considered a placebo as regards foetal growth. Therefore, the effect of UNIMMAP on foetal growth comparatively to IFA is in addition to the birth weight increment due to IFA itself. It is also important to realize that the mean 22.4g increase in birth weight reported in meta-analyses relates to an average intake of micronutrient tablets and that this intake was not optimal in every study.

As suggested by our results, increasing the number of micronutrient tablets provided during pregnancy could result in a greater effect on foetal growth. This can be achieved by starting the supplementation very early during pregnancy or even pre-conceptually. Increasing the overall micronutrient intake, however, must be weighed against the potential for harm in some context. Each additional tablet of micronutrient, either of UNIMMAP or IFA, increased the head circumference by 0.07 mm. This observation bears potentially important health implications as regards delivery complications in mothers receiving high amounts of IFA or UNIMMAP, particularly in settings with sub-optimal obstetrical care. Further prenatal supplementation studies should include cautious safety monitoring. In settings where low maternal BMI is prevalent, micronutrient supplements should be coupled with increasing energy intake.

Chapter 7: Impact of prenatal multiple micronutrients on survival and growth during infancy

In this chapter, we assessed if the effects of UNIMMAP extend beyond the neonatal period. We assessed monthly anthropometry and health parameters of offspring up to age 12 months. Children were assessed again at a mean age of 30 months. Mixed-effects models accounted for repeated measurements. UNIMMAP resulted in a 27% [HR=0.73; (95%CI: 0.60, 0.87); p=0.002] reduction in the rate of stunting among 15,261 infant-months, with a length-for-age higher by 0.13 Z-score (95%CI: 0.02, 0.24; p=0.02) over the whole observation period. However, by age 30 months this difference was not observed anymore. An effect of UNIMMAP on weight-for-length (p-interaction=0.004) and head circumference-for-age (p-interaction=0.03) became apparent by the end of the first year of life. By age 30 months, children from the UNIMMAP group had a weight-for-height higher by 0.20 Z-score (95%CI: 0.06, 0.34; p=0.004). This corresponded to a difference of 178 g (95%CI: 52, 305; p=0.006). The prevalence of wasting was 9.7% (45/462) in the IFA group vs. 6.7% (30/419) in the UNIMMAP group (p=0.093). No difference in mortality or morbidity was identified among groups, except a 14% reduction in reported episodes of fever (95%CI: 1%, 28%; p=0.04).
We hypothesized that UNIMMAP affects infant growth through two mechanisms: improved linear foetal growth with continuation into early life and enhanced post-natal growth. In spite of our intervention, the nutritional status of infants was sub-optimal with a wasting and a stunting rate of 35.1 and 29.2 per 1000 infant-months, respectively, in the UNIMMAP group.

Chapter 8: Discussion and recommendations
We have shown in the previous chapters that UNIMMAP increased significantly foetal and infant growth in comparison to IFA. We found no evidence that this effect was mediated through hormonal changes in the cord blood or related to a better haemoglobin concentration in the mother. We have also reported that IFA itself had an effect on foetal growth, and that the effect of both IFA and UNIMMAP was proportional to the number of supplements received.

The crucial question to address now is about whether or not to recommend the scaling up of prenatal UNIMMAP supplements. Therefore, we assessed in this chapter the risk-benefit balance of prenatal UNIMMAP supplementation on the basis of current evidence. We appraised the quality of evidence and strength of recommendations following the GRADE approach.

The relatively small effect of UNIMMAP on foetal growth could be explained by two sets of explanations. First, there is consistent evidence that IFA is also active on foetal growth, and UNIMMAP contained half the amount of iron as the IFA supplement, reducing the comparative benefit of UNIMMAP. Second, the presence of modifying factors, notably a low maternal BMI, and a sub-optimal overall supplement intake in study populations contributed to a modest mean intervention effect. Regarding the benefits provided by UNIMMAP in the post-natal period, the evidence is to date scanty and somehow contradictory. Some studies have reported a trend of UNIMMAP towards increased perinatal mortality. This has often been explained by a higher risk of cephalopelvic disproportion and birth asphyxia in large babies. This hypothesis presents a number of shortcomings. We alternatively propose that the apparent excess of perinatal mortality observed with UNIMMAP in some setting is plausibly related to the lower concentration of iron in the UNIMMAP supplements, as there is evidence that IFA, as well as UNIMMAP, might improve infant survival, potentially through an increased gestational length.

In conclusion, there is high quality evidence that prenatal IFA increases foetal growth and/or gestational length, even in iron replete women. These effects do not seem to be mediated through changes in maternal haemoglobin. There is moderate quality evidence that prenatal IFA reduces perinatal and neonatal mortality. There is insufficient evidence to conclude on the long-term effects (positive or negative) of prenatal IFA. There is also insufficient evidence regarding the best daily dose of IFA.

Therefore, we recommend (strong recommendation) that pregnant women be supplemented with IFA irrespective of their haemoglobin level. It is also recommended to carry out research testing the efficacy of various doses of iron in improving foetal health, gestation length and infant survival. Such studies should integrate an important mechanistic component, i.e. assess the intermediate physiological pathways.

There is high quality evidence that UNIMMAP increases foetal growth and reduces the risk of LBW and SGA in comparison with IFA. There is moderate quality evidence that this does not translate in a better survival in the neonatal period. There is low quality evidence that UNIMMAP could increase perinatal mortality. There is currently insufficient evidence to conclude on other health benefits of UNIMMAP vs. IFA in infancy or on a longer term. For example, in our setting, infant growth remained generally poor in spite of prenatal
UNIMMAP supplements and a greater mean birth weight. There is also currently insufficient data to understand the molecular pathways involved in women receiving UNIMMAP instead of IFA.

Therefore, we recommend (weak recommendation) that pregnant women be supplemented with UNIMMAP instead of IFA in settings with adequate health care at delivery\(^{19}\). Such programmes should be thoroughly evaluated, particularly on the outcomes of perinatal mortality and child morbidity. We also recommend that more research be carried out on: the long-term effects of UNIMMAP on health outcomes; the benefit of articulating prenatal and post-natal UNIMMAP; the differential effects of various compositions of multiple micronutrient supplements; the molecular pathways involved in women and offspring receiving multiple micronutrients.

There is high quality evidence that maternal BMI modifies the effect of UNIMMAP on foetal growth comparatively with IFA, with no effect in women presenting a low BMI. There is currently insufficient evidence on the functional importance of this finding on postnatal health, and on a specific BMI threshold below which micronutrient supplements would be useless or detrimental.

Therefore, we recommend (strong recommendation) that IFA or UNIMMAP supplements be proposed to any pregnant women independently of her BMI. However, women with a low BMI and/or a low pregnancy weight gain should also be encouraged to increase their energy intake. More research is needed to explain the modifying effect of maternal BMI on UNIMMAP.

\(^{19}\) On the assumption that other health needs are also adequately covered during pregnancy