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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.

One of the purposes of our study was to provide policy-makers with the best possible evidence-based recommendations on prenatal micronutrient supplementation. The crucial question to address now is about whether or not to recommend the scaling up of prenatal UNIMMAP supplements. The response to this question requires a detailed appraisal of the risk-benefit balance of such a strategy. We apply in this section the GRADE[8,9] approach for grading the quality of evidence and the strength of recommendations (1;2;5).

8.1 Benefits of UNIMMAP

8.1.1 A relatively small effect on foetal growth

The results of our research are consistent with those from other similar trials. We present in Table 1 (page 93) the summary evidence from the four meta-analyses carried out on this topic. There is high quality evidence that UNIMMAP increases birth weight and reduces SGA in comparison to IFA. However, the relative risk reduction in SGA was consistently around 10%. Such an effect is disappointingly low from a public health perspective. In the Burkina setting for example, the incidence of SGA was still 37.4% in the UNIMMAP group, whereas the incidence of LBW was 14.6%. There are two main explanations which may explain these results. Firstly, the comparator (IFA) could also have been active in promoting foetal growth. Secondly, we could have provided pregnant women and their offspring with a supplement which was insufficient to cover their nutritional needs. These two points are examined further in the following sections.

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[8] In the GRADE approach:
-high quality level means "We are very confident that the true effect lies close to that of the estimate of the effect";
-moderate quality level means "We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different";
-low quality level means "Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect";
-very low quality level means "We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect" (1).

[9] In the GRADE approach, the strength of a recommendation reflects the extent to which we can be confident that desirable effects of an intervention outweigh undesirable effects. GRADE classifies recommendations as strong or weak.
Strong recommendations mean that most informed patients would choose the recommended management and that clinicians can structure their interactions with patients accordingly
Weak recommendations mean that patients' choices will vary according to their values and preferences, and clinicians must ensure that patients' care is in keeping with their values and preferences
Strength of recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, quality of evidence, variability in values and preferences, and resource use (2)

Table 1: Effects of prenatal multiple micronutrients on foetal growth: summary findings from published meta-analyses

	Nb of trials	Mean birth weight		LBW (<2500g)		SGA (<10th percentile)		Evidence level[1]
		Gain	95%CI	RRR	95%CI	RRR	95%CI	
Fall et al. (6)[2]	12	22g	(8, 36)	11%	(3, 19)	10%	(1, 18)	High
Shah et al. (7)	13	54g	(36, 71)	17%	(7, 26)	11%	(-1, 23)	High
Haider et al. (8)	14	-	-	-	-	9%	(4, 14)	High
Kaway et al. (9)	15	44 g	(28, 60)	14%	(7, 21)	15%	(7, 22)	High

LBW: Low Birth Weight; RRR: Relative Risk Reduction; SGA: Small-for-gestational age

[1]: The quality of evidence was appraised with the GRADE approach (5) using the software GRADEpro.3.6. The following parameters were assessed: 1.risk of bias; 2. inconsistency among studies; 3. indirectness of results; 4. imprecision of results; 5.likely publication bias; 6. size of effect; 7. existence of a dose response; 8. residual confounding likely to reduce effect size.

[2]: only UNIMMAP trials were included in this meta-analysis

8.1.1.1 An active control

In our study, IFA, which is currently recommended by WHO to reduce the risk of iron deficiency anaemia among pregnant women, was considered a placebo. A recent Cochrane review also reported no overall effect of IFA on birth weight (10).

One important indirect finding of our research, as explained in Chapter 6, was the possible active role of IFA on foetal growth. This finding was consistent with the results of a few other trials, but not all, published several years after the UNIMMAP trials had been launched.

In a cluster randomized controlled trial in Nepal-Sarlahi, antenatal IFA supplementation (but not folic acid alone) significantly reduced the incidence of low birth weight by 16% (11). In China, IFA resulted in an increase of 24.3g (95%CI: -10.3, 59.0; p=0.17) in birth weight in comparison with folic acid alone (12). Even more striking were the results from two RCTs among non-anaemic, iron-sufficient women at enrolment in the USA where iron supplementation vs. a placebo (13), or multiple micronutrient tablets (14), increased birth weight by 100 to 200g and reduced the incidence of LBW.

Consistent with these trials, an observational study, based on data from Demographic and Health Survey (DHS), reported a higher birth weight [103g; (95%CI: 42, 164); p=0.001] in offspring of women who had taken prenatal iron supplements during pregnancy (15).

In contrast, such an effect of iron supplementation on birth weight was not observed in a RCT carried out in Niger (16), although the small sample size (n=197) and late enrolment during pregnancy might have contributed negatively to the findings. Although such an effect of IFA is not yet fully understood, we have already discussed in Chapter 6 reasons which support its plausibility (see also paragraph 8.1.2.2 for a discussion of the effect of IFA on gestational length). It is also important to realize that it is iron, not folic acid, which is the active component in IFA, as indicated by the results of the Nepalese and Chinese studies where IFA was compared to folic acid alone (11;12).

As a consequence of this, the comparative effect of UNIMMAP has been reduced proportionately, and figuring out its true effect on foetal growth must allow for the effect of the IFA component of the UNIMMAP supplement.
In view of the effects of iron on foetal growth and health, it is also worth emphasising that UNIMMAP contains half the amount of iron as the IFA supplement. Moreover, the zinc in UNIMMAP interacts with iron, which is likely to reduce further the quantity of iron bio-available. The rationale for the lower dosage was that other vitamins in the supplement would be likely to enhance iron metabolism (17). This rationale was plausible, and we have indeed shown in Chapter 5 that maternal haemoglobin responded similarly to either IFA or UNIMMAP supplementation, and the pooled analysis of UNIMMAP trials reported consistent results (18). However, beyond contributing to the expansion of the red blood cell mass, a substantial amount of iron is also deposited directly in the foetus and the placenta, particularly in the last 10 weeks of pregnancy (19;20). It is plausible that prenatal supplement of iron affects foetal growth with little or no mediation of maternal haemoglobin (21), as also suggested by the trials in non-anemic, iron-replete women in the USA (13;14). Therefore, it can be hypothesized that with 60 mg of iron, as in IFA, UNIMMAP would have displayed a greater effect on birth weight.

In conclusion, the total benefits of UNIMMAP have been underestimated in meta-analyses because the effects of the comparator (IFA) were unknown, or vaguely suspected, when the trials were designed (22). Moreover, UNIMMAP contains less iron than IFA. Comparing an alternative intervention with the usual standard of care or policy, instead of comparing it with no intervention, is certainly good scientific practice. Nevertheless previous knowledge of the effects of IFA on foetal growth would have resulted in a different study design, notably the sample size would have been larger, and possibly the lower iron content of UNIMMAP would have seemed a less relevant research hypothesis. Also, a third arm with participants receiving a placebo would have generated invaluable information. However, such design was deemed impossible in pregnant women due to the fact that the WHO and many other advisory groups recommend universal iron supplementation for all pregnant women, regardless of their baseline haemoglobin or iron status (19).

8.1.1.2 An insufficient supplementation?

The importance of energy
A striking finding of our research was the modifying effect of maternal BMI. In women with a better nutritional status, UNIMMAP had a greater effect on foetal growth. We have shown in our study that UNIMMAP increased birth weight [119g, (95% CI: 26,212); p=0.012] in women in the upper quartile of BMI at inclusion (22 kg/m^2), but had no effect on mother's with poorer nutritional status. The same observation was found using maternal MUAC for biometry, a more stable indicator of maternal nutrition during pregnancy (23). The interacting effect of maternal nutrition has been confirmed in almost all the other trials of prenatal multiple micronutrient supplements (6). The same interaction was also observed using thoracic and cephalic circumference measurements as outcomes (24). Although this was a counterintuitive finding, we have discussed previously the plausibility of this observation (see Chapter 6).

This is, of course, another important factor blurring the assessment of a UNIMMAP effect. For example, in our study population, 10.4% of the participants had a BMI<18.5kg/m^2 at enrolment, and the mean BMI was 20.9±2.1kg/m^2. In a population with such sub-optimal

nutritional status, UNIMMAP displays overall a moderately beneficial effect. It is possible that a critical supply of macronutrients is required to ensure an improved birth weight response to UNIMMAP (23). The action of some micronutrients, such as riboflavin, niacin and thiamine, may require utilization of energy and protein as substrates (25).

This is a hypothesis we have tested in a second randomized controlled trial carried out in the same population (26). In that trial, we hypothesized that providing a daily prenatal balanced energy/protein (>25% of the energy from protein) dietary supplement enriched with UNIMMAP (FFS) would result in a higher birth weight and birth length than would a daily UNIMMAP supplementation alone. The food supplement contained 1.56 MJ (372 kcal) and 14.7 g protein, with energy mainly coming from fat. Although there was overall no difference in birth weight between groups (+31 g; $p = 0.197$), the effects of FFS, as expected, tended to be greater in women who were underweight at enrolment (BMI<18.5 kg/m2), with an increase in birth weight of 111 g ($p = 0.133$) and birth length of 12.0 mm ($p = 0.005$).

The modifying effect of maternal nutritional status also helps to understand an apparently spurious finding of our study: although UNIMMAP increased the overall birth weight, the risk of LBW or SGA was not reduced in comparison with IFA (see Chapter 3). This was due to variations of treatment effect across the distribution of birth weight, the effect being substantial only for the larger infants (27). A similar observation was reported in Nepal-Sarlahi (28). This association is most likely confounded by maternal nutritional status, UNIMMAP displaying a greater effect in better nourished mothers and better nourished mothers delivering newborns with higher birth weights even in the absence of UNIMMAP.

In conclusion, in mothers with a low BMI, UNIMMAP might exert an effect on foetal growth which is not greater than IFA and it is only in mothers with a better nutritional status that it increases foetal growth comparatively to IFA. As a result, the overall effect of UNIMMAP over IFA appears moderate. These findings also emphasize the absolute need of considering maternal malnutrition a priority in maternal and child heath programmes. More work is needed on the screening and efficient nutritional support of malnourished pregnant women.

An appropriate formulation?

Whether a single RDA, as defined for pregnant women in the USA and Canada, for nutrients contained in UNIMMAP is sufficient to correct existing micronutrient deficiencies, especially when pregnancy provides a narrow window of opportunity during which to intervene, is an important question. This implies that higher doses of micronutrients would result in a greater effect on foetal growth. Unfortunately, there is today no answer to that question. On the one hand, our study, as well as the other UNIMMAP trials, has shown that a single RDA does indeed increase foetal growth. On the other hand, there is currently no evidence that a higher dosage would be more beneficial, as discussed in Chapter 6. The only two studies with a design appropriate to address this question reported no significant differences on birth outcomes when a single RDA, or more, were used (29;30).

Another aspect of the UNIMMAP formulation relates to its composition. Some micronutrients whose deficiency might also influence foetal growth could be omitted. This could be the case for magnesium, biotin, and panthotenic acid, for example (31;32), although there is very limited trial data from on the benefits of single micronutrients during pregnancy. Even the role of iron supplements in preventing or promoting maternal infections is unclear. On the one hand, the safety and effectiveness of iron supplements, particularly in areas of endemic malaria, has been questioned (8). On the other hand, it has been proposed that iron deficiency,

not iron supplementation, could increase the risk of maternal infections, which can stimulate the production of corticotrophin-releasing hormone and provoke preterm delivery (21). Interactions between micronutrients are also poorly evaluated, and some combinations might attenuate effects of individual micronutrients, as demonstrated for the combination iron+folic acid+zinc in the Nepal-Sarlahi trial (11;33).

In conclusion, whether supplements containing more micronutrients and/or higher daily dosages would yield more benefit is unknown. The evidence on the burden of maternal micronutrient deficiencies in different settings, the biological mechanisms involved and the interaction between nutrients are still limited and this research should be prioritised. This said, trials such as ours contribute to the evidence base with a very pragmatic approach by testing plausible hypotheses although intermediary molecular mechanisms are poorly known. The UNIMMAP trials demonstrated that for the populations in which they were conducted there were deficiencies in at least some multiple micronutrients, in addition to iron and folic acid. This is an important contribution because indicators of deficiency are inadequate for many micronutrients (34;35). In fact, efficacy trials are fundamental tools for demonstrating remediable deficiencies, and, when they are well designed, they can also identify those who most benefited from the supplementation (22). It should be emphasised that such trials should also adequately measure adverse events (see paragraph 8.2.1), and require rigorous interpretation. Moreover, their contribution to science would expand if mechanistic research could be simultaneously carried out (36).

8.1.2 A complex effect on postnatal health

We hypothesized that improving foetal growth would result in improved nutritional status during infancy and improved survival rates, although our trial was not powered to assess the latter outcome. UNIMMAP increases foetal growth in comparison with IFA, and its absolute effect is likely to be greater than that reported in comparative trials, as discussed in paragraph 8.1. Yet, paradoxically, we observed a complex picture on postnatal health – a reduction of stunting rates diminishing with time, and a reduction in wasting rates emerging towards the end of the first year of life, and no apparent survival advantages.

8.1.2.1 Postnatal growth

As discussed in Chapter 7, experimental studies on post-natal effects of prenatal micronutrients in humans are scarce, and their results are conflicting. This emphasises the innovative contribution of the present research, but clearly limits comparison with the few other studies.

Two trials from Nepal-Sarlahi and Nepal-Janakpur reported results on the post-natal effect of prenatal multiple micronutrients (37;38). These 2 trials did not follow children longitudinally, so growth rates could not be assessed. An important piece of information provided by these two trials however, is that prenatal supplementation of micronutrients exerts long-term effects. The assessment in Nepal-Janakpur was carried out in children of almost the same age as the last home-based evaluation in our trial, i.e. 30 months of age, and also observed very similar results (37). In contrast, in the second study, no difference between children of mothers who had received multiple micronutrients vs. IFA was observed 6-8 years after birth (38). The latter trial also found no improvement in symptoms of neonatal morbidity in the first 10 days of life or at 6 weeks of age for UNIMMAP or IFA in comparison with a control group (3).

The trial in Nepal-Janakpur also reported a small but significant decrease in systolic blood pressure in the UNIMMAP group at age 2.5 years (37). This observation, requires confirmation over a longer follow-up period, but is consistent with the notion of neonatal

programming and might have implications for the development of adult hypertension[10]. However, it was not observed in the second Nepalese study (39), which reported no effect of UNIMMAP or IFA on blood pressure, cholesterol, triglycerides, glucose, insulin, or insulin resistance (39). The reason of such discrepancies between the two study populations is unknown.

The results of a longitudinal follow-up of child growth from birth to 54 months of age from the UNIMMAP trial in Bangladesh were recently published (40). A slight increase in stunting rate was reported in the UNIMMAP group (from 31.3% in the IFA group to 36.1% in the UNIMMAP group). This is a spurious finding that the authors could not explain, and which is difficult to interpret as the results of UNIMMAP on birth anthropometry were never published. Moreover, this study presented methodological flaws, in particular unclear statistical analysis and missing data, and the results should be considered cautiously. Another study in China following the children up to 30 months of age reported no difference in stunting or wasting rates between children whose mother had received UNIMMAP or IFA during pregnancy, although a trend towards less stunting was apparent in the UNIMMAP group [OR=0.82, (95% CI: 0.63, 1.07)](41).

Finally, two studies evaluated the effect of UNIMMAP on mental development. In the same Chinese study as mentioned above, multiple micronutrient supplementation was associated with a significant increase in mental development raw scores for infants at 1 year of age compared with IFA (42). However, UNIMMAP did not increase significantly the psychomotor development. In the above-cited study in Bangladesh, infants whose mother had received UNIMMAP had slightly better motor scores and activity ratings at 7 months of age, but this was only observed in infants of low-BMI mothers (43).

In conclusion, the evidence on benefits provided by UNIMMAP in the postnatal period is to date scanty and somehow contradictory. As discussed in chapter 7, this might reflect the predominance of environmental factors on post-natal linear growth and pinpoint the need to improve micronutrient intake also during infancy. This is what suggested the results of a study in Tanzania. This study using a different formulation of multiple micronutrients[11] and including only HIV-infected women found that multivitamins given during pregnancy and lactation had a significant positive effect on attained weight [459 g; (95% CI: 35, 882); p=0.03] and on weight-for-age [0.42; (95% CI: 0.07, 0.77); P=0.02] and weight-for-length [0.38; 95% CI: 0.07, 0.68; p=0.01) z scores at 24 months in comparison to daily 120 mg ferrous iron and 5 mg folate (44). Alternative explanations to the apparent low effect of UNIMMAP during infancy could relate to a too short follow-up duration or use of inappropriate health indicators. However, studies in Nepal-Janakpur, Burkina Faso and China point towards a long-term effect of UNIMMAP on child growth. Further follow-up of these cohorts is warranted.

It is also noteworthy that the effect of multiple prenatal micronutrient supplements on post-natal maternal health has been poorly assessed so far. To our knowledge, only one study in Nepal-Sarlahi studied that important aspect (45). It reported a significant decrease of puerperal infections [RR=0.74; (95%CI: 0.56, 0.98)] with multiple micronutrients. This was however not greater than the protection offered by IFA.

[10] It is also worth emphasizing that, in contrast with their lower blood pressure, the children of the UNIMMAP group exhibited a small but significant increase in adiposity (37).

[11] 20 mg thiamine, 20 mg riboflavin, 25 mg vitamin B-6, 100 mg niacin, 50 µg vitamin B-12, 500 mg vitamin C, 30 mg vitamin E, and 0.8 mg folic acid+120 mg ferrous iron and 5 mg folate as in all participants.

8.1.2.2 Survival

Comparing UNIMMAP with IFA

The assessment of UNIMMAP effect on child survival in our trial is faced with the same difficulty as that for assessing effects on foetal growth, i.e. IFA might influence the same parameter. However, two other studies had a design appropriate for assessing the effect of IFA on neonatal mortality (4;12). Their results presented in Table 2 show a contrasted picture. In China, there was a 47% (95%: 3, 71) reduction in neonatal mortality in women who received IFA supplements compared with folic acid alone (FA), despite absence of a clear effect on birth weight (12). Remarkably, UNIMMAP also showed a trend towards a reduction in neonatal mortality in comparison with FA. As a result, there was no apparent difference between UNIMMAP and IFA. In Nepal-Sarlahi, IFA also displayed a trend towards a lower mortality risk which was not statistically significant (4). However, there was a significant reduction in mortality (31%) for children aged 0–7 y whose mothers had received IFA supplements compared to control subjects (33). In that same study, multiple micronutrients did not perform better than control, in contrast to IFA.

Table 2: Neonatal mortality in groups receiving multiple micronutrients vs. IFA vs. control

	Control[1]	**IFA**	**MN**	**IFA vs. C**	**MN vs. C**	**MN vs. IFA**
	n	***n***	***n***	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**
Nepal-Sarlahi (4)	40/876	28/772	47/870	0.87 (0.65, 1.16)	1.08 (0.89, 1.32)	1.19 (1.00, 1.43)
China (12)	33/1636	16/1499	18/1469	0.53 (0.29, 0.97)	0.61 (0.34, 1.10)	1.07 (0.78, 1.47)

C: control ; IFA: Iron+Folic Acid; MN: Multiple Micronutrients

[1]: Control was 400 µg of folic acid in China and 1000 µg of vitamin A in Nepal

Evidence is thus emerging that prenatal IFA might also be beneficial for neonatal and/or child survival. Very recently, a large scale observational study reported consistent findings (46). In that study, prenatal IFA reduced the risk of death of children<5 years of age by 34% [HR: 0.66, (95%CI: 0.53, 0.81), p<0.0001], with the greatest protective effect observed in the first day of life. Moreover, a strong dose response of greater protection from child death with increasing numbers of IFA tablets consumed was reported (46).

So the apparent absence of an effect of UNIMMAP on survival in comparison with IFA in meta-analyses could be interpreted as an equivalence of effect[12], as observed in the Chinese trial (12). However, this should be confirmed in further studies.

12 An indirect indication of this can be found in the low mortality rates observed in both IFA and UNIMMAP groups in a number of trials included in the meta-analyses. In Burkina Faso, a recent prospective cohort study, following up more than 800 pregnant women in the same region as ours, provided interesting comparative mortality information (47;48). Although birth weight was not available, the rates of perinatal mortality [79 per1000; (95%CI: 59, 99)] and neonatal mortality [46 per 1000; (95%CI: 22, 70)] were assessed accurately, and reflected the actual mortality rates in a neighbouring population with usual prenatal care. The corresponding figures were remarkably lower in our study population, with 33 per 1000 (95%CI: 24, 43) and 14 per 1000 (95%CI: 8, 21) for perinatal and neonatal mortality, respectively, with little difference between IFA and UNIMMAP groups (27).

In Pakistan (Sindh), the neonatal mortality rate in the IFA group of the UNIMMAP trial was 38.8 (33/850) per 1000 live births (49), whereas it was estimated at 53.3 (439/9432) per 1000 live births in the control group of another intervention study at the same time period (50). In Bangladesh (Matlab), the perinatal and early neonatal mortality rates in the IFA group of the UNIMMAP trial were 41.9 (51/1218) and 16.8 (20/1187) per 1000, respectively (51), whereas the corresponding rates were estimated at 57.8 and 27.1 per 1000 for the same period (years 1987-2005) and using the same Health and Demographic Surveillance System (52). In Tanzania also, the rate of LBW in the control group was substantially lower than previously reported rates for the general population (53). However, these differences between expected and observed rates in the control group of UNIMMAP trials do not rule out the possible influence of other components of the studies (e.g. better general care than usual care).

Only one of the UNIMMAP trials in Indonesia reported an effect of UNIMMAP on survival. Early infant mortality (from birth to age 3 months) was reduced by 18% (95%CI: 5, 30; P=0.01) in the UNIMMAP group in comparison with the IFA group (54). This is an important finding, which contrasts with the results of the other UNIMMAP trials. The big sample size (n=31,290) and the corresponding higher statistical power might be part of the explanation. Another element to note is that the controls received only 30mg of iron, not 60 mg as in all the other UNIMMAP trials (except the one in Bangladesh). Therefore, in this case, UNIMMAP differed from IFA only by the additional micronutrients of UNIMMAP tablets, and the role of prenatal iron on infant survival was equivalent between study groups. An increase in perinatal or postanatal survival (from 28 weeks gestation to 60 d postpartum) of 14% (RR: 0.86; 95% CI: 0.72, 1.02; p=0.08) was also reported in Tanzania in the multiple micronutrient group in comparison with the IFA one (53). Strikingly, this latter study also provided an equal dose of iron (60 mg) to trial participants irrespective of their allocation group. However, the different composition of the multiple micronutrient supplements precludes extrapolation of findings to UNIMMAP.

In conclusion, there is emerging and converging evidence that prenatal IFA could improve infant and even child survival. This effect of IFA could be mediated by an increase of gestation length (see the following paragraph on the importance of prematurity). Therefore, the absence of an effect of UNIMMAP on survival in comparison with IFA in most trials may be in reality an equivalence of effect, although the iron content of UNIMMAP was half than that of IFA. The only two trials reporting an improved survival with UNIMMAP in comparison with IFA used the same amount of iron in both groups.

Importance of prematurity

Prematurity is an important cause of perinatal mortality. For example, in our study population, 50% (20/40) of perinatal deaths occurred in babies born prematurely, and the risk of death in the perinatal period was nearly 10% for these newborns. Prematurity is also a risk factor for LBW. Although the prevalent view when we started this research was that the majority of LBW in developing countries was due to IUGR (55), not to prematurity, in our study population 33% of the LBW cases were also premature. Therefore, prematurity is a powerful confounding factor of the effect of LBW on perinatal death. Small size due to preterm delivery may be more strongly associated with perinatal mortality than is low birth weight per se (56).

It is acknowledged that UNIMMAP had no effect on gestational length in comparison with IFA (57), and this might partly explain the disappointingly small effect of UNIMMAP on birth weight. Alternatively it could be proposed that UNIMMAP does increase gestational length, but not to a greater extent than IFA. There is high quality evidence in support of this alternative hypothesis. As already mentioned, four trials had a design appropriate for assessing the effect of IFA on gestational length as they included a control group receiving only folic acid, or a placebo (11-14). In the USA, 30mg of iron in non-anaemic women resulted in a gestational length longer by 0.6±2.2 wk (P=0.049) in comparison with placebo (13). The proportion of preterm outcomes did not differ between groups, but the distribution of gestational length was shifted to the right. In a second trial undertaken in a similar population, the proportion of preterm births was reduced from 7.5% to 13.9% (p=0.05) when mothers received multiple micronutrients containing 30mg of iron vs. the same multiple micronutrients without iron (14). It should be emphasised that in both studies, women were given iron supplements after 28 weeks of gestation according to their ferritin level and

independently of their allocation group. So the effect of iron supplements in the intervention group was obtained in a remarkably short period. In China, IFA compared to folic acid alone increased the gestational length by 0.23wk [(95%CI: 0.10, 0.36); p=0.001] (12). Strikingly, UNIMMAP exerted a similar effect [+0.19wk; (95%CI: 0.06, 0.32); p=0.004]. Only in Nepal-Sarlahi, IFA, but also UNIMMAP, had no effect on the incidence of preterm birth in comparison to the control group, but gestational length was not reported (11).
There are plausible biological mechanisms linking iron deficiency and prematurity (21). These include a stimulation of the synthesis of corticotrophin-releasing hormone, possibly in association with anemia and/or maternal infections, and an increased oxidative damage to the fetoplacental unit.

In conclusion, it is plausible that both IFA and UNIMMAP had an effect on gestation length in our study. This effect was likely modest and the high incidence of prematurity (15.8% in our study) in spite of either IFA or UNIMMAP supplementation, and the high mortality rate associated to it remains a crucial challenge for improving infant health and survival. The prematurity rate in our study was notably higher than what is described in West Africa (58). We believe that this is due to the accurate assessment of gestational age with ultrasonography in our community-based study, whereas estimates for Africa are from facility-based studies applying undescribed procedures (58).

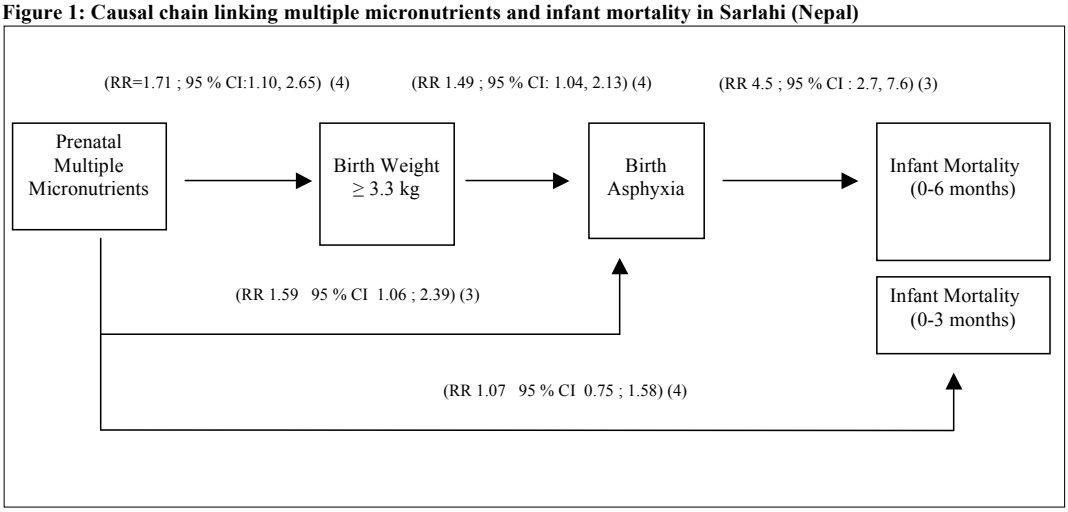
8.2 Harms associated with UNIMMAP

Whether UNIMMAP supplements provide benefit or harm to the mothers and their offspring is a central question related to this research, the answer to which is not straightforward. The comparative benefits of UNIMMAP over IFA, discussed in paragraph 8.1, appear limited, even if a longer follow-up of children is needed in order to get a more comprehensive assessment. Moreover, a number of studies, including ours, have raised some concerns regarding the safety of UNIMMAP, in particular a potential increase in perinatal mortality (27;59;60). The pooled analysis of the results has been published (51). UNIMMAP was not associated with an increased rate of stillbirth [OR = 1.01; 95% CI: 0.88, 1.16); p=0418], but the increase in early neonatal mortality [OR = 1.23; 95% CI: 0.96, 1.59); p=0.148] and perinatal mortality [OR = 1.11; 95% CI: 0.93, 1.33); p=0.066] was close to statistical significance. Excluding the large Indonesia (Lombok) study (61), the odds ratios for stillbirth, early neonatal death, and perinatal death were 1.12 (95% CI, 0.93 to 1.34), 1.40 (95% CI, 1.08 to 1.82), and 1.20 (95% CI, 1.01 to 1.42), respectively. The authors of the review appropriately highlighted the need to address very carefully possible increases in early neonatal and perinatal mortality in women taking UNIMMAP, especially in some low resource settings.

8.2.1 Plausibility of a detrimental effect

Cephalopelvic disproportion and increased risk of birth asphyxia in large babies is the hypothesis most often put forward by authors for explaining the potential excess mortality associated with UNIMMAP (4;51). We have shown in Chapter 3 that UNIMMAP does not reduce the risk of LBW but rather increases the incidence of babies who are large-for-gestational age, as also reported in the Nepal-Sarlahi trial (28). Increased asphyxia of children born at the upper end of the birth weight distribution may partly explain the adverse effects of multiple micronutrients on perinatal mortality (60). The researchers of the Nepalese trial have particularly explored this hypothesis and we present in Figure 1 the main elements of the causal chain their work points to.

Figure 1: Causal chain linking multiple micronutrients and infant mortality in Sarlahi (Nepal)



RR: Relative risk. All RR have the control group as reference. The control group received vitamin A (1000 µg retinol equivalents)

Subsequently, various authors have recommended that prenatal multiple micronutrients must be accompanied by the provision of skilled care at delivery and facility births to offset any potential increase in the risk of obstructed labour and birth asphyxia (9;62). We consider that this recommendation is valid – who would deny the utmost importance of skilled care at delivery? – but for wrong reasons, i.e. the fear of an increased risk of birth asphyxia in UNIMMAP users is not supported by strong evidence.

Firstly, although it has been consistently reported that maternal BMI (63) or MUAC (23) at enrolment interacts positively with UNIMMAP (see paragraph 8.1.1.2), such a modifying effect has not been described in relation to perinatal or neonatal mortality. If UNIMMAP increases birth weight mostly in newborns of mothers with the highest BMI, then the highest risk of perinatal mortality should also be observed in that group, that is if the hypothesis of birth asphyxia in large babies were true. In our study, these interaction terms were non-significant (p for interaction between intervention group and maternal BMI or MUAC=0.45 and 0.75, respectively, on perinatal mortality; unpublished data). To our knowledge, equivalent results from the other UNIMMAP trials have not been published. A consistent piece of information is provided by a meta-regression of supplementation trials which reported no difference in risk of perinatal mortality associated with UNIMMAP when stratifying the results by maternal BMI at enrolment, by effects of supplementation on risk of LGA, or by effects of supplementation on birth weight (9). However, the statistical power of this analysis was low. Although a mediation analysis of the role of birth weight on the association between UNIMMAP use and perinatal mortality carried out within studies would have provided more relevant evidence on this issue, anthropometric measurements were often unavailable for stillbirths.

Secondly, the only study that assessed the association between prenatal multiple micronutrients and birth asphyxia, and reported a positive association between these two parameters, used a debatable definition of birth asphyxia (3). Birth asphyxia was defined as any infant [((who did not cry or cried weakly at birth and was unable to breathe after birth) AND (who had an obstructed or prolonged labour: >12 h for parity=0 and >8 h for parity >1)) OR ((who died within the first 7 days of life) AND (had a birth weight >2000 g))]. The

second part of the definition is particularly problematic as it encompasses all early neonatal deaths with no specific, or unrecognized, symptoms, particularly as data collection was based on 24h-maternal recall. The proportion of birth asphyxia based on this non-specific component of the definition was not reported. Another reason why these results should be interpreted cautiously is the problem of missing data. The risk of birth asphyxia was increased from 5.3% in the control group to 8.1% in the multiple micronutrients group, i.e. an absolute difference of 2.8% (3). On the other hand, the authors reported up to 22.7% missing data, and whether the missing data were evenly distributed among intervention groups was not reported (3). Figure 1 also shows that the direct association between the use of multiple micronutrients and an increased mortality risk is non-significant.
Lastly, it is unclear how the excess mortality could relate to an increase incidence of cephalopelvic disproportion in the UNIMMAP group whereas none of the trials found evidence that UNIMMAP increases cephalic circumference in comparison with IFA (57). Moreover, it should be kept in mind that the definition of an LGA baby was done within the study cohorts and that a small minority of newborns in our study were above 2 SD of the international reference distribution of birth weight, with standardization for gestational age at delivery and sex. LGA babies in these studies were actually light babies by international standards. In the Nepal-Sarlahi trial for instance, large babies were defined as a birth weight ≥3300g and the incidence was 7.7% and 6.0% in the multiple micronutrients and IFA group, respectively (28).

8.2.2 An alternative explanation

This part of the discussion is centred on perinatal mortality, which includes both stillbirths and early neonatal deaths, because misclassifications between these two outcomes occur not infrequently and considering them separately may be misleading (51). "A non-significant 11% increase in perinatal mortality" [OR = 1.11; (95% CI: 0.93, 1.33); p=0.066) with UNIMMAP was reported in a meta-analysis (51). Another meta-analysis, which included trials of prenatal multiple micronutrients differing from UNIMMAP concluded that multiple micronutrient supplementation "had no overall effect on perinatal mortality" [RR: 1.05; (95% CI: 0.90, 1.22)], which might be a more appropriate conclusion (9). It has been proposed that the impression that MMN does not decrease, and may even increase, perinatal mortality is based on the comparison of a group taking multiple micronutrients including iron and folate with a control group taking iron and folate without other micronutrients (22). In the China trial, IFA tended to reduce perinatal mortality in comparison to FA, which was not the case for UNIMMAP (12). As a result, UNIMMAP seemed to increase perinatal mortality in comparison with IFA (Table 3). A similar phenomenon was apparent in the Nepalese trial (4). This also fits with the observations previously described on neonatal mortality (see paragraph 8.1.2.2 for a more detailed discussion of this point).

Table 3: Perinatal mortality in groups receiving multiple micronutrients vs. IFA vs. control

	Control[1]	**IFA**	**MN**	**IFA vs. C.**	**MN vs. C**	**MN vs. IFA**
	n	***n***	***n***	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**
Nepal-Sarlahi (4)	70/916	50/801	80/919	0.89 (0.71, 1.17)	1.07 (0.91, 1.25)	1.17 (1.01, 1.35)
China (12)	76/1688	57/1546	78/1532	0.84 (0.59, 1.19)	1.18 (0.85, 1.63)	1.17 (1.01, 1.36)

C: control ; IFA: Iron+Folic Acid; MN: Multiple Micronutrients
[1]: Control was 400 µg of folic acid in China and 1000 µg of vitamin A in Nepal

Still, in this alternative explanation, it remains to clarify why the efficacy of multiple micronutrients would be less than that of IFA. Kaway et al. have proposed some sub-group analysis in their meta-analysis (9). Differences between trials in maternal underweight,

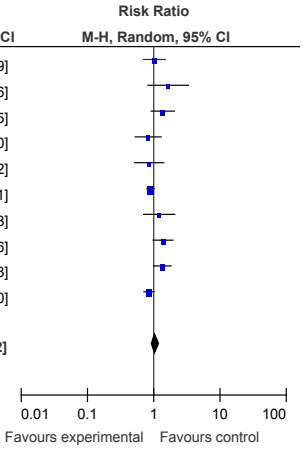
maternal height, risk of large size for gestational age, parity and iron dosage did not explain the heterogeneity of effect estimates on perinatal mortality. Only earlier gestational age at enrolment (<20 weeks), or a high proportion of uneducated mothers (≥50%) appeared influential factors on the association between multiple micronutrients and perinatal mortality. However, underlying mechanisms are highly speculative. Moreover, the results of such meta-regression should be interpreted cautiously because of their low statistical power, and the risk of ecological fallacy inherent to such study design. It might also be that the heterogeneity between studies was not due to differences in population characteristics, but rather to differences in the interventions.

Figure 2 a: Meta-analysis of the effect of multiple micronutrient supplements on perinatal mortality (all studies)

	Multiple micronutrients		IFA			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Bangladesh	51	1194	51	1218	9.2%	1.02 [0.70, 1.49]
Burkina Faso	20	607	12	604	3.7%	1.66 [0.82, 3.36]
China	54	1508	40	1529	8.5%	1.37 [0.92, 2.05]
Guinea-Bissau	32	544	39	547	7.3%	0.83 [0.52, 1.30]
Indonesia (Indramayu)	27	806	31	792	6.2%	0.86 [0.52, 1.42]
Indonesia (Lombok)	457	14473	500	14170	19.9%	0.89 [0.79, 1.01]
Nepal (Janakpur)	28	571	23	568	5.7%	1.21 [0.71, 2.08]
Nepal (Sarlahi)	76	907	48	792	10.1%	1.38 [0.98, 1.96]
Pakistan	83	813	68	898	11.6%	1.35 [0.99, 1.83]
Tanzania	227	4141	268	4136	17.7%	0.85 [0.71, 1.00]
Total (95% CI)		**25564**		**25254**	**100.0%**	**1.05 [0.91, 1.22]**
Total events	1055		1080			

Heterogeneity: Tau² = 0.02; Chi² = 18.93, df = 9 (P = 0.03); I² = 52%

Test for overall effect: Z = 0.66 (P = 0.51)



We carried out a meta-analysis of trials comparing multiple micronutrients with IFA with perinatal mortality as main outcome (Figures 2a & 2b). It is extremely striking that in all the studies where an equal dose of iron was given in both UNIMMAP and IFA groups (Indonesia-Lombok (61); Tanzania (64); Bangladesh (43), no difference in perinatal mortality was observed. In contrast, in all, but two, studies where the intervention group received less iron than the control group, a trend towards an increased perinatal mortality was reported[13]. When excluding the 3 studies using an equal dose of iron in both groups, the overall risk was increased by 22% [RR: 1.22; (95%CI: 1.03, 1.44); p=0.02] (Figure 2 b), an estimation very close to the one produced by Ronsmans et al. when they removed the Indonesia-Lombok study from the meta-analysis (although their rationale to do so was unexplained)[14] (51).

In conclusion, there is evidence of moderate quality that IFA, as well as UNIMMAP, might improve infant survival. 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. There was no consistent evidence regarding the causal contribution of birth asphyxia to this excess of perinatal mortality.

[13] We included in this group the Nepal-Sarlahi trial although 60 mg of iron was given in each group, because 30 mg of zinc was also included in the multiple micronutrient tablets, an amount twice the RDA, and given the interactions between zinc and iron for absorption, the composition of the multiple micronutrient supplements was close to that of UNIMMAP, i.e. less iron in the intervention group.

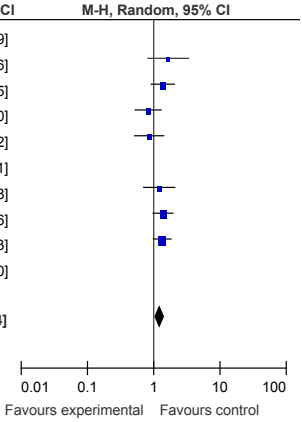
[14] The Tanzanian study was not considered in the meta-analysis by Ronsmans et al. because the composition of the multiple micronutrient tablets were different from that of UNIMMAP.

Figure 2b: Meta-analysis of the effect of multiple micronutrient supplements on perinatal mortality (only studies with less iron in the intervention group than in IFA)

	Multiple micronutrients		IFA			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Bangladesh	51	1194	51	1218	0.0%	1.02 [0.70, 1.49]
Burkina Faso	20	607	12	604	5.6%	1.66 [0.82, 3.36]
China	54	1508	40	1529	15.9%	1.37 [0.92, 2.05]
Guinea-Bissau	32	544	39	547	12.9%	0.83 [0.52, 1.30]
Indonesia (Indramayu)	27	806	31	792	10.5%	0.86 [0.52, 1.42]
Indonesia (Lombok)	457	14473	500	14170	0.0%	0.89 [0.79, 1.01]
Nepal (Janakpur)	28	571	23	568	9.4%	1.21 [0.71, 2.08]
Nepal (Sarlahi)	76	907	48	792	20.4%	1.38 [0.98, 1.96]
Pakistan	83	813	68	898	25.3%	1.35 [0.99, 1.83]
Tanzania	227	4141	268	4136	0.0%	0.85 [0.71, 1.00]
Total (95% CI)		**5756**		**5730**	**100.0%**	**1.22 [1.03, 1.44]**
Total events	320		261			

Heterogeneity: Tau² = 0.01; Chi² = 6.70, df = 6 (P = 0.35); I² = 10%

Test for overall effect: Z = 2.26 (P = 0.02)



It is noteworthy that the other potential adverse events in relation to prenatal micronutrient supplements have been seldom studied. For example, it has been proposed that iron supplements could increase the risk of placental malaria (65). However, this association is yet not well document and further research is needed to assess if reversing iron deficiency through iron supplementation during pregnancy increases malaria risk. We also wish to emphasize that maternal and child health is unlikely to improve greatly with health programmes focused on one specific health problem at a time. Outcomes in woman, maternal, newborn, and child health can be improved through integrated packages of cost-effective health-care interventions that are implemented incrementally in accordance with the capacity of health systems (66). The possible interaction between iron and malaria emphasizes the need to tackle both problems together. Indeed, it has been recently reported that the use of antenatal iron/folic acid supplements combined with appropriate intermittent preventive treatment of malaria during pregnancy is an important intervention to reduce neonatal mortality in malaria-endemic regions (67).

8.3 Recommendations

1. 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[15]. It is also recommended to carry out research testing the efficacy of various doses in improving foetal health, gestation length and infant survival. Such studies should integrate an important mechanistic component, i.e. test how potential pathways such as hormonal adaptations (decreased stress hormones, increased somatotrophic hormones, lower corticotropin-releasing hormone and cortisol), maternal susceptibility to infections, maternal micronutrient stores and oxidative stress are affected by the supplementation. Effectiveness trials including a well-conceptualized program theory are also needed to investigate how program delivery issues can be improved as access and adherence to prenatal micronutrient supplements are often sub-optimal.

2. 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[16] 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. There is also currently insufficient data to understand the molecular pathways involved in women receiving UNIMMAP instead of IFA.

Therefore, we recommend (weak recommendation[17]) that pregnant women be supplemented with UNIMMAP instead of IFA in settings providing adequate health care at delivery[18]. 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. A follow-up of child cohorts from the UNIMMAP trials would be invaluable.
- the differential effects of various compositions of multiple micronutrient supplements, in particular higher contents of iron
- the molecular pathways involved in women and offspring receiving multiple micronutrients (hormonal and metabolic adaptations, susceptibility to infections, micronutrient stores)

[15] On the assumption that other health needs are also adequately covered, in particular malaria prevention in malaria-endemic areas.
[16] This was rated low quality evidence because inconsistency among studies.
[17] We propose a weak recommendation as the effect of UNIMMAP on fœtal growth is clearly established, but the functional importance of it is unclear and a slight increase in perinatal mortality has been evoked.
[18] On the assumption that other health needs are also adequately covered during pregnancy

3. 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 receive food supplements. More mechanistic research is needed to explain the modifying effect of maternal BMI on UNIMMAP.

4. Lastly, during our research, we have been confronted to a number of questions. Although they were not underlying our research hypothesis, they are relevant to maternal and child health in developing countries and deserve further attention:

- What would be the benefits of improving the micronutrient status of women of child-bearing age before or around conception?
- What would be the benefits for both mother and offspring of continuing micronutrient supplementation post-delivery?
- What would be the effects of an integrated and timely package of prenatal interventions, including multiple micronutrients and management of infections, on prematurity and perinatal mortality?
- What would be the most efficient package of interventions to improve the survival and development of LBW or SGA newborns?

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