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

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Chapter 1  Introduction and study objectives

1.1  Setting the stage

This is the story of an idea. This is the account of its journey from birth to the delivery of new hypotheses. Reproduction, birth, but also death, are indeed at the heart of this research in which we assessed, in Burkina Faso, the health benefits of providing pregnant women with multiple micronutrients. The main expected benefit of such interventions was the prevention of intrauterine growth retardation, with subsequently improved health during infancy.

This is also the story of how fast science can progress nowadays. It was in 1999 that the UNICEF/WHO/UN University proposed a prenatal supplement UNIMMAP containing 1 Recommended Daily Allowance (RDA) of 15 micronutrients which could potentially replace standard iron-folate (IFA) supplements for pregnant women in low and middle income countries (LMIC) (1). Less than a decade later, high-quality studies comparing UNIMMAP to IFA had been carried out in Bangladesh (2), China (3), Indonesia-Lombok (4), Indonesia-Indramayu (5), Nepal-Janakpur (6), Nepal-Sarlahi (7), Pakistan (8), Burkina Faso (9), Guinea-Bissau (10), and Niger (11), and we know much better today what benefits UNIMMAP can, and cannot, provide. This thesis was an important component of that fast-growing evidence. As an example, the main results of our Burkina Faso trial published less than 3 years ago have been already cited in more than 25 high-ranked scientific papers, among which 4 were meta-analyses (12-15).

2 In Nepal-Sarlahi, a slightly different formulation of multiple micronutrients than UNIMMAP was used (7). Details are provided in Chapter 3.
1.2. Importance of intra-uterine growth retardation

That mother-to-child relationships have long-lasting effects in our lives is common wisdom. Yet it is only recently that the physical reality of this adage has emerged in the field of scientific evidence. Health pathways or trajectories are built – or diminished – over the lifespan, as outlined by the life course theory (16). This theory also states that early experiences can “program” an individual’s future health and development. Adverse programming can either result directly in a disease or condition, or make an individual more vulnerable or susceptible to developing a disease or condition in the future. While adverse events and exposures can have an impact at any point in a person’s life course, the impact is greatest at specific critical or sensitive periods of development. The foetal period is obviously one such sensitive period. The foetal period is the very first step in our life course and unfavourable health conditions at that time might have chronic impact on our health trajectory. Foetal growth retardation is an important marker of such an unfavourable prenatal environment.

1.2.1 Measuring intra-uterine growth retardation

Under field conditions, foetal growth retardation is assessed and classified using body measurements at birth, and particularly categorisation of low birth weight (LBW), which is defined as body weight at birth less than 2500 grams (g). There are two main causes for LBW: prematurity and intrauterine growth retardation (IUGR). Although not differentiating these 2 problems, LBW is often used as a proxy indicator to quantify the magnitude of IUGR in developing countries because valid assessment of gestational age is generally not available (17). However, when gestational age at delivery is assessed, preterm LBW and term LBW (birth weight < 2500 g and gestational age ≥ 37 weeks) are reported separately as term LBW is more likely to result from foetal growth retardation alone. IUGR is preferably defined as a birth weight < -2 Standard Deviations (SD) of the reference mean weight for gestational age and sex (18). There is currently no universal recommendation on a preferred reference population (19). The term “small for gestational age” (SGA) is often used synonymously with IUGR (20) and is defined as a baby whose weight is below the 10th percentile for its gestational age, although some investigators also use the 3rd or 5th centiles (17).

LBW and SGA are the commonly used indicators of intra-uterine growth retardation both at the individual and population level because they rely on birth weight, which is a routinely collected measurement. This practice presents two potential drawbacks. Firstly, birth weight alone or birth weight-for-age do not allow classification of newborns as short, thin, or both, although these different phenotypes might result from different prenatal mechanisms³, and predispose individuals to different disorders later in life (17;21). It is thus important to specify if growth retardation relates to a small crown-heel length-for-age and/or to a low ponderal index (weight-for-length or weight/length³). Secondly, the health risk associated with IUGR is an epidemiological continuum, i.e. the greater the distance between the individual measurement and the reference mean, potentially the higher the subsequent risk of ill-health for that individual. Although setting specific cut-offs might be useful for case detection, this

³ It has been proposed that stunted infants have been chronically undernourished in utero, resulting in a proportionate reduction in both skeletal and soft tissue growth. Wasted infants have normal linear growth but reduced tissue mass resulting in a low ponderal index reflecting later gestational onset, primarily in the third trimester (17).
approach may mis-classify individuals with sub-optimal foetal growth but who are above the defined cut-off. It is therefore important to consider the actual values of the anthropometry indices, and not only general indicators, in order to evaluate interventions aimed at improving foetal growth.

### 1.2.2 Consequences of 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 their life course. It is the most important predictor of neonatal mortality and morbidity (18;22;23). It is estimated that for term infants weighing 2000-2499 g at birth, the risk of neonatal death is four times higher than for infants weighing 2500-2999 g, and ten times higher than for infants weighing 3000-3499 g (17). A recent pooled analysis of five community-sampled prospective birth cohorts (India, Pakistan, Brazil, and two in Nepal) reported that infants born at term weighing 1500–1999 g were 8.1 (95% CI: 3.3–19.3) times more likely to die, and those weighing 2000–2499 g were 2.8 (95% CI: 1.8–4.4) times more likely to die from all causes during the neonatal period, than those weighing more than 2499 g at birth (24). The odds ratio of adverse perinatal outcomes (stillbirths, neonatal deaths, referral to special care unit, or Apgar score lower than 7 at 5 min) in infants SGA compared to non-SGA was 2.87 (95%CI: 2.73, 3.01) in 237 025 births from 24 countries in Africa, Latin America and Asia (19). Even in the USA, SGA is associated with an increased risk of neonatal death (25). Poor foetal growth is rarely a direct cause of death, but rather can contribute indirectly to increasing the risk of neonatal death, particularly for babies with birth asphyxia and/or infections (sepsis, pneumonia, and diarrhoea), which together account for about 60% of neonatal deaths (24).

The deleterious association between IUGR and health is not limited to the neonatal period. The risk of post-neonatal death in term infants weighing 2000-2499 g is estimated to be two times higher than for infants 2500-2999 g, and four times that of infants weighing 3000-3499 g (17). IUGR is also a very important factor in predicting early postnatal growth (26;27), as well as growth (28), cognitive development (29) and health during childhood (18;27;30-32). Birth weight is also a predictor of adult size, intellectual ability, economic productivity, reproductive performance, and metabolic and cardiovascular diseases as demonstrated by research advances in the area of developmental origins of health and disease (24;33;34). Therefore, improving foetal growth may confer both short- and long-term benefits for the offspring.

### 1.2.3 Incidence of intra-uterine growth retardation

Although IUGR can also be observed in affluent populations, the vast majority of the cases are observed in Asia and sub-Saharan countries (17). This serious health problem is impressively widespread. As many as 16 % of all live births worldwide have LBW, of which more than 90% are from low-income countries (35). In developing countries, LBW at term occurs annually in 10.8% of live births (35). It has been estimated that LBW at term contributes 3.3% and 3.1% of deaths and disability-adjusted life-years (DALYs) lost in the under-5 population in developing countries (24). This is clearly an over-optimistic estimation because it does not account for the deaths and DALYs lost attributable to stunting and wasting during childhood, whereas IUGR is an important contributor to the poor nutritional status later in life.
1.2.4 A brief history of the emergence of the UNIMMAP concept

Factors interacting with embryonic and foetal development are numerous, such as medical complications (e.g. preeclampsia, severe chronic infections), maternal social conditions (e.g. low maternal BMI, smoking, delivery at age<18 y), foetal problems (e.g. intrauterine infection, multiple births), abnormalities of the placenta (e.g. reduced blood flow, partial abruption), and environmental problems (e.g. high altitude) (20;36;37). Among them maternal infection, multiple births), abnormalities of the placenta (e.g. reduced blood flow, partial abruption), and environmental problems (e.g. high altitude) (20;36;37). Among them maternal nutritional factors are usually assumed to be major determinants of IUGR in developing countries and may account for more than 50% of the aetiology of LBW in those countries (38). Numerous observational studies have consistently reported that IUGR was associated with maternal height, pre-pregnancy weight, and pregnancy weight gain (32;39). These observations motivated researchers to test the effect of balanced protein/energy supplements on pregnancy outcome. However, results of meta-analyses were disappointing with an effect on birth weight only in wasted women (estimated between 49.40 g (95%CI: -1.98, 100.78; p=0.06) (40) and 74.89g (95%CI: 42.42, 107.36; p<0.00001) (41)). No difference in birth length was observed in the five studies reporting on that variable, and ponderal index at birth was studied in none of the trials. These trials were all published prior to year 2000.

The disappointing results, particularly in non-wasted women, fostered the hypothesis that deficiencies in multiple micronutrients could have been an important limiting factor (42). This hypothesis had a good scientific basis (43). By the end of the 1990s, evidence had been accumulating from observational studies on the association between deficiencies in iron, zinc, calcium, magnesium, vitamin A, B-complex vitamins, copper and selenium and LBW (44;45). That previous micronutrient supplementation trials had not demonstrated a substantial effect on improving foetal growth (46-50) was a contradictory information only in appareance. These trials had tested mainly supplements containing only a single micronutrient at a time, and were organized in non-deficient subjects, mainly Western, populations. In contrast, deficiencies in multiple micronutrients are prevalent in developing countries, even in individuals with no clinical signs of under-nutrition, given the usual low quality of the diet and the extra requirements associated with pregnancy (51).

During this same period (1998), a high-quality RCT indirectly provided support for the hypothesis that prenatal multiple micronutrients could prevent IUGR (52). That trial on the effect of supplementing Tanzanian HIV-infected pregnant women with either multiple micronutrients, vitamin A, or a placebo to counter vertical transmission of HIV reported that multiple micronutrients reduced the risk for an SGA outcome by 43% (95%CI: 18%, 61%; p=0.002). Although the exact mechanism was – and remains – unknown, this effect of multiple micronutrients was plausible. It could be mediated through different pathways including increased placental surface available for maternal-foetal exchanges; improved maternal haematological status; modification of gene expression; reinforcement of maternal immunity (53); or interactions with hormononal regulation of foetal growth, in particular the insulin-like growth factor-I (IGF-I) which circulating levels are very sensitive to nutrient availability and correlate with foetal size (33;37;54).

In 1999, experts from UNICEF, WHO and UN University proposed to test the benefits of a prenatal multiple micronutrient supplement containing a single Recommended Daily Allowance (USA/Canada RDA\(^4\)) of 15 micronutrients (UNIMMAP) on pregnancy outcomes

\(^4\) Except for folate (400 µg instead of the 800 µg in USA/Canada RDA) in order to comply with WHO recommendations.
in comparison to the usual WHO recommended iron+folic acid supplement (IFA) (Table 1) (1).

Table 1: Composition of the UNIMMAP and IFA supplement

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Form</th>
<th>IFA</th>
<th>UNIMMAP</th>
</tr>
</thead>
<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>
<td>-</td>
<td>1.4</td>
</tr>
<tr>
<td>Vitamin B-2, mg</td>
<td>Riboflavin</td>
<td>-</td>
<td>1.4</td>
</tr>
<tr>
<td>Vitamin B-3, mg</td>
<td>Nicotinamide</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>Vitamin B-6, mg</td>
<td>Pyrodoxine</td>
<td>-</td>
<td>1.9</td>
</tr>
<tr>
<td>Vitamin B-9, μg</td>
<td>Folic acid</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Vitamin B-12, μg</td>
<td>Cyanocobalamine</td>
<td>-</td>
<td>2.6</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>Ascorbic acid</td>
<td>-</td>
<td>70</td>
</tr>
<tr>
<td>Vitamin D, μg</td>
<td>Cholecalciferol</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Vitamin E, mg</td>
<td>Tocopherol</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>Zinc, mg</td>
<td>Zinc sulfate</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Iron, mg</td>
<td>Ferrous fumarate</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>Copper, mg</td>
<td>Copper sulfate</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Selenium, μg</td>
<td>Sodium selenite</td>
<td>-</td>
<td>65</td>
</tr>
<tr>
<td>Iodine, μg</td>
<td>Potassium iodide</td>
<td>-</td>
<td>150</td>
</tr>
</tbody>
</table>

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

This composition of UNIMMAP was proposed by the expert group so as it could be used safely by pregnant woman globally. Firstly, the 15 micronutrients included are the ones for which widespread deficiencies are documented. Some micronutrients were excluded from UNIMMAP because the evidence base of an association with pregnancy outcomes was weak, and/or including them would have been impractical. For example, including calcium in the UNIMMAP composition would have increased considerably the size of the tablet, whereas evidence linking calcium with prevention of preeclampsia was considered weak. Secondly while acknowledging that a single RDA as defined for a healthy pregnant woman in USA/Canada5 might be insufficient to cover the needs in populations with low dietary intakes, and low stores of fat-soluble micronutrients, experts considered that such a conservative approach presented the advantage of the lowest exposure risk to potential harms (1).

1.2.5 Relevance of the supplementation approach

Micronutrients should ideally be obtained from food, although this seems wishful thinking in the short- or even the mid-term. Firstly, in many parts of developing countries, and particularly in the rural area where this research has been carried out, the diversity of the diet is low, not only because poverty limits access to high-quality foods, but also because food markets are under-developed in places where subsistence agriculture is the norm. Secondly, the high nutritional requirements of pregnancy are almost impossible to meet through dietary intake alone. Even in industrialized countries, use of multiple micronutrient supplements is common during pregnancy. Finally, supplementing pregnant women with IFA is a well-established practice within maternal care programmes. Therefore, should the superiority of UNIMMAP over IFA be demonstrated, the distribution channels of IFA could be used with little opportunity costs. This particular aspect also contributed to the relevance of the present research: we did not aim to test a fashionable intervention that would not, in due course, be available and affordable to the populations who were most in need of it, but instead we

5 UNIMMAP contains 50% less iron than IFA because vitamin C, vitamin A and vitamin B2 are expected to enhance the absorption and/or utilisation of iron.
evaluated whether a programme which was already recommended universally could be optimized.

1.2.6 Relevance of the research to Burkina Faso

In Burkina Faso, it is estimated that 19% of all live births in 1999-2005 were LBW (55), although the exact prevalence estimate is unknown due to the difficulty of compiling data from rural areas where 65% of deliveries occur at home. A preparatory survey that we carried out of 1625 singleton term babies born in 2000-2001 in the District Hospital of Houndé, which is in our research setting (see paragraph 1.2.8) yielded similar results (56). Nearly 17% of babies were LBW, and the majority (91.3%) had a weight below 3000 g. Both maternal height and maternal BMI had a strong association with birth weight, even after adjusting for confounding factors. Neonatal, post-neonatal and infant mortality rates reach 31, 50 and 81 per 1000 live births respectively (INSD & ORC Macro, 2003). Moreover, the prevalence of stunting (height-for-age < 2 SD of the reference population) was high, with 38.7% of children under the age of five moderately stunted, and 19.5% severely stunted. Furthermore, wasting prevalence was 18.6% for moderate wasting and 5.1% for severe wasting (INSD & ORC Macro, 2003). Micronutrient deficiencies during pregnancy were also very common, mainly in relation to a poor diet variety (57-59), as documented in Chapter 2. Anaemia during pregnancy was highly prevalent (60), as described in Chapter 5. Around 10% of women in our study area were malnourished at enrolment (BMI <18.5 kg/m²) (9).

1.2.7 Objectives of the research

The objective of our research was to test the beneficial effect of UNIMMAP supplements during pregnancy on foetal and infant growth. The research hypothesis was evidence based, relevant for public health and appropriate for the country hosting the research. Two specific research questions were addressed:

- Supplementation pregnant women with UNIMMAP increases birth weight and reduces risk of SGA compared to IFA supplementation alone.
- Infants of mothers supplemented with UNIMMAP have improved health and growth during infancy.

Beyond the public health objective of the trial, it was expected that the present research bring significant insights in the theoretical understanding of the link between micronutrients, intrauterine and infant growth. In particular, we aimed to assess if:

- The effect of UNIMMAP supplements could be mediated through changes in maternal haemoglobin and/or hormonal changes in cord blood.
- The number of UNIMMAP tablets received and/or the timing of supplementation were influential parameters.

These hypotheses were tested in the MISAME trial, a double-blind randomized controlled trial organized in the catchment area of two health centres in Houndé district, Burkina Faso (registered at Clinicaltrials.gov as NCT00642408). Participating women (n=1426) were recruited as early as possible during pregnancy and randomized to receive either UNIMMAP supplements or IFA until delivery7. The intake of both supplements was directly observed by home visitors, and participants and assessors were blinded to allocation of participants. After 6 weeks post partum (61), the delivery babies were weighed and examined for growth indicators. Adjustments were made for dietary practices, use of antimalarials, and other confounding factors associated with birth weight and growth. The study found that supplementation with UNIMMAP tablets resulted in a significantly higher birth weight compared to IFA supplementation alone. Analysis of the data also revealed that the effect of UNIMMAP supplementation on birth weight could be mediated through changes in maternal haemoglobin and hormonal changes in cord blood. The number of UNIMMAP tablets received and the timing of supplementation were also found to be influential parameters. These findings suggest that UNIMMAP supplementation may be an effective intervention for improving birth outcomes in areas with high malaria prevalence.

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6 MISAME is an acronym standing for “MIcronutrients et SAnté de la Mère et de l’Enfant” (Micronutrients and Maternal and Infant Health)
These hypotheses were tested in the MISAME6 trial, a double-blind randomized controlled trial organized in the catchment area of two health centres in Houndé district, Burkina Faso. Participating women (n=1426) were influenced by parameters. The number of UNIMMAP tablets received and/or the timing of supplementation were influential parameters. The effect of UNIMMAP supplements could be mediated through changes in maternal haemoglobin and/or hormonal changes in cord blood.

Finally, the interest of this research was also academic as it was based on a close scientific collaboration between institutions from industrialized and low-income countries, with expected cross-fertilization and mutual reinforcement of capacity.

1.2.8 Presentation of the research setting

Burkina Faso

Burkina Faso, with its capital Ouagadougou, is a landlocked Sub-Saharan country in West-Africa. It is classified as the sixth least developed country in the world with 81.2% of its population earning less than 2$ a day. Poverty has significantly declined from 55% in 1998 to 42.6% in 2007.

The dry season is characterised by a dry dusty wind which is called Harmattan and carries sand from the Sahara to the gulf of Guinea. There is one rainy season that occurs between May-June and September, which makes for only one harvest season. The country’s major food crops include sorghum, millet maize, sugar cane and cowpeas. Cash crops are limited to cotton lint, which is produced in the south and South-West of the country.

In 2003, HIV prevalence was estimated at 1.8%. Burkina Faso is located in the ‘Meningitis belt’, a zone that stretches from Senegal to the West of Ethiopia. This area is characterised by annual outbreaks of meningococcal meningitis during the dry season. Malaria is holoendemic, with high transmission between July and December. At the time of the study, National Guidelines for malaria prevention in pregnant women recommended a full treatment course of chloroquine (1500 mg over 3 days) at the first antenatal visit followed by 300 mg weekly until 6 weeks post partum (61).

The Houndé health district

This research’s study area is located in the Houndé Health district (province of Tuy, region of Hauts-Bassins) in the mid-west of the country. The city of Houndé is in the province capital and counts 39,800 inhabitants. Houndé is located along the highway that connects the two major cities of Burkina Faso, namely the capital Ouagadougou and Bobo-Dioulasso. The province Tuy is situated in the cotton producing zone, and houses a major cotton fiber production plant in the centre of Houndé town.

The health system of the district consists of 27 rural health centres and one District Hospital which employs two physicians. The MISAME project was implemented in two villages that coincide with two health sectors: Karaba in Health Sector one and Koho in Health Sector three (Figure 1). Karaba is a small village counting approximately 2,400 inhabitants. The village is for the most part populated by the indigenous Bwa people. Koho is a village that stretches out along the highway and counts approximately 4,200 inhabitants. Koho has a slight majority of Mossi people, the largest ethnic group in Burkina Faso and predominantly Muslim, and has a smaller group of Bwa people mainly of Christian faith. A third minority group consists of Peul who are mainly nomadic pastoralists that live outside the village centres.

7 The trial had a factorial design. Participants were also randomly assigned to receive either the malaria chemoprophylaxis recommended by health authorities (300 mg chloroquine/wk) or intermittent preventive treatment (1500 mg sulfadoxine and 75 mg pyrimethamine once in the second and third trimester). The results of the malaria intervention are not presented in this thesis.
In 2002, the MISAME project organised a preliminary census with the purpose of mapping the project area, attributing a number to every house and allocating a unique identification number to every woman of childbearing age.

Figure 1: Situation of the project zones (blue) in the health district of Houndé (yellow), Tuy province, Burkina Faso (Source: Health district of Houndé, 2006)

1.2.9 Structure of the thesis

From Chapter 2 to Chapter 7, each chapter is constituted of a published scientific paper. In Chapter 2, we characterize the dietary habits and the food intake in the study population (p.23). Chapter 3 presents the main results of the MISAME trial on birth outcomes (p.33). Chapters 4 (p.51) and 5 (p.63) explore the intermediate changes induced by UNIMMAP on cord hormone concentrations and maternal haemoglobin concentration. In Chapter 6, we analyse how the effects of UNIMMAP, but also of IFA, related to the cumulative intake of tablets (p.73). Chapter 7 presents the effects of UNIMMAP on growth and survival during infancy (p.83). Finally, we analyse in Chapter 8 the risk-benefit balance of UNIMMAP based on current evidence, and we propose recommendations for policy-makers and researchers (p.95).
1.2.10 References

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