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Effect of balanced energy-protein supplementation during pregnancy and lactation on birth outcomes and infant growth in rural Burkina Faso: study protocol for a randomised controlled trial

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ABSTRACT

Introduction Adequate nutrition during pregnancy is crucial to both mother and child. Maternal malnutrition can be the cause of stillbirth or lead to poor birth outcomes such as preterm delivery and small-for-gestational-age newborns. There is a probable positive effect of providing pregnant women a balanced energy-protein (BEP) food supplement, but more evidence is needed. The MIcronutriments pour la SAnté de la Mère et de l'Enfant (MISAME) III project aims to improve birth outcomes and infant growth by testing a BEP supplement during pregnancy and lactation in rural Burkina Faso. This paper describes the study protocol.

Methods and analysis MISAME-III is a four-arm individually randomised efficacy trial implemented in six rural health centre catchments areas in the district of Houndé. Eligible pregnant women, aged between 15 and 40 years old and living in the study areas, will be enrolled. Women will be randomly assigned to one of the four study groups: (1) prenatal intervention only, (2) postnatal intervention only, (3) prenatal and postnatal intervention or (4) no prenatal or postnatal intervention. The intervention group will receive the BEP supplement and iron/folic acid (IFA) tablets, while the control group will only receive the IFA tablets following the national health protocol. Consumption will be supervised by trained village women on a daily basis by means of home visits. The primary outcomes are small-for-gestational age at birth and length-for-age z-score at 6 months of age. Secondary outcomes will be measured at birth and during the first 6 months of the infants' life. Women will be enrolled from October 2019 until the total sample size is reached.

Ethics and dissemination MISAME-III has been reviewed and approved by the University Hospital of Ghent and the ethics committee of Centre Muraz, Burkina Faso. Informed consent will be obtained. Results will be published in relevant journals and shared with other researchers and public health institutions.

Trial registration number NCT03533712.

Strengths and limitations of this study

- This trial will help to fill the evidence gap on the effect of balanced energy-protein (BEP) supplements in pregnant and lactating women on birth outcomes and infant growth.
- Formative research to select the most suitable BEP supplement ensured that the selected BEP is well accepted by the study population.
- The daily intake of BEP supplements and iron/folic acid tablets during pregnancy and lactation will be directly observed by study workers.
- This study will assess the impact of factorial combinations of prenatal and postnatal BEP on child growth to elucidate the relative importance of BEP during pregnancy and/or early lactation.
- Blinding of study participants and staff members will not be possible, as the supplements are identifiable.

INTRODUCTION

Pregnancy is a challenging period in the life of many women in low-income and middle-income countries (LMICs). Maternal mortality remains high, and many neonates suffer from premature delivery and/or intrauterine growth retardation, both in length and in weight accumulation.[1] An indicator to measure neonatal growth is small-for-gestational age (SGA). SGA is defined as a birth weight below the 10th percentile of a standard optimal reference population for a given gestational age and sex.[2] SGA is often caused by growth restriction in the womb and has been associated with neonatal and postneonatal mortality.[2] It has also been linked to an increased risk of morbidity later

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in life, especially non-communicable diseases.[3] SGA affected 23.3 million term children in LMICs in 2012.[4] Adequate nutrition during pregnancy is crucial for optimal maternal and newborn health,[5 6] and maternal malnutrition has been associated with fetal growth restriction.[7] An adequate dietary balance is necessary to ensure sufficient energy intake for adequate growth of the fetus.[8] Unfortunately, maternal undernutrition remains a public health challenge in regions across sub-Saharan Africa and Asia.[9 10]

Several types of food supplements have been developed and evaluated over the past years. A positive effect of multiple micronutrient supplements (MMS) during pregnancy on birth outcomes has been found in previous studies.[11] Keats *et al*[11] concluded in their review that MMS during pregnancy gave a probable reduction in SGA and preterm births and can thus be used for future guidance. According to a multicountry randomised controlled trial (RCT) done in LMICs, a positive effect of lipid-based nutrient supplements on fetal growth-related birth outcomes can be seen when starting supplementation before conception or during the first trimester.[12] Moreover, the latest evidence indicates a possible positive effect of providing pregnant women a balanced energyprotein (BEP) food supplement.[5 13–15] In line with that evidence, the 2016 WHO's antenatal care guidelines state that pregnant women in undernourished populations should receive, depending on the context, BEP supplements to reduce the risk of stillbirth and SGA.[6] Researchers, however, still highlight the limited amount of evidence and a need to evaluate the effect of balanced supplements on birth outcomes, such as SGA.[5 13] Experimental trials of high-quality and large sample sizes, especially in undernourished pregnant women, are thus needed.[13] Following this recommendation, compositional guidance for a ready-to-use food supplement for pregnant women was developed by the Bill and Melinda Gates Foundation (BMGF) in 2016.[16]

Two previous projects, MIcronutriments pour la SAnté de la Mère et de l'Enfant (MISAME) I and II, conducted in Burkina Faso, investigated the effect of supplementation during pregnancy and the effect on birth outcomes in infants.[17 18] MISAME-I compared the effect of the UNICEF/WHO/UNU international multiple micronutrient preparation (UNIMMAP) with the effect of iron/folic acid (IFA) alone on fetal growth in a double-blind RCT and concluded that UNIMMAP modestly but significantly increased fetal growth.[17] The second study (MISAME-II) assessed the effect of a lipid-based nutrient supplement fortified with UNIMMAP compared with a UNIMMAP tablet during pregnancy in an open-label, individually randomised controlled trial on birth anthropometry. It was found that combining energy with micronutrients during the prenatal phase led to larger birth lengths.[18] Since MISAME-II used the UNIMMAP as a control, a complete assessment of the impact of the fortified lipid-based UNIMMAP was not possible. Therefore, MISAME-III will study the effect of a BEP supplementation, compared with a control group, and extend the supplementation postnatally to investigate the net contribution of prenatal and postnatal BEP supplementation on child linear growth up to 6 months of age.

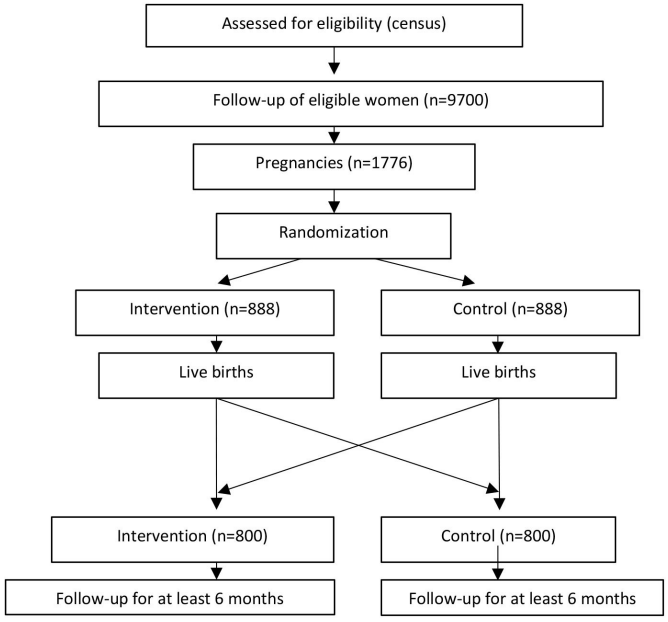


Figure 1 Study design of the randomised controlled trial.

In summary, the MISAME-III study hypothesises that: (1) providing women with a BEP supplement during pregnancy will decrease the incidence of SGA compared with the control group; and (2) providing them with a BEP supplement during the postnatal period will increase children's length by the age of 6 months compared with the control group.

METHODS

This protocol has been developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines (online supplemental file 1).

MISAME-III study design

The MISAME-III project is an individually randomised 2×2 factorial efficacy trial aiming to improve birth outcomes and infant growth in rural Burkina Faso by testing a BEP supplement during pregnancy and lactation (figure 1). At inclusion, pregnant women will be individually and randomly allocated to a prenatal intervention or control group and a postnatal intervention or control group. The intervention group will receive a daily BEP supplement to be consumed under supervision for the duration of pregnancy/lactation. Both intervention and control groups will receive the standard IFA tablet through the national antenatal care. In addition to the main trial, we propose a number of substudies to test specific hypotheses in a subsample of pregnant/lactating women and children. MISAME-III began with a formative study to identify the preferred product type for the provision of a fortified BEP supplement during the RCT.

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Study setting

The study will be conducted in the district of Houndé in Burkina Faso, a landlocked country situated in West-Africa; similar to the previous MISAME studies, Burkina Faso has an infant mortality rate of 53 per 1.000 live births,[19] with an estimated Low Birth Weight (LBW) prevalence at 14% in 2013.[20] The prevalence of SGA has been estimated to be between 32.2% and 41.6% in the district of Houndé.[17] The Demographic and Health Survey of 2010 reported that 16% of women had a body mass index (BMI) below 18.5 kg/m^2, which indicates the presence of chronic energy deficiencies in the zone.[21] The highest prevalence can be found in the Eastern region, where 31% of women have a BMI lower than 18.5 kg/m^2, that is, low BMI.[22] Moreover, in particular, adolescent Burkinabèe girls between the age of 15 and 19 years have a low BMI, with an estimated prevalence of 23%.[23] Micronutrient deficiencies also remain a major problem in both infants and women of reproductive age in the country.[23 24]

The climate of the country is Sudano-Sahelian, with a dry season from October to March/April and a rainy season from May until September/October. The diet is essentially cereal based[25] with maize as the main staple food.[26]

MISAME-III will be conducted in the same health district where the two previous MISAME studies were organised. The study villages are concentrated around six health centres, which are within an accessible range from the district hospital. A list of all study sites can be found on: www.misame3.ugent.be

Study population and recruitment

Women living in the study villages and aged between 15 and 40 years will be identified through a census. The villages were selected based on their accessibility and distance to the nearest health centre, number of facility-based deliveries per year and their agricultural model as some households tend to reside on their fields during the harvest season. Trained village women (femme accompagnante (FA)), selected in collaboration with the community leaders, will visit the households every 5 weeks to ask about women's menstruation. In case of amenorrhoea, women will be sent to the nearest health centre for a pregnancy test and a first antenatal consultation by our project midwife when tested positive. An ultrasound examination will be completed soon after inclusion by the project medical doctor to assess gestational age. A baseline interview will also be done by the project interviewers to assess the household members' characteristics, household properties, water sanitation and hygiene (WASH) and household food security.

Inclusion criteria:

- Women between 15 and 40 years old at study inclusion.
- Confirmed pregnancy by a pregnancy test and ultrasound.
- Women who signed the informed consent form.

Exclusion criteria:

- Pregnancies >20 weeks of gestational age.
- Women planning on leaving the area during their pregnancy.
- Women planning on delivering outside the study area.
- Women who are allergic to peanuts.
- Women with multifetal gestations (exclusion from analysis).

FAs will be informed by the project midwife when a participant has been included. FAs will visit pregnant women on a daily basis to distribute the BEP supplement and/or IFA tablet and to supervise consumption. During the postnatal period, FAs will distribute the supplements and IFA tablets to the intervention group on a daily basis until 6 weeks after birth. From that moment onwards, they will receive a week's worth of BEP supplements. The postnatal control group will receive the IFA tablets on a daily basis during the first 6 weeks after birth, and participants will thereafter be visited once a week (without any supplementation) to minimise the effect of home visits. The FA will inform women on the supplement's function, the importance of antenatal visits during pregnancy, maintaining a healthy diversified diet, the importance of delivering at a health facility, the importance of exclusive breast feeding and the introduction of complementary foods at the age of 6 months. Throughout the study, the FAs will be supervised by project interviewers. Supervision visits will be conducted using Lot Quality Assurance Sampling schemes and empty sachet counts to ensure that study participant are visited according to the project protocol.

Manufacturing of 12 fortified BEP supplements and the formative study

Twelve fortified BEP supplements were pretested before the start of the RCT during a formative research phase. Several food manufacturing companies were invited to produce ready-to-use BEP supplements following the compositional guidelines proposed during an expert meeting hosted by the BMGF[16] in September 2016 (table 1). The BEP supplements had to be: (1) ready to consume, (2) not need a cold chain and (3) microbiologically stable.

Seven out of 12 supplements were characterised as sweet and five as savoury. Products were produced in different forms, including a biscuit, pillow, wafer, bar, paste, instant drink and soup.

In a first screening step of the formative study, the two most preferred BEP supplements were identified by using a combined evaluation approach consisting of a single meal test, sensory evaluation and focus group discussions, in a convenience sample of 40 pregnant women. In a next step, we compared the acceptability of the two preselected BEP supplements using a 10-week home-feeding study, with 80 pregnant women, to select to most preferred product for the RCT. We refer to both papers for detailed information.[27 28]

Study intervention

At inclusion, pregnant women will be randomly allocated to four different study groups: (1) prenatal intervention

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Table 1 The compositional guidelines for macronutrients and micronutrients

Nutrition component	Target per serving
Total energy	250–500 kcal per serving.
Fat content	10%–60% of energy intake.
Protein content	16 g (14–18 g) with a digestible indispensable amino acid score of ≥0.9.
Carbohydrates	Between 45 g and 32 g per 100 g (added sucrose between 20 g and 10 g per 100 g).
Trans fats	<1% of energy intake.
Fatty acid	(Optional): min of 1.3 g of n-3 or 300 mg docosahexaenoic acid (DHA)+eicosapentaenoic acid (of which 200 mg DHA) to achieve a healthy n-6: ratio of the supplement of 5:1.
Micronutrients	Vitamin A, D, E, K, B1 (thiamin), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B9 (folate), B12 and C; minerals: iron, zinc, iodine, calcium, phosphorous, copper and selenium.
Optionally	Pantothenic acid, manganese, potassium, biotin and choline will be included.
	The final composition of the product will be determined by the selected product as the manufacturing process will influence the macronutrient composition.

only, (2) postnatal intervention only, (3) prenatal and postnatal intervention or (4) no prenatal and no postnatal intervention. Prenatal and postnatal supplementation will start right after inclusion and birth, respectively. The prenatal intervention group will receive the BEP supplement and IFA, while the control group will receive IFA tablets alone. The IFA tablets contain 65 mg iron and 0.4 mg folic acid. The postnatal intervention group will receive the BEP supplement for 6 months in combination with the IFA tablets for 6 weeks following the national protocol of Burkina Faso; the control group will receive IFA alone for 6 weeks.

Allocation/randomisation

We will apply a stratified permuted block randomisation schedule to allocate women to the prenatal intervention or control group and in a next step to allocate women to a postnatal intervention and control group. Per health centre (ie, stratum), women will be individually randomly in permuted blocks of 8 so that, per block, equal numbers are obtained in the prenatal intervention (n=4) and control (n=4) group and equal numbers are also obtained in the postnatal intervention (n=4) and control (n=4) group. The double random sequence will be generated before the start of the study using Stata V.15.1 (Statacorp, Texas, USA) by an external research analyst. The allocation group will be coded with two letters (A or B for the prenatal and Y or Z for the postnatal study group) and placed in a sequentially numbered sealed opaque envelopes by project employees, not in direct contact with participants. At study enrolment, the project midwife will draw the next sealed envelope and allocate the participant to the study group defined by the letter code in the envelope. Blinding of participants and community-based project workers will not be possible since the supplements are identifiable. Field staff responsible for measuring primary and secondary study outcomes are not directly involved in the daily supplementation of the study participants and can therefore be considered to be partially blinded.

Outcomes

Primary outcomes of the RCT

The trial has two primary study outcomes that will be used to assess the impact of the prenatal and the postnatal intervention, respectively:

- Incidence of SGA, defined as birth weight <10th centile of the Intergrowth 21st reference.[29]
- Length-for-age z-score (LAZ) calculated using the WHO 2006 growth reference at 6 months of age.[30]

Secondary outcomes of the RCT

A list of the trial's secondary outcomes can be found in table 2.

Birth weight measurements will be defined using the Intergrowth 21st reference,[29] and child anthropometry will be defined using the Child Growth Standards developed by the WHO.[30]

Outcomes of the substudies

Substudy 1: impact of the intervention on neonatal and maternal body composition 2–3 weeks after delivery.

Body composition will be determined in mother–child dyads by deuterium dilution and analysis of saliva by a Fourier Transform Infrared reader (Agilent FTIR 4500 series). The substudy will also assess if early gestation maternal BMI (defined as body weight in kilograms divided by the square of height in metres) modifies the intervention's effect on neonatal body composition.

Substudy 2: impact of the intervention on dietary intake.

A dietary assessment study will be conducted, using a 24-hour dietary recall in a subsample of women. This substudy will enable us to assess possible substitution of the prenatal diet by the BEP supplement.

Substudy 3: impact of the intervention on breastmilk.

Breastmilk samples will be taken in the four study groups to compare the composition and to analyse the interaction between the supplementation periods.

Sample size

With an SGA prevalence of 32% and an anticipated decrease of 7%, a sample of 652 subjects per prenatal arm is required with α=0.05 and β=0.2.[26] To accommodate for possible losses, the number of subjects per arm was increased to 888 (total subjects: 1776). Possible losses are based on previous MISAME studies where the prevalence

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Table 2 Secondary outcomes of the RCT on maternal, newborn and child level

Maternal outcomes	Newborn	Child
Total and trimester-specific prenatal weight gain and gestational weight change.	Birth weight (measured within 72 hours after birth).	Weight-for-age Z-score at 6 months of age (WAZ) (and 9 and 12 months on a subsample).
Probable and possible maternal postnatal depression at 2 and 6 months of child age.	Birth length (measured within 72 hours after birth).	Weight-for-length Z-score at 6 months of age (WLZ) (and 9 and 12 months on a subsample).
Maternal anaemia at the third antenatal consultation.	Ponderal or Rohrer's index at birth.	Stunting at 6 months of age.
Women's mean and minimum dietary diversity score (measured twice weekly).	Gestational age at delivery.	Wasting at 6 months of age.
	Large-for-gestational age.	Underweight at 6 months of age.
	Chest circumference (measured within 72 hours after birth).	Duration of exclusive breastfeeding during the first 6 months of age.
	Head circumference (measured within 72 hours after birth).	Incidence of child wasting over first 6 months of life.
	Arm circumference (measured within 72 hours after birth).	Weight gain over first 6 months of life.
	Incidence of preterm birth.	Child mortality (between birth and 6 months of age).
	Fetal loss.	Monthly change in LAZ over first 6 months of life.
	Stillbirths.	Monthly change in WLZ over first 6 months of life.
		Monthly change in WAZ over first 6 months of life.
		Monthly change in head circumference over first 6 months of life.
		Child morbidity symptoms over first 6 months of life.
		Anaemia at 6 months of age.
		Haemoglobin concentration at 6 months of age.

LAZ, length-for-age z-score; RCT, randomised controlled trial.

was ~26 % due to a combination of miscarriage, stillbirths, multifetal pregnancies, outmigrants, maternal deaths and incomplete data.[18] For the analysis of an effect of the postnatal intervention on LAZ at 6 months of age, the minimally detectable effect depends on the presence or absence of an interaction effect between the prenatal and postnatal intervention. In the absence of a statistically significant interaction between prenatal and postnatal intervention, at sample size of 588 children per postnatal study arm would allow us to detect a difference of 0.18 Z-score (SD=1.1) based on a cross-sectional survey conducted in the Gourcy health district in Burkina Faso,[31] between study arms with α=0.05 and β=0.20. This implies that if ~1400 singleton live births are available, we allow for a maximum loss to follow-up of 16%. In the presence of a statistically significant interaction between prenatal and postnatal intervention, a total sample size of 1176 represents 294 children per factorial combination of the prenatal and postnatal study group (four groups in total). A subgroup size of 294 would allow us to detect a difference in LAZ at 6 months of age of 0.28 assuming an SD of 1.1, α=0.025 (Bonferroni correction for two primary endpoints analyses) and β=0.20.

Data collection

Anthropometric and clinical procedures

At enrolment, anthropometric measurements from all women will be taken. Gestational age will be determined during an ultrasound consultation by measuring crown-rump length (7–13 weeks) or by calculating the mean of three to four measurements: biparietal diameter, head circumference, abdominal circumference and femur length (12–26 weeks).[32]

During pregnancy, clinical follow-up will consist of antenatal visits following the national guidelines.

At birth, anthropometric measurements of all neonates will be assessed in duplicate within the first 72 hours of life (in practice, the aim is to measure within the 24 hours of life). After birth, mother and child will visit the healthcare centres monthly for a follow-up on clinical,

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Table 3 Participant timeline schedule of enrolment, interventions, assessment and visits

	Enrolment		Allocation	Postallocation: Pregnancy and birth				After birth							
	Start	5-weekly visits	ANC 1	Household visit	Ultrasound	ANC 2, 3 and 4	Birth	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Month 12
Enrolment															
Census	×														
Pregnancy identification		×													
Pregnancy confirmatory test			×												
Informed consent and allocation to study group			×												
Study groups															
Prenatal BEP+IFA			x	—	—	—	x								
Prenatal IFA			x	—	—	—	x								
Postnatal BEP+IFA*							x	—	—	—	—	—	x		
Postnatal IFA							x	—	x						
Assessments															
Mothers															
Baseline questionnaire				×											
Gestational age determination					×										
Skinfold measurements					×										
Weight (kg) and arm circumference (mm) †/‡			×			×	×	×	×	×	×	×	×	×	×
Height (cm)			×												
Haemoglobin (g/dL)			×			× (ANC3)									
Women's Dietary Diversity Score (twice weekly)				×											
Maternal depression			×						×				×		
Infants															
Birth weight (kg)							×								
Birth length (cm)							×								
Head circumference (mm)							×	×	×	×	×	×	×		
Chest circumference (mm)							×								
Arm circumference (mm)							×	×	×	×	×	×	×	×	×
Morbidity								×	×	×	×	×	×		
Mortality							×	×	×	×	×	×	×		
Weight (kg) and height (cm)								×	×	×	×	×	×	×	×

Continued

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Table 3 Continued

	Enrolment		Allocation	Postallocation: Pregnancy and birth				After birth							
	Start	5-weekly visits	ANC 1	Household visit	Ultrasound	ANC 2, 3 and 4	Birth	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Month 12
Breastfeeding practices								×	×	×	×	×	×		
Haemoglobin (g/dL)													×		

*The IFA tablets will be given during the first 6 weeks after birth in the postnatal intervention group, according to the national health protocol.
†Only maternal weight will be taken at birth.
‡In a subsample at months 9 and 12.
BEP, balanced energy–protein; IFA, iron/folic acid.

anthropometric and child morbidity measures (signs including fever, vomiting, diarrhoea, cough, difficulty breathing and running nose). A subsample will be measured at the healthcare centres or at home by the project interviewers to collect postnatal data at months 9 and 12.

Haemoglobin concentrations will be measured in women at enrolment and during the third antenatal care visit. This will be conducted at 6 months of age among children.

Baseline questionnaires

Prenatal and postnatal maternal depression will be assessed using the standardised Edinburgh Postnatal Depression Scale questionnaire consisting of 10 questions.[33] Project midwives will be trained for this, and the questionnaire will be asked at inclusion and at months 2 and 6 after birth. Socioeconomic and demographic information from all participants will be collected once included. Trained project interviewers will ask questions on household members' characteristics, household properties, WASH environment and household food security.[34] The women's dietary diversity score will be measured in all participating women by the FA during the home visits. This will be enumerated twice a week per participant using the Women's Dietary Diversity Score with 11 food groups.[35]

Table 3 shows the overview of the time schedule and measurements of the trial.

Quality of all study data will be insured by a thorough training of all field staff. Procedures to handle data collection tools (questionnaires, anthropometric and clinical measurement material, and laboratory procedures) will be pretested in the field during a dry-run of ±3 months. Anthropometric measurement standardisations of the field staff will be repeated bimonthly throughout the trial. Anthropometric measurements will be taken in duplicate. Newborns will be measured within 72 hours after birth (preferably within the 24 hours), and all weighing scales and HemoCue 201+ devices will undergo weekly quality control. A WhatsApp group will be set up where problems can be communicated and solved quickly.

All data collection forms of the trial can be found on: www.misame3.ugent.be

Women will be designated as lost to follow-up if they move from the study area or withdraw their participation. Reasons for discontinuation will be recorded.

Women will be enrolled in the study from October 2019 until the total sample size has been reached.

Data management and analysis

FAs will use smartphones with computer-assisted person interviewing programmed in CSPRO (version 7.3.1) to collect data during household visits. The study data collected by the project medical doctor, project midwives and interviewers will be done by Survey Solutions data entry software (V.19.12.6) on tablets. This data will be uploaded to a central server on a weekly basis. All questionnaires were programmed and have been tested on the Survey Solutions Designer website and include validation codes to promote the quality of the data entry in the field. Assignments will be sent once a week to the tablets of the field team, and preloaded data collected at an earlier contact moment will be used to lower the amount of incorrect data. Paper forms will also be available on the field as a backup.

Further data quality checks will be conducted in Stata V.14.2 (Statacorp, Texas, USA). Missing or inconsistent data outliers will be sent back to the field for revision.

Statistical analysis

We refer to the Statistical Analysis Plan of the trial '*Statistical analysis plan: Impact of a prenatal and postnatal balanced energy-protein supplement on birth size and postnatal child growth in Burkina Faso*' published on: www.misame3.ugent.be

Data monitoring

Data monitoring and auditing

The Data and Safety Monitoring Board is an independent multidisciplinary group whose members are not involved in the trial. The board consists of a Belgian endocrinologist, a Belgian paediatrician, a Burkinabè paediatrician, a Belgian gynaecologist and a Belgian ethicist.

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Serious adverse events (SAEs)

FAs will be trained to recognise health issues and will actively refer those participants to see the project midwife in the primary health facilities or Centre de Santé et Promotion Sociale (CSPS) in the event they occur. All SAEs will be recorded on a case-by-case basis, and verbal autopsies will be conducted for maternal, neonatal and infant deaths by the field medical doctor.

ETHICS AND DISSEMINATION

Ethics approval and consent to participate

MISAME-III has been reviewed and approved by the University Hospital of Ghent University (B670201734334) and the Burkinabe ethics (N°2018–22/MS/SG/CM/CEI) committee. Important protocol changes will be noted on ClinicalTrials.gov. When eligible women meet the inclusion criteria, project midwives will explain the background and procedure of the complete trial. Written informed consent or assent will be asked from the participating women. In case of illiteracy, a thumb print will be asked and witnessed by the recruiting investigator and one extra witness. Participants will be told that all data collected during the trial is confidential and that they are allowed to withdraw at any time. A copy of the informed consent and assent can be found on www.misame3.ugent.be and as supplementary file (online supplemental file 2).

Patient and public involvement

MISAME-III has been well accepted by the community, because of the previous positive experiences they had with the MISAME-I and II studies. Through the formative study, women were involved in the choice of BEP supplement. Workshops will be planned at the end of the study in order to communicate the study results to the community.

Ancillary care

The MISAME-III project will pay for ancillary care when participants have health issues and in case the costs are not covered by the national healthcare programme. Participants suffering harm due to their trial participation will be covered.

Confidentiality

A data management plan has been put in place to address concerns regarding the General Data Protection Regulation rules. During the trial, the data files containing personal identifying information will be stored on the Survey Solutions server. Only the principal investigators and the project coordinators will be able to access those files.

Dissemination plan

On completion of the trial, all anonymised study data will be available on request. Final results will be communicated to the participants, the Burkinabè Ministry of health, the field staff, the BMGF, Ghent University researchers and students, AFRICSanté, healthcare professionals and other relevant international public institutions. Papers on the study results will be published in peer-reviewed journals and will be available on the project website. All investigators contributing to the realisation of the project and publication of results will be included as an author. Other contributors such as the participants, FA and field staff members will be mentioned in the acknowledgements.

MISAME-III has been well accepted by the community, because of the previous positive experiences they had with the MISAME-I and II studies. Through the formative study, women were involved in the choice of BEP supplement. Workshops will be planned at the end of the study in order to communicate the study results to the community.

DISCUSSION

In this paper, the protocol of an individually randomised four-arm efficacy trial in rural Burkina Faso has been described in which pregnant and lactating women in the intervention group will receive a BEP supplement together with IFA tablets. The control group will only receive the standard IFA treatment.

The key features of the present trial are, first, the inclusion of a formative study for a better understanding of which type of supplement is preferred, what taste is most acceptable and which factors affect adherence in the study population. Second, the supplementation will be given during pregnancy and during the first 6 months after birth. This will give us the opportunity to assess the specific value of postnatal supplementation on several outcomes. Third, the observed daily intake of intervention and control supplements is a key feature to ensure compliance and to avoid sharing of the supplements with other household members. Fourth, MISAME-III has the advantage of being the third trial of its kind in the study area. This presents an opportunity to anticipate the issues that arose in previous trials. For instance, women in specific villages tended to leave their homes for a longer period to go work on the fields outside the village. This posed problems in the continuation of the supplementation in the past and will be taken into consideration during MISAME-III. Fourth, four substudies are nested in the main trial that will provide insight into the mechanism by which prenatal BEP supplementation affects birth and infant outcomes. And last, similar studies are being conducted in other countries, allowing for comparison between results from different contexts.

The MISAME-III study will provide evidence on the impact of BEP supplements on birth and infant size using a rigorous study design. The study results will further strengthen and refine WHO's recommendation on the use of context-specific BEP supplementation during pregnancy and lactation.

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MASTERPROEF HAIO : REFLECTIEVERSLAG MISAME-III STUDIE

Vanslambrouck Katrien

1. De MISAME-III studie

Inleiding

Malnutritie blijft globaal een groot probleem; wereldwijd zijn er 149 miljoen (22%) kinderen onder de leeftijd van 5 jaar stunded (*Engels: low height-for-age*) en 49,5 miljoen (6,7%) kinderen wasted (*Engels: low weight-for-height*) (1). Er zouden jaarlijks 3,2 miljoen kinderen onder de leeftijd van 5 jaar sterven als gevolg van ondervoeding, dit komt overeen met 45% van alle kindersterftes. Maternele ondervoeding ligt jaarlijks aan de oorzaak van 3,5 miljoen moedersterftes (2). De gevolgen van ondervoeding blijven dus – vooral in lage en middeninkomenslanden –nog een zeer groot probleem voor moeders en hun (ongeboren) kinderen. Het is in deze context dat deze MISAME-III studie werd opgezet.

De MISAME-III (*Frans: MIcronutriment pour la Santé de la Mère et de l'Enfant*) is een individueel gerandomiseerde studie uitgevoerd in het district van Houndé in ruraal Burkina Faso (West-Afrika) rondom zes gezondheidscentra. De opzet van de studie was om het effect van een energie-proteïne supplement (*Engels: balanced-energy protein, BEP*) op primaire en secundaire zwangerschaps- en geboorte uitkomsten te onderzoeken in een context waar het dagdagelijkse dieet vaak niet voldoet aan de nodige hoeveelheid micro- en/of macronutriënten tijdens de zwangerschap.

Methodologie

Voor de studie werden zwangere vrouwen tussen de leeftijd van 15 en 40 jaar met een zwangerschapsduur van < 21 weken op een gerandomiseerde manier toegewezen aan een interventiegroep of aan een controlegroep. De interventiegroep bestond uit de dagelijkse consumptie van het BEP supplement en een standaard, door de Burkinese gezondheidszorg geleverd, ijzer- en foliumzuur (*Engels: iron and folic acid, IFA*) tablet. De controlegroep consumeerde dagelijks het standaard IFA tablet. De inname van de supplementen werd tijdens de zwangerschap op dagelijkse basis gesuperviseerd door community health workers (*CHW*). Voor meer gedetailleerde informatie wordt verwezen naar het protocol van de MISAME-III studie (3).

De resultaten

In totaal namen 1788 vrouwen deel aan de MISAME-III studie. De onderzoekers zagen geen significant effect op de primaire outcome; er was geen significante daling van de prevalentie van het aantal te klein geboren baby's (*Engels: small for gestational age, SGA*). Men zag wel dat een BEP leidde tot een langere zwangerschapsduur, een minder aantal baby's met een laag geboortegewicht (gewicht < 2,500kg), een hoger geboortegewicht en geboortelengte, een grotere omtrek van de thorax en bovenarm van de pasgeborenen. De studie onderzocht hiernaast ook de impact van het BEP supplement op de moeder en het effect hiervan op de eerste levensmaanden van het kind tot en met de leeftijd van 6 maanden (en een subgroep tot en met de leeftijd van 12 maanden). Deze laatste studies zijn nog lopende en de bevindingen hiervan worden binnenkort gepubliceerd (4).

Discussie

De studie had enkele sterke punten zoals de vroege detectie van zwangerschappen met als gevolg ook de vroege inclusie van zwangere vrouwen: vrouwen namen gemiddeld rond de

11de week van hun zwangerschap deel aan de studie. Daarnaast werd ongeveer 83% van de supplementen dagelijks onder supervisie ingenomen waardoor de effecten van het supplement goed onderzocht konden worden (4).

De eigenlijke RCT werd ook voorafgegaan door twee kleinere verkennende studies in hetzelfde gebied waarbij in een groep van een 100tal zwangere vrouwen werd gepeild naar de acceptatie van 12 verschillende BEP supplementen. Het supplement werd namelijk in eerste instantie in meerdere vormen (een pasta, een drankje, een koekje en een soep) en in verschillende smaken (zoete of zoute smaak) geproduceerd en in deze twee studies uitgetest. Het product dat de voorkeur kreeg werd dan uiteindelijk gebruikt (5, 6).

De MISAME-III studie was ook al gekend bij de mensen ter plaatse aangezien zij de 3de in haar reeks was. Er werden in de voorbije jaren in hetzelfde gebied al twee MISAME studies uitgerold, deze onderzochten telkens ook het effect van een supplement tijdens de zwangerschap (7, 8). Daarnaast werd de MISAME-III studie ook voorafgegaan door een campagne in de regio ter introductie.

Tijdens de studie werd er wel geen rekening gehouden met acute en/of chronische infecties, stress en fysieke activiteit tijdens de zwangerschap met als gevolg dat de impact hiervan op de nutritionele status van de mama en de geboorte outcomes niet kon worden onderzocht. Men zag dat het effect van het supplement groter was als de nutritionele status van de moeder bij aanvang beter was. Met als bedenking dat het starten van supplementatie preconceptioneel een grotere impact zou kunnen hebben op de studie uitkomsten (4).

2. Mogelijke andere interventies rond malnutritie

Het is belangrijk te weten dat ondervoeding een benadering nodig heeft op verschillende niveaus waarbij alle onderliggende en contextuele factoren worden aangepakt. Deze factoren zijn complex en meestal ook met elkaar verbonden (9) en worden ingedeeld in drie grote groepen; de basisdeterminanten (dit zijn sociale, socio-economische en demografische factoren), de onderliggende determinanten (zoals voedingspraktijken, gezondheid, educatie, adequate voeding die voor handen is) en de onmiddellijke determinanten (zoals dieet en zorg) (10).

Tot op heden hebben de meeste studies rond maternele ondervoeding zich vooral gefocust op het tackelen van één enkel van deze factoren met één enkele interventie (net zoals de huidige studie). Zo stelt men in de literatuur voor om eerder in te zetten op een combinatie van zowel voedingsspecifieke als voedingssensitieve interventies voor een meer holistische benadering (11-14). Met voedingsspecifieke interventies worden interventies bedoeld die de directe oorzaken van honger aanpakken. Voorbeelden hiervan zijn studies rond voedingssuplementen, borstvoeding of complementaire voeding. Voedingssensitieve interventies zijn interventies die de indirecte oorzaken van ondervoeding aanpakken zoals landbouw, voedselzekerheid, sociale veiligheidsnetwerken, WASH, maternele mentale gezondheid etc (15). *The Lancet Nutrition Series* van 2013 en 2021 maakten een opsomming van de belangrijkste kosteneffectieve nutritionele interventies. Zij rapporteerden daarnaast dat voedingssensitieve interventies op grote schaal 80% van de malnutritie kan reduceren (15, 16).

3. Kritische reflectie

Enerzijds kunnen studies zoals de MISAME-III studie een belangrijke bijdrage leveren om via hoogkwalitatief en robuust onderzoek verder uit te zoeken welk specifiek supplement (juiste hoeveelheden aan macro- en micronutriënten) er aan wie (identificeren van de juiste risicopopulaties) kan worden gegeven om de hallucinante cijfers van malnutritie te reduceren. Anderzijds blijven er toch een aantal vragen/bedenkingen naar boven komen bij dergelijke studies. De studie werd in grote lijnen al uitgeschreven en gesponsord door de Bill and Melinda Gates Foundation *(BMGF)*. Mijn eerste grote vraag was eigenlijk wat de BMGF met dergelijke studie op termijn wil bereiken. Hun doel om de grote mondiale problemen te willen uitroeien, wat zeker en vast een nobele zaak is, zou volgens mij beter overgelaten worden aan een instantie zoals de World Health Organisation (*WHO*). Organisaties zoals de BMGF hebben door hun kapitaal een grote invloed op het bepalen van de agenda van de wereldgezondheidszorg.
Daarnaast koos de BMGF zelf ook hun partners om mee in zee te gaan voor deze MISAME-III studie. Eén van deze partners was Nutriset, een Frans bedrijf dat bekend werd door zijn productie en wereldwijde levering van de Ready-To-Use Therapeutic Food (*RUTF*) Plumpy'nut. Plumpy'nut wordt sinds de jaren 90 gebruikt om ernstige en acute ondervoeding bij jonge kinderen - met succes - te behandelen. Het bedrijf verwierf daarbij ook een patent op het supplement. Daardoor kon het niet door andere landen zelf worden geproduceerd en gedistribueerd. Dit leidde tot felle kritiek internationaal. Het patent werd hierdoor na enige tijd in sommige landen opgeheven maar er blijven wel nog restricties rond de productie bestaan. Het BEP supplement van deze studie werd ook op Europese bodem geproduceerd door Nutriset en verscheept naar Burkina Faso. De vraag stelt zich dan hoe het bedrijf zal beslissen over de toekomstige productie hiervan en of het bedrijf hier ook een patent op zal krijgen. Indien men een gelijkaardig voedingssupplement – na het aantonen van een duidelijk robuust effect - op grote schaal zou willen laten consumeren door zwangere vrouwen als deel van een nationaal prenataal gezondheidsprotocol, zou een land als Burkina Faso er eerder voordeel aan hebben om het product zelf te kunnen produceren (zowel met producten die lokaal te vinden zijn als door mensen ter plaatse). Op deze manier wordt Burkina Faso niet afhankelijk van donorlanden of andere externe partijen en kan het zelfvoorzienend zijn. Daarnaast wordt er op deze manier ook lokaal werk gecreëerd. De vraag is ook of een arm land als Burkina Faso de middelen kan vrijmaken om een dergelijk product gratis aan zwangere vrouwen te kunnen uitdelen. Families in ruraal Burkina Faso zullen dergelijke supplementen niet als prioriteit zien en hier dan ook geen eigen middelen voor vrijmaken. Daarnaast werd tijdens de studie de dagelijkse inname gesuperviseerd. Bij een grootschalige implementatie zal deze dagelijks inname omwille van praktische redenen niet gesuperviseerd kunnen worden en kan men de vraag stellen hoe hoog de compliance rate zal zijn.
Een andere grote vraag die men zich kan stellen, is wat de meerwaarde is van dergelijke producten op lange termijn en of dit niet kan gezien worden als een quick fix. Dit product kan zeker wel zijn nut hebben voor een korte en acute fase van hongersnood maar malnutritie blijft in het grootste deel van de gevallen wel een chronisch probleem en wordt veroorzaakt door een complex gegeven van socio-economische, geografische en politieke wortels. Een meer duurzame oplossing moet dan ook gezocht worden. Het zou daarnaast ook te duur zijn om een dergelijk product aan iedereen te kunnen blijven aanbieden.
Duurzame oplossingen die in Burkina Faso volgens mij meer zouden kunnen doen aan het probleem van malnutritie zijn; fortificatie van afgewerkte producten voor mensen die in de steden/grotere dorpen leven en voldoende geld hebben om deze te kopen, bio-fortificatie van gewassen/zaden van armere boeren op het platteland en het overtuigen van boeren tot het (meer) inzetten van stable crops in plaats van cash crops. Er zou meer kunnen ingezet worden

rond onderwijs en het aanleren van kinderen wat voedzame voeding juist inhoudt en hoe zij met wat daar al beschikbaar is, toch aan de dagelijkse noden kunnen voldoen. Aangezien gezond eten en dierlijke producten vaak te duur zijn voor de overgrote meerderheid in het land, zou de politiek hierin moeten investeren.
Bovendien werd er voor deze studie meer top-down gewerkt dan omgekeerd waardoor er geen rekening werd gehouden met de eigenlijk prioriteiten van de mensen ter plekke. Men heeft in het verleden al verschillende keren gezien dat deze approach op lange termijn niet werkt. Een voorbeeld hiervan is de strijd om malaria uit te roeien en het uitdelen van muggennetten om dit te bekomen. Zolang mensen voor wie zij bedoeld zijn niet overtuigd zijn dat dit een prioriteit voor hen is, zullen dergelijke goed bedoelde initiatieven nooit tot een duurzame oplossing leiden. Zo wordt Burkina Faso ook de laatste jaren geteisterd door verwoestijning door de klimaatopwarming waardoor er meer mislukte oogsten zijn dan vroeger. Daarnaast blijft de bevolking ook groeien. Het land wordt verder ook op grote schaal ontmijnd op plekken die eerder voor landbouw zouden kunnen dienen en dit door buitenlandse bedrijven (het gaat hier vooral om goud). De lokale mens zien hier ook geen enkele cent van. Maar het grootste probleem waar het land nu mee kampt is een terreurcrisis die veel (politieke) onzekerheid en interne vluchtelingen met zich meebrengt. Dit maakt het natuurlijk allemaal zeer moeilijk te kunnen inzetten op duurzame oplossingen rond voeding.

4. Foliumzuur tijdens de zwangerschap

Foliumzuur (of vitamine B11) is tijdens de zwangerschap noodzakelijk voor de preventie van neurale buisdefecten (*NTDs*) zoals spina bifida en anencefalie. Zwangere vrouwen hebben nood aan extra foliumzuur welke (meestal) niet via de klassieke voeding kan worden geleverd.

Voedingssupplementen

Er is harde evidentie dat inname van foliumzuursupplementen peri-conceptioneel in de juiste dosis en tijdspanne een reductie geeft van het aantal NTDs (17, 18). Om de beste effecten te hebben wordt aangeraden om deze extra hoeveelheden aan foliumzuur pre-conceptioneel te starten aangezien extra foliumzuur vooral tijdens de eerste 4 weken van de zwangerschap van groot belang is. Het grote nadeel van voedingssupplementen is dat zij frequent te laat worden ingenomen (vaak start men pas na de cruciale eerste 4 weken van de zwangerschap), de verantwoordelijkheid rond inname eigenlijk volledig bij de vrouw zelf ligt en de adherence rate hierdoor laag is. Campagnes die ingezet worden om zwangeren hiervan bewust te maken blijken niet duurzaam of effectief te zijn (19).

(Bio-)fortificatie

Er wordt daarom geprobeerd om meer in te zetten op andere technieken zoals de fortificatie van voedsel. Onlangs verscheen er rapport in de Lancet om de fortificatie van staple foods met foliumzuur wereldwijd te gaan verplichten (20). Volgens dit rapport zou dit een zeer hoog kosteneffectieve manier zijn voor de economie van een land en zou men op deze manier het aantal NTDs drastisch kunnen doen dalen (zie *figuur 1* voor enkele concrete voorbeelden) (20).

	Number of people reached (millions)	Expected number of cases of anaemia averted in women of reproductive age	Expected number of NTDs averted	Expected number of deaths under the age of 5 years averted	Expected number of DALYs averted	Expected economic value of DALYs averted (million US$)
India*	553	24 950 107	22 006	20 410	2 198 103	5532
China	1285	28 831 810	14 037	11 681	1 701 396	20 298
Bangladesh	145	3 194 605	4154	3857	369 392	594
Nigeria	109	5 374 530	3731	3519	362 564	2364
Egypt	89	1 896 955	2077	1783	161 352	699
Ethiopia	85	1 695 531	1397	1315	140 088	141
Philippines	81	809 657	1089	954	102 517	537
Angola	9	365 698	816	769	57 522	383
Morocco	32	1 016 226	547	454	66 193	310
Ghana	20	722 468	531	499	54 008	147
Benin	10	503 202	375	354	38 998	64
Indonesia	25	540 840	312	274	35 071	196

Estimates are for mandatory fortification of wheat flour or rice, or both, in selected low-income and middle-income countries in 2019 with a high potential for food fortification.[35] Data are sorted by expected number of NTDs averted. DALYs=disability-adjusted life years. NTDs=neural tube defects (largely comprising spina bifida and anencephaly). *Includes 17 Indian states: Andhra Pradesh, Assam, Bihar, Chhattisgarh, Haryana, Himachal Pradesh, Jharkhand, Karnataka, Kerala, Madhya Pradesh, Maharashtra, Orissa, Punjab, Rajasthan, Tamil Nadu, Uttar Pradesh, and West Bengal.

***Table*: Estimated annual health and economic benefits of implementing mandatory food fortification with folic acid**

Figuur 1

Tot op heden wordt dit in Europa – behalve in Moldavië en Kosovo – nergens toegepast, ook niet bij ons hier in België hoewel de evidentie hier rond zeer duidelijk en veelbelovend is. Volgens het rapport liggen verschillende redenen hier aan de oorzaak; er is schrik rond overdosering en nadelige effecten op de volksgezondheid (hoewel hier geen enkel bewijs voor is), economische beperkingen van landen, trage processen om dergelijke fortificatiesystemen uit te bouwen, het hebben van andere nationale prioriteiten etc (20).

Een andere manier om de foliumzuurtekorten aan te pakken is aan de hand van bio-fortificatie. Bio-fortificatie is de verrijking van gewassen via plantenveredeling of via genetische modificatie (*GMO*) met micronutriënten zoals met foliumzuur. Zo heeft een vakgroep aan de Universiteit van Gent een rijsvariëteit gecreëerd waarvan 1 kop rijst voldoende foliumzuur bevat om aan de noden van zwangere vrouwen te voldoen. Hoewel dit als muziek in de oren klinkt en een oplossing zou kunnen zijn voor de wereldwijde epidemie van micronutriënten deficiënties (waaronder deze van foliumzuur), zijn er nog zeer grote struikelblokken om deze op grote schaal toe te passen. Volgens deze onderzoekers ligt de oorzaak hiervan in de weerstand die er is rond deze techniek van genetische modificatie waardoor deze moeilijk van de grond komt. Dit geldt ook voor onze context hier in België.

Foliumzuur tijdens de zwangerschap in België

Het advies van de Belgische Hoge Gezondheidsraad naar de suppletie van foliumzuur luidt als volgt *“ Zodra vrouwen actief zwanger proberen te worden zouden ze een foliumzuursupplement moeten nemen (400 µg/dag) tot 12 weken na de conceptie. Vrouwen bij wie een neuraalbuisdefect van de foetus werd vastgesteld of die bevallen zijn van een baby met dit type misvorming moeten worden geïnformeerd over het risico op herhaling, over het beschermend effect van foliumzuursuppletie in de periconceptionele periode en ze moeten een hoge dosering (5 mg foliumzuur per dag) krijgen ”* (18, 21).

Een exacte weergave van de epidemiologie van NTDs in België is niet mogelijk (22, 23). In de jaren 1990 en 2010 lag de prevalentie van NTDs vermoedelijk tussen de 8 à 10 per 10000 zwangerschappen en tussen 2 à 4 per 10000 levendgeborenen. De prevalentie van spina bifida bedroeg ongeveer 6 à 8 per 10000 zwanger- schappen en 1 à 4 per 10000 levendgeborenen (24).

In België zijn er tot op heden verrassend weinig (tot geen) studies te vinden die een licht doen schijnen op de situatie van de inname van foliumzuur bij zwangere vrouwen noch rond preventiecampagnes en hun effecten op de inname van de supplementen. Eén rapport van de Hoge Gezondheidsraad gepubliceerd in 2019 toonde dat slechts één derde van de Belgische zwangere vrouwen een foliumzuursupplement inneemt (21). Een andere Vlaamse studie, de *JOnG!-studie* in 2010 toonde dat een groot deel van de moeders (86,4%) foliumzuur had ingenomen tijdens de zwangerschap maar men zag dat slechts 36,3% van de moeders deze supplementen had ingenomen volgens de aanbevelingen van de Hoge Gezondheidsraad. Belangrijke risicofactoren voor zowel een lage prevalentie van supplementgebruik als een niet-correcte inname waren; een lage socio-economische status, een ongeplande zwangerschap en een niet-Belgische moeder. Daarnaast ziet men ook dat het gebruik beter is bij het eerste kind (25). De studie komt ook met een aantal aanbevelingen om de supplementatie meer gericht aan te pakken in de toekomst; naast algemene mediacampagnes die een effect kunnen hebben op korte termijn, ziet men een belangrijke rol van de huisarts om zijn patiënten voldoende te informeren. Dit kan bijvoorbeeld tijdens een preconceptioneel consult (25). Verschillende andere buitenlandse studies hebben hier de effectiviteit reeds van aangetoond (26, 27). Daarnaast wordt er aanbevolen om de kostprijs van een foliumzuursupplement zo laag mogelijk te houden, deze strategie kan helpen bij het willen bereiken van vrouwen uit een lagere socio-economische klasse. Een andere strategie die in Nederland werd gehanteerd was via apothekers; daar werden vrouwen bij elke aankoop van anticonceptiva geïnformeerd en gemotiveerd naar een correcte inname van foliumzuur bij een toekomstige zwangerschapswens aan de hand van een informatieve sticker. De JOnG!-studie benadert ook het belang van informatieve lessen rond contraceptiva en vruchtbaarheid bij adolescenten in middelbare scholen. Voedselverrijking zou volgens de studie ook een optie kunnen zijn hoewel zij ook melden dat de effecten hiervan op lange termijn nog niet gekend zijn. Volgens de studie houdt een efficiënt beleid een combinatie in van de hierboven vermelde voorbeelden.

Kunnen community health workers in België een rol spelen in de foliumzuur supplementatie?

Een rol zou hier ook kunnen worden opgenomen door de CHW. Zij zouden zich kunnen inzetten om risicopopulaties te identificeren, te informeren en te ondersteunen in de correcte inname van foliumzuursupplementen tijdens de zwangerschap. CHW werden door de WHO in de jaren 70 naar voren geschoven als een cruciaal onderdeel van de primaire gezondheidszorg en zij werden sindsdien vooral in lage en middeninkomenslanden (*Engels: low and middle income countries, LMIL*) ingezet. Hun rol werd initieel vooral ingezet in de zorg van moeder en kind en het beheer van infectieziektes daar waar er een grote druk heerste op de gezondheidszorg (28). Het wordt nu ook duidelijk dat CHW niet enkel in LMIL kunnen worden ingezet maar ook in hoge inkomenslanden waar de druk op de primaire gezondheidszorg ook toeneemt en de taken op deze manier beter kunnen worden verdeeld (29). Tot op heden werden vooral studies hierrond opgezet in de Verenigde Staten (30). Een studie van de Universiteit van Gent door Vanden Bossche D. et al naar de ondersteuning van mentale gezondheid bij kwetsbare patienten door CHW tijdens de COVID-epidemie toonde het potentieel van CHW om taken van huisartsen en andere primaire gezondheidswerkers over te nemen en zo de werklast te verdelen. De studie toonde aan dat de interactie tussen de

CHW en de patienten gebaseerd is op een vertrouwensrelatie. Meer onderzoek blijft wel nog nodig om te onderzoeken of de omgevingsfactoren en de determinanten die aan de basis liggen van dit vertrouwen, dezelfde zouden zijn voor bijvoorbeeld preventieve campagnes zoals de foliumzuursupplementatie (31). Rond dit onderwerp werd tot op heden geen onderzoek uitgevoerd in Belgie.

Kritische reflectie rond foliumzuur

Na het lezen van de literatuur rond foliumzuur in België en in het buitenland, lijkt het mij efficiënter om vooral in te zetten op fortificatie en bio-fortificatie om zwangere vrouwen en hun baby's te ondersteunen. Uit de literatuur en ervaring die werd opgebouwd lijkt dit een veilige, kosten-baten en efficiënte keuze te zijn om deficiënties de wereld uit te helpen, ook in België.

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