

Research Proposal: Malnutrition Interventions

Description

Treating Pregnant Women with Moderate Malnutrition in Malawi

Project Investigator

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Geographical Locations

Malawi

United States of America

Project Duration

The proposed duration is three years, beginning in November of 2013 through October of 2016.

Year	1	2	3
RUSF development, IRB approval, site selection and staff training	■		
Participant recruitment and enrollment		■	
Participant follow-up		■	■
Data analysis			■

Executive Summary

Malnutrition during pregnancy is more common in poor women in the developing world due to inadequate dietary intake combined with increased nutrient requirements; high risk pregnancy is more consequential with increased risk of maternal and infant mortality in the developing world (1-5). Also, maternal undernutrition exerts a lifelong effect on fetal, infant and child health and nutrition (6, 7). HIV infection, prevalent in such populations, exacerbates the risk of poor outcomes associated with malnutrition during pregnancy (8-12). Recommendations based on expert advice for the treatment of moderate malnutrition in pregnancy exist at international agencies and in many national nutrition programs, but are rarely implemented. The benefits of treating moderate malnutrition during pregnancy remain largely undocumented. Peanut butter-based foods have remarkably improved recovery rates and outcomes in malnourished children. It seems likely that the tremendous benefits of peanut butter-based supplementary foods could be extended to the vulnerable group of malnourished pregnant women. This study tests the hypothesis that providing a fortified peanut paste-based supplementary food designed to replete the nutrient deficits during pregnancy will result in improved maternal nutritional recovery rates and higher infant birth weights and lengths. This proposal is for a randomized, controlled clinical trial of 3 supplementary foods in 1800 moderately malnourished Malawian women who are pregnant. Moderate malnutrition will be defined by mid-upper arm circumference (MUAC) of less than 23.0 cm among pregnant attendees at antenatal clinics, where up to 20% of the women are HIV infected. The study design will implement all relevant principles of good clinical practice. Subjects will receive one of 3 food rations: 1) a ready-to-use supplementary food formulated to deliver about 200% of the recommended dietary allowance of most micronutrients in pregnancy (RUSF-P), 2) corn soy blend with a multiple micronutrient tablet chosen to deliver about 200% of the recommended dietary allowance of most micronutrients (CSB-P) or 3), the standard of care which is a corn soy blend with supplementary iron and folic acid (CSB), delivering between 0-350% of the recommended dietary allowance. Subjects will receive the supplementary food until they recover from moderate malnutrition. The outcome of the pregnancy and maternal nutritional status will be followed until 3 months after delivery. The primary outcomes will be moderate malnutrition recovery rate, birth weight and birth length. Secondary outcomes include duration and adherence of moderate malnutrition treatment, maternal changes in MUAC, mid upper arm muscle circumference, skin fold thicknesses, change in CD4 count among the HIV infected, infant weight and length, gestational age as measured by fundal height and survival at 3 months of age. Subgroup analyses for HIV+ and HIV- women will be conducted. It is anticipated that such a study will document the benefits of treating moderate malnutrition in pregnancy with a ready-to-use peanut-based food using 21st century evidence-based medicine methodology, so that international agencies and national nutrition programs can

make the most appropriate choices as they strive to improve the lives of the world's most vulnerable people.

Project Description

Goal

The goal of this project is to determine the benefits of treating pregnant women with malnutrition with a peanut butter-based nutritional supplement. Through our clinical trial comparing 3 nutritional supplementation strategies in moderately malnourished pregnant women, we hope to provide significant evidence that with using a peanut paste-based supplementary food, maternal mortality is reduced and infant growth and development is improved in Malawi.

Relevance and Justification

The negative synergy between poor nutritional status and infectious diseases in the developing world is doubly detrimental in pregnancy. It is estimated that 5-20% of African women of child-bearing age have a body mass index $<18.5 \text{ kg/m}^2$ (1), meaning that they often enter pregnancy in a malnourished state. In Malawi, general malnutrition is estimated to affect about 15% of pregnant women while iron deficiency is found in 52-92% of pregnant women (2). Maternal mortality is the third highest in the world and stunting in the newborn is present in 15% of live births in Malawi (13). An informal survey of clinics in ante-natal peri-urban and rural areas in southern Malawi was conducted in May and June, 2012 and we found prevalence rates of malnutrition in pregnant women, as determined by MUAC ≤ 23 cm, to be between 2% and 37%, with higher rates in the rural areas. This survey was conducted in the post-harvest season, when food insecurity was least likely (14).

Poor nutritional status in pregnancy results in increased risk for both mother and fetus. Hemorrhage and hypertension in pregnancy are the leading causes of maternal mortality worldwide (15). Hemorrhage is associated with anemia and iron deficiency anemia while inadequate calcium intake is associated with the development of gestational hypertensive disorders (15). Few countries are on track to achieve the **Millennium Development Goal 5** to reduce maternal mortality; much attention has recently shifted to ways to improve maternal health and nutrition. Malnutrition during pregnancy is likely to have a long standing adverse effect on the fetus/infant, resulting in increased infant mortality, stillbirths and spontaneous abortions (3). Certain maternal characteristics such as anemia, short stature, low pre-pregnant weight or body mass index and low weight gain during pregnancy are associated with increased risk of maternal mortality, fetal loss, and small for gestational age, low birth weight and preterm delivery. Maternal HIV infection further compromises maternal nutrition and health, and exacerbates poor maternal and child outcomes (8-12). It is estimated that about 15-20% of pregnant Malawian women are infected with HIV.

Causes of maternal malnutrition in low income settings include food insecurity and poor diet quality (limited diet diversity), combined with increased nutrient requirements during pregnancy. Food supplements during pregnancy may ameliorate malnutrition in the mother as well as improve infant birth outcomes. There are numerous examples of food supplementation programs targeting malnourished mothers, however there is a lack of evidence concerning the effectiveness of these supplementation programs.

Internationally, there is no agreement on the definition of malnutrition during pregnancy and its treatment. The World Health Organization and the World Food Programme suggest that a MUAC < 22-23 cm is indicative of malnutrition. In the review of outcomes associated with anthropometric measurements during pregnancy, a MUAC of <23 cm was associated with intrauterine growth retardation, so it was selected as a cut-point for moderate malnutrition for this study.

Although food supplementation of pregnant women with moderate malnutrition is the codified standard of care in Malawi, currently food supplementation of malnourished pregnant women is uncommon even at sites supported by the World Food Programme. The World Health organization does recommend that all pregnant women living in areas where iron deficiency is common receive iron and folic acid supplementation. In addition, a new World Health Organization recommendation is that pregnant women living in regions with low calcium intake receive a calcium supplement of 1500-2000 mg/d. National Malawian guidelines for the management of moderate acute malnutrition in pregnancy (2006) recommend a 2kg/ week ration of corn soy blend (CSB) with added oil and sugar be provided biweekly to any adult or child over 2 years with moderate malnutrition with a treatment duration of 2-4 months. This ration provides about 300g/d (936 kcal) for the mother and an additional 60g/d for sharing with the family.

In a meta-analysis of multiple micronutrient supplementations during pregnancy, it was found that supplementation reduced the risk of low birth weight by 17%, small for gestational age by 8% and maternal anemia by 39% compared to supplementation with less than two micronutrients. A review of fortified food and beverages during pregnancy showed that they prevented maternal anemia, improved infant birth weight and length and reduced premature delivery, with beneficial effects most evident in undernourished women. A meta-analysis of multiple micronutrient supplementations during pregnancy and lactation in women with HIV found that supplementation increased maternal weight gain, CD4 cell count, and hemoglobin, reduced HIV viral load and risk of low weight gain. Improvements were found in mean birth weight and reduced rates of low birth weight and small for gestational age.

Most existing RUSF products for pregnant women are designed and tested in pregnant women without malnutrition and without HIV; therefore they do not

provide adequate macro- or micronutrients for recovery from moderate malnutrition. There are no existing products in widespread usage at present designed to meet the needs of pregnant women with moderate malnutrition.

Research Plan

Objective

To determine whether distribution of a supplementary ration designed to meet the nutritional needs of moderately malnourished women in pregnancy, using either a micronutrient fortified ready-to-use supplementary food (RUSF-P) or a corn soy blended flour provided with a multiple micronutrient tablet (CSB-P), will result in improved recovery from malnutrition and better maternal, birth and infant outcomes compared with the standard of care. The control standard of care group will receive CSB with an iron and folic acid supplement.

Role of Each Scientist/Partner

Ken Maleta MD, PhD,

College of Medicine, University of Malawi: provides overall local supervision and management of the project.

Chrissie Thakwalakwa,

College of Medicine, University of Malawi: Is the on-site daily manager and supervisor of the study, supervising the field workers and nurses, assuring supplies are available and data are collected.

Annual Work Plan, Milestones and Timeline

We will conduct a randomized controlled clinical effectiveness trial in pregnant women with moderate malnutrition, with and without HIV-infection examining the effectiveness of three supplementary foods: RUSF-P, CSB-P, and CSB. The study will enroll 1800 pregnant women presenting at any time during their pregnancy with moderate malnutrition as defined by mid-upper arm circumference (MUAC) ≤ 23 cm at one of fourteen antenatal clinics in rural and peri-urban southern Malawi. HIV testing of all pregnant women will be conducted following Malawi national guidelines.

Over the enrollment period, a study team member will attend each participating antenatal clinic site for subject recruitment. All women attending the study antenatal clinic will be informed of the study and entry criteria in a group setting (after the usual morning song and education). After women have their routine weight measured, the study team member will measure the MUAC and screen each woman for study eligibility.

All women meeting eligibility criteria will be offered enrollment in the study and agree via informed consent. Upon enrollment participants will be interviewed; demographic information will be recorded, as well as time of last menses and

estimated date of delivery; anthropometry will include current weight, height, MUAC, and triceps skinfold and weight history if available. Anemia will be assessed (hemoglobin or Hg). If HIV testing results are available the results will be confirmed via medical records and CD4. HIV status will be determined in women not already HIV tested; available medical records will be reviewed.

All women enrolled will return to clinic every two weeks for clinical follow-up to collect their 2 week supply of nutrition treatment. All study women will receive at least two-fold of the recommended daily allowance for iron so that anemia treatment is provided for all women. HIV negative women with hematocrit < 27% or a hemoglobin < 90 g/L, will be referred for standard iron supplementation therapy.

When enrolled women achieve MUAC ≥ 23.5 cm on 2 consecutive visits they will no longer receive supplementary food. Upon recovery from moderate malnutrition treatment, women will be advised to take iron and folic acid tablets for the remainder of pregnancy. Women will be monitored for moderate malnutrition relapse throughout pregnancy, and if relapsed, provided with their previously assigned therapeutic treatment.

Participation in the study, with provision of the supplement until recovery, will continue throughout pregnancy, and follow-up with the mother and infant will continue 3 months postpartum. Participants may be referred for assessment of clinical staging at any time during the study if the standard clinical symptoms questionnaire or interval weight loss indicates HIV progression. Adverse events will be defined as reactions to RUSF, vomiting, diarrhea or rashes suggestive of food allergy. Child birth date, weight and length will be obtained from maternal clinic registry records. Mothers and infants will be followed at the scheduled infant clinic follow-ups at 2 and 4 weeks, and once a month for the next two months, for a total of four infant/mother follow-ups during the first 3 months postpartum. Infant weight, linear growth, and morbidity will be checked and maternal weight, MUAC and morbidity will be assessed at these visits. If mothers and their infants fail to return for follow-up, a home visit will be made to determine the reason for failed visit and to request the mother to return to clinic for follow up in a timely manner. If women fail to gain sufficient weight such that MUAC remains < 23 cm after delivery, they will be referred to a supplementary feeding program.

Schedule of activities for subjects by week of study participation while malnourished

Week:	0	2	4	6	8
Socio-demographic questions, 24-hr dietary recall					
Clinic visit for intervention and control food supply					
Adherence/ educational messages					
Surveillance of clinical events					
Anthropometric measurements					

QOL, HFIAS, diet diversity survey Hemoglobin;CD4 count and viral load, if HIV infected					
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Upon all enrollment and follow-up, the data will be double entered, cleaned and sealed in an electronic database before the randomization code is broken. Descriptive statistics will be used to characterize the population. Women who are HIV+ and HIV- will be analyzed separately, so the data will be reported as if two independent intervention studies were conducted. This is because the effect of supplementary feeding is likely to be quite different in these groups. The Student's t-test will be used to compare numerically continuous outcomes (MUAC, infant weight and length) between dietary groups. The Chi-squared test will be used to compare categorical outcomes between dietary groups (recovery rate, low birth weight and premature delivery). Linear regression models will be run to investigate potential influence of environmental and demographic parameters on maternal and infant outcomes. Independent variables to be considered for inclusion in the models include: maternal age, MUAC at enrolment, average weekly weight gain rate in 2nd and 3rd trimesters, number of previous pregnancies, years of education, marital status, clinic location, HIV status, anemia, illness and number of weeks of intervention as covariates. For longitudinal measures, such as time to recovery, the groups will be compared using repeated measures mixed model analysis of variance. Possible covariates include maternal age, MUAC at enrolment, , average weekly weight gain rate in 2nd and 3rd trimesters, number of previous pregnancies, years of education, marital status, HIV status, anemia, illness and number of weeks of intervention and clinic location.

Timeline of Events

Year 1

- Develop novel RUSF for pregnant women
- Conduct field acceptability trial for novel RUSF amongst women in the community
- Secure local ethical approval through the College of Medicine in Malawi by COMREC
- Secure Washington University Human Research Studies Approval
- Conduct in-depth site selection in Malawi, using population sampling techniques
- Conduct staff training with staff nurses and with local field workers
- Implement site randomization and develop a site visit schedule
- Initiate trial, starting participant recruitment and enrollment

Year 2

- Continue participant recruitment and enrollment
- Conduct all follow-up with mothers at birth and 3 months post-partum

Year 3

- Complete all enrollment and participation including follow-up
- Complete all lab data analysis
- Complete results and data field analysis by conducting all statistical analyses
- Report results

Gender Research Strategy

The entire focus of this project is on improving women's health and well-being during the most vulnerable times in their lives: pregnancy and birth. Girls who are undernourished as children become small women; these same women oft become undernourished during pregnancy and face a slew of complication risks for themselves and for their babies. These mothers tend to have more complications during their pregnancies, and are at a far greater risk for hemorrhage, preterm births and preterm abortion. Children born to these mothers are often underweight and small. It has been surmised that promoting nutrition and providing counseling to pregnant women and new mothers may help to improve not only the mother's pregnancy but also her newborns health. However, little interventional research has been conducted investigating the effects of a supplemental nutrition programs on the outcomes of pregnancy, birth and newborn health. Our research project seeks to identify a nutritional intervention for these mothers to improve their pregnancy experience, birth experience and their newborn's general health. The effect of this kind of study could be life-altering for mothers and for her newborn child, as children who are of a higher weight at birth fair better in their early years of life and it could also have great implications for communities as well. If a mother has a healthy birth, she will be able to return to the community to continue to farm, or provide for her family. If more healthy children are born, they will grow into healthy adults.

This clinical research study does not examine the roles of women and men in farming and processing peanuts.

Environmental Considerations

This project is a clinical research study; there will be no direct impacts on the environment.

Outcomes and Impacts

Our research study will document the benefits of treating moderate malnutrition in pregnancy using a modern evidence-based clinical research methodology, so that international agencies and national nutrition programs can make the most appropriate choices as they strive to reach the Millennium Development Goals of improving maternal health and reducing infant mortality.

Study milestones, by which progress can be monitored

1. Approval of protocol by University of Malawi and Washington University
2. Local production of peanut-based study food
3. Enrollment of 1st subject
4. Enrollment of 900th subject
5. Enrollment 1800th subject
6. Data cleaned and unlocked
7. Data analyses complete

Measureable indicators we have chosen include within the study:

- Changes in mid-upper arm circumference (MUAC) in women diagnosed with moderate malnutrition, a MUAC of less than 23 cm and recovery will be defined as a MAM and a MUAC above 23 cm will be healthy. MUAC will be measured bi-weekly by trained staff until recovery is reached.
- Changes in CD4 counts in women identified as HIV+
- Gestational age at birth of the newborn child
- Child weight and height at birth, two weeks, four weeks, two months and 3 months post-partum

Primary Study Outcomes

1. Maternal recovery rate from moderate malnutrition
2. Birth weight and birth length of the newborn and their continued growth to three months

Secondary Study Outcomes

- Duration and adherence to treatment
- Maternal changes in MUAC (mid upper arm muscle circumference,) and skin fold thicknesses
- Infant linear and ponderal growth, gestational age as measured by fundal height and survival at 3 months of age.
- Subgroup analyses will be conducted amongst the HIV+ women compared to HIV-; comparisons will be made using a time-event analyses (Kaplan-Meier), which uses information gathered from each visit made by the pregnant woman.
- Amongst the HIV+ women, changes in CD4 counts will be measured as well

Adverse outcomes could occur at any point during treatment, they include allergic reactions to any of the interventional foods, non-recovery from malnutrition, or a loss of weight or MUAC, relapse into moderate malnutrition after recovery, complications during birth and/or death of the mother or infant.

Results

As has previously described, the benefits of treating women with moderate malnutrition during pregnancy remain largely undocumented. By conducting this large scale study comparing three different intervention foods amongst Malawian pregnant women, we hope to provide significant evidence for using a peanut paste-based supplementary food. We anticipate that with this intervention maternal mortality will be reduced and infant growth and development will be improved. We hope to leverage our results into the development of a large-scale intervention protocol for treating pregnant women with moderate malnutrition to be adopted by local, national and international agencies across the developing world.

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