INTEGRATING STRATEGIES FOR PREVENTION OF PREECLAMPSIA AND ANEMIA IN PREGNANCY INTO PRIMARY HEALTHCARE DELIVERY IN KENYA

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BACKGROUND: Hypertensive disorders in pregnancy are major contributing factors to maternal and perinatal mortality globally. The World Health Organization has issued guidelines on calcium supplementation in pregnancy to prevent these conditions, but there is limited guidance on how to translate the WHO guidelines into public health impact, especially in conjunction with iron-folic acid (IFA) supplementation. The over-arching objective of this dissertation was to investigate key issues that would influence translation into public health impact, through primary care facilities in rural Kenya.

METHODS: With the trials of improved practices (TIPs) approach, we studied acceptability of the guidelines among 38 pregnant women in 6 community groups in western Kenya. We assigned participants to 3 dosage regimens, representing potential trade-offs between bioavailability and acceptability. Participants selected either of two Ca products with different organoleptic properties. They were provided with supplements, counseled on the guidelines, and interviewed 4 times over 6 weeks to assess barriers and facilitators. Building on findings from this formative research, we used a program impact pathway (PIP) model to guide the design and evaluation of integrated Ca and iron-folate supplementation in Kakamega county in western Kenya. We embedded a cluster-randomized trial in the district-wide program, to examine the impact of regimen complexity on adherence and supplement consumption. We provided healthcare workers with job aids, trained them on counseling techniques and supplementation guidelines, and developed behavior change materials (calendars) for pregnant women. We randomly allocated health facilities to prescribe either 1.0 or 1.5 g / d Ca, along with standard IFA. We collected data from 16 health facilities and 990 pregnant women between 16-30 weeks gestational age, through facility spot-checks and client exit interviews, including amount of Ca supplement consumed (mg/d), measured by pill counts assessed at 4wks and 8wks after recruitment.

RESULTS: In the TIPs, all participants were willing and actually tried consuming the supplements. Participants preferred the 'sweet taste' of the chewable product and liked the ability to consume it without water. Difficulties with the complex regimen included afternoon doses when women were likely to forget, and having to wait hours after supper for last dose. Daily tracking of consumption with a calendar, keeping supplements in conspicuous locations and requesting support from relatives were identified as strategies that supported adherence. In the PIP analysis, supplements and job aids were available during 90% of facility spot-check episodes; calendar availability was lower (78%). Most clients (91%) during 1st ANC visits had calendars at exit interviews, and over 80% reported being counseled with counseling guides. Over 98% of clients received Ca and IFA supplements, but only 76% received enough Ca supplements to last until return date. In the intention-to-treat analysis with regimen as fixed effect and healthcare facility and participant identifiers as random effects in a mixed effects model, pregnant women in facilities with 1.5 g/d prescription consumed an average of 388 mg/d (95% CI 341, 434) more supplemental Ca than those in facilities with 1.0 g/d prescription.

CONCLUSIONS: Pregnant women are likely to adopt Ca supplementation, with appropriate programmatic adaptations. Careful attention to product attributes, regimen complexity and strategies for reassuring and reminding women is needed to adapt the WHO guidelines to context. The district-wide implementation illustrates a feasible approach to integrating Ca supplementation with prenatal IFA supplementation in primary healthcare delivery, guided by a comprehensive program model. Policy makers and program planners should pay careful attention to supply chain, healthcare worker dispensing behaviour and appropriateness of regimen for their setting. Recommending a lower and simpler 2-dose regimen led to lower calcium intake in Kenya, and therefore might be less effective than the current WHO recommendations.

BIOGRAPHICAL SKETCH

Moshood Omotayo graduated with the medical degree from the Lagos State University College of Medicine, where he was president of the student body. He earned a Master in Public Health degree, concentrating in Global Health and Infectious Diseases Epidemiology at the Harvard School of Public Health, before completing his PhD at Cornell University. He worked as a house officer at Lagos Island Maternity and Massey Children Hospitals, the busiest maternal and pediatric care centers in Nigeria, before serving as medical officer and practice manager for a family medicine practice in sub-urban Lagos, Nigeria.

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CHAPTER ONE

INTRODUCTION & BACKGROUND

Introduction

The primary challenge in improving global maternal, neonatal and child health is the sustainable and effective delivery of high impact interventions for pregnant women and nursing mothers at scale. Public health programs fail to achieve impact due to two main reasons: a) lack of validity of the program theory; and b) inadequate implementation of core activities in the program model [1].

Ante-natal nutrition in developing countries has had limited programmatic success, [2] and integration of new programs into existing platforms will benefit from comprehensive and detailed theory-based programming and evaluation. Preeclampsia/eclampsia remains a major contributor to maternal and perinatal morbidity and mortality globally[3–5] . Systematic reviews of randomized controlled efficacy trials confirm that Calcium (Ca) supplementation significantly lowers the risk of preeclampsia[6,7]. The World Health Organization (WHO) recommends Ca supplementation in populations with low habitual intake as part of antenatal care (ANC) programs, to prevent preeclampsia [8].Integrating calcium supplementation into existing ante-natal programs will likely benefit from a comprehensive approach to avoid implementation failure, given the challenges faced by existing ante-natal iron supplementation programs. Increased risk of maternal and child morbidity and mortality due to severe anemia, impaired physical and neuropsychological development due to iron deficiency and limitations of iron supplementation programs are well known.

As reproductive health and nutrition programs seek to integrate the WHO guidelines on calcium supplementation for prevention of preeclampsia with existing ante-natal care platforms, further research is warranted to clarify issues related to not only minimum effective dose, timing of initiation, and mode of administration of prenatal supplements but research to also understand barriers and factors that will influence acceptability, adherence, and feasibility of full scale implementation is needed. This dissertation addresses key components of this research gap.

The overall objective of this work is to provide insight into issues that will influence success in large-scale implementation. I examine development, implementation and evaluation of primary healthcare and micronutrient interventions, aimed at primary prevention of preeclampsia and anemia among pregnant women in rural Kenya. Chapter one provides an introduction and background to key issues related to integration of strategies for primary prevention of preeclampsia and anemia into ante-natal care delivery in resource-limited settings. Chapter two reports rationale, design, analysis, results and conclusion of a trials of improved practices study, examining socio-cultural factors influencing adoption and acceptability of calcium and iron supplementation among pregnant women in rural western Kenya. Chapter three examines design, implementation and evaluation of a district-wide program aimed at integrating strategies for primary prevention of preeclampsia and anemia into primary healthcare delivery, guided by the program impact pathway approach. Chapter 4 describes the design, analyses, results and conclusions of a cluster-randomized non-inferiority comparison of the WHO regimen and an alternative regimen, with supplement consumption and adherence as primary outcomes. Taken together, these studies advance knowledge regarding design, implementation and evaluation of policies and programs to integrate primary prevention of preeclampsia and anemia in pregnancy into existing ante-natal care platforms in resource-limited settings in Africa. They also provide a model for the development of programs for integrating primary prevention of preeclampsia into existing ante-natal care platforms.

Background

A. Burden of pregnancy-related hypertension and iron-deficiency in pregnancy

Pregnancy-related hypertension and maternal iron deficiency are major threats to global maternal and neonatal health. Anemia in pregnancy is a leading cause of maternal and neonatal morbidity. Thirty-eight percent of pregnant women, approximately 32million globally, were estimated to have anemia in 2011 [9].Iron deficiency is believed to account for more than half of the burden of maternal anemia [10].Increased risk of maternal and child morbidity and mortality due to severe anemia, and impaired physical and neuropsychological development due to iron deficiency are well documented. Iron-deficiency has been shown to increase risk of adverse pregnancy outcomes, including maternal hemorrhage, preterm labor, low birth weight and mortality. Iron supplementation has long been known to be efficacious in preventing and treating iron-deficiency anemia, and there are policies supporting iron supplementation for pregnant women in several developing countries [10], yet iron deficiency remains a major cause of maternal morbidity and mortality globally [3,11].

Pregnancy-related hypertension is the 2nd leading cause of maternal mortality globally, after hemorrhage [12]. Pre-eclampsia and eclampsia complicate 2-8% of pregnancies, most of which occur in developing countries [13]. The 2010 global burden of diseases analyses attribute 41 DALYs/100,000 women and 47,000 deaths globally to pregnancy-related hypertension. Pre-eclampsia is the most severe form of pregnancy-related hypertension, and it is also an important cause of neonatal mortality [5]. It is a pregnancy-specific multi-systemic disorder characterized by proteinuria and onset of hypertension during pregnancy [14]. Eclampsia is the occurrence of otherwise inexplicable convulsions or coma in a pre-eclamptic patient. The etiology and pathophysiology of pre-eclampsia is believed to be multi-factorial in origin with maternal and fetal determinants, including teenage pregnancy, elderly primigravida, maternal obesity, multiple gestation, diabetes mellitus and family/prior history of pre-eclampsia[14].

Several etiologic theories have attempted to integrate the various pieces of evidence related to the pathological changes associated with this condition, but none of the proposed theories can be said to be directly and conclusively proven [12,15].Of the leading causes of maternal mortality, pre-eclampsia and eclampsia are among the least understood in terms of etiology and pathophysiology. Accordingly, there has been a dearth of interventions to prevent these conditions. Furthermore, the only known cure for preeclampsia is delivery of the placenta [15,16,17] often requiring pre-term delivery, which is the leading single cause of neonatal mortality globally.

B. WHO Guidelines on Calcium Supplementation for Prevention of Preeclampsia

Background

An association between calcium intake and pre-eclampsia risk was first suggested about 35 years ago, following the unexpected observation of low incidence of pre-eclampsia among Mayan Indians in Guatemala [18]. High pre-eclampsia incidence had been associated with resource-limited settings. Despite living in a low-resource setting, the Mayan Indians had low incidence of preeclampsia. This led to the hypothesis that the practice of soaking corn in lime, which was prevalent in this setting, and the consequently high calcium intake, in comparison to other low-resource settings, might explain the low incidence of pre-eclampsia in this population [18,19].

Several observational studies and clinical trials have since investigated the relationship between calcium intake and hypertensive disorders in pregnancy[6] . Recent meta-analyses of randomized controlled trials have confirmed that pregnant women taking at least 1g of calcium supplement daily reduced their risk of pre-eclampsia by approximately half, with largest effects in women with high underlying risk and 'low' habitual consumption levels. Reduction in preterm incidence and the composite measure 'severe maternal morbidity or death' was also reported [6].

Prominent obstetrics professional organizations have issued statements about efficacy of calcium supplementation for prevention of preeclampsia, in populations with 'low' dietary intake and high risk of preeclampsia [15,20]. In April 2011, the WHO reproductive health group, for the first time, recommended calcium supplementation for pregnant women in communities with habitual calcium intake below 900mg daily. The WHO nutrition expert guidance group issued global guidelines in 2013.This was based on evidence from updated meta-analyses which indicated that approximately half of cases in such communities can be prevented with calcium supplementation. It was a strong recommendation and strength of the evidence was judged to be moderate, using the GRADE classification system. The WHO guideline states that, "In populations where calcium intake is low, calcium supplementation as part of antenatal care is recommended for the prevention of preeclampsia among pregnant women, particularly among those at higher risk of hypertension."[8]. There was also a remark urging separation of calcium administration from iron administration by several hours to prevent negative iron-calcium interactions. However there were no guidelines for programmatic implementation of the recommendations [21].

Similar evidence-informed interventions such as iron and folic acid (IFA) supplementation in pregnancy have failed to meet expectations when scaled up, due to product composition, supply chain, and demand-related barriers that hamper implementation under routine delivery conditions. Despite the efficacy of iron supplementation, about 1 billion people are still estimated to suffer from iron deficiency globally. Thus, to realize the benefits of calcium and IFA supplementation, feasible and acceptable protocols for integration into existing antenatal care systems are essential.

Dosage and Targeting

Ideally, a policy of routine supplementation should be preceded by an assessment of dietary calcium adequacy at the population level, enabling the intervention to be targeted to populations with diets low in calcium. However, the threshold of habitual intake, below which calcium supplements become efficacious remains unknown. Furthermore, habitual calcium intake is poorly characterized in many developing countries where low calcium intakes and preeclampsia are most common. Where it has been studied, habitual calcium consumption has usually been found to be lower than the recommended dietary allowance. For example, in a review of dietary intakes of pregnant women in low- and middle-income countries, 35 of 42 studies found average calcium intakes to be < 900 mg/day, and this was consistent in studies from Asia, Africa, or Latin America [22]. It is therefore reasonable to assume that average population consumption is inadequate in most low-income country settings unless local dietary studies indicate otherwise.

The WHO-recommended daily dose of elemental calcium, 1.5 to 2.0 g, is higher than both the estimated average requirement and the recommended dietary allowance (800 mg and 1000 mg, respectively for pregnant women19 years and above) [23]. The recommended dose is based on the range of doses that have been tested in the most relevant and highest quality trials, and at these doses, the WHO guideline group considered the benefits to clearly outweigh the potential harms[8]. This dosage range however could not be interpreted as either the minimal effective dosage or the optimal dosage, as no trials to date have specifically examined dosing strategies. Meta-analyses of lower dose regimens have suggested comparable benefits to the WHO-recommended dosages [6]; however, the primary trials were of lesser relevance and/or poor quality.

Calcium load influences fractional absorption; as the load increases beyond 500mg, the marginal true absorption decreases significantly. Doses of 500 mg or less per administration are recommended [23]. This

implies that the WHO recommendations will involve at least 4 pill-taking events daily. Research on other drugs and supplements has found that adherence decreases as the number of pill-taking events increases [24]. Clinical trials appropriately designed to determine relationship between amount of habitual intake, supplement intake and risk of preeclampsia are needed.

Integrating Ca with IFA

IFA supplementation as part of routine antenatal care has long been recommended to improve maternal and neonatal outcomes, also based on a significant body of evidence [25] . Most health systems moving to adopt the new calcium recommendation already have a policy to provide IFA. Aligning and integrating both interventions could lessen logistic complexities of adding a new intervention. It is essential to evaluate whether biological, epidemiological or behavioral considerations dictate otherwise. Calcium has been reported to interfere with iron absorption in *in vitro,* single meal and short-term studies[26]. However, over longer periods, the clinical effects of the interaction is minimal, as short-term interaction may be overcome by adaptive responses in iron regulatory mechanisms [27]. The recommended WHO calcium regimen calls for at least three daily doses, if kept to 500 mg /dose. Separation of calcium and IFA supplements would necessitate at least four separate administrations per day, increasing complexity with possible negative impact on both calcium and IFA supplement adherence. On balance, the magnitude of the benefit of separating calcium from IFA is unknown, but can plausibly be outweighed by the impact of dosing complexity on adherence.

Timing of supplementation

The WHO recommends that calcium supplementation be initiated at 20 weeks gestational age, based on the reference timing utilized in the meta-analyses on which the guidelines are based. This does not necessarily represent a clinically-optimal time point, because the studies reviewed did not explore the effects of differential timing on outcomes [28].

Pragmatically, initiation of supplementation at the first ANC visit would allow synchrony of calcium and iron supplementation, as iron supplementation is recommended to begin as soon as possible in pregnancy. Implementation of the calcium supplementation recommendations is likely to be delivered through focused antenatal care (FANC) platforms in several settings. The second FANC visit typically occurs later than 24 weeks of gestation, even when attendance is regular and on schedule. Whether Ca supplementation to reduce the risk of preeclampsia is delivered through FANC or by lay health workers [29], starting both supplements at first contact with the health system, even when earlier than 20 weeks gestational age, would reduce complexity, confusion and possible delays that might arise with two different supplementation protocols. Also, women present for initial ANC services very late in pregnancy in several settings, beyond the 20th week of gestation. This should not preclude provision of calcium supplements, along with iron supplements. The mechanism of action of calcium supplementation is postulated to involve modulation of both placental vascularization and systemic vasomotor activity. Although these postulations are yet to be directly tested, this suggests that peri-conceptional calcium supplementation might be more beneficial and initiation of supplementation beyond 20 weeks of gestation, when inevitable, will still be useful. There are on-going studies examining the clinical impact of initiating supplementation in the peri-conceptional period [30].

Side-effects of calcium supplementation

Calcium supplementation increased the risk of HELLP (Hemolysis, Elevated liver enzymes and Low Platelet count) syndrome in two studies[6,8]. HELLP syndrome is a rare, life-threatening obstetric complication, however, extremely few number of cases were reported in these studies. Calcium supplementation was also associated with post-natal bone resorption in Gambian women, persisting through subsequent lactation [31], but it is difficult to draw definitive conclusions from this finding, because it was contrary to the hypothesis, and the result of a secondary analysis. The implication of this finding for bone health later in life remains unknown. It is also not known whether either of these side-effects is dose-dependent, therefore dosage recommendations cannot be based on these effects. Calcium supplementation has been reported to increase risk of myocardial infarction[32]. The validity of this finding is still questionable as it is based on a set of studies that failed to account for multiple testing. There is a need for more rigorous investigation of side-effects and Initial programs should put in place detailed surveillance measures for potential side-effects. It is also useful to continue to investigate factors that will potentially influence side effects, including timing, dosage, salt type and co-administration with other supplements. Balancing the magnitude and severity of known risk with the benefit of supplementation, however, consideration of these side-effects should not impede initiation of policies and programs to implement the guidelines.

Supplement formulation

Several calcium salt formulations that are useful for supplementation are currently available in the market, in a variety of doses. Both calcium citrate and carbonate are highly bioavailable sources, compared to calcium gluconate. Calcium carbonate is cheaper, but may be less readily absorbed when taken between meals [33–35]. Calcium citrate bioavailability is not affected by meals, but this has to be weighed against its higher cost and content of almost 50 % less calcium by weight [33,34]; more or larger pills would be needed to deliver doses comparable to calcium carbonate, potentially reducing acceptability and adherence. Balancing all of these considerations, calcium carbonate is likely to be the most cost-effective choice in most settings.

Food-based approaches

Besides supplementation, food-based approaches and nutritional education are potentially more sustainable and acceptable approaches to increasing calcium intake among pregnant women. However, guidelines for the development of evidence-informed policy and program recommendations on food-based approaches to delivering calcium for prevention of preeclampsia are yet to be developed. Feasibility of meeting requirements through dietary counseling alone might be remote, given limited access to calcium-rich foods in many resource-limited settings. Effectiveness of combining dietary counseling with other food based approaches and supplementation in public health programs need to be investigated.

C. Calcium intake and metabolism in pregnant women

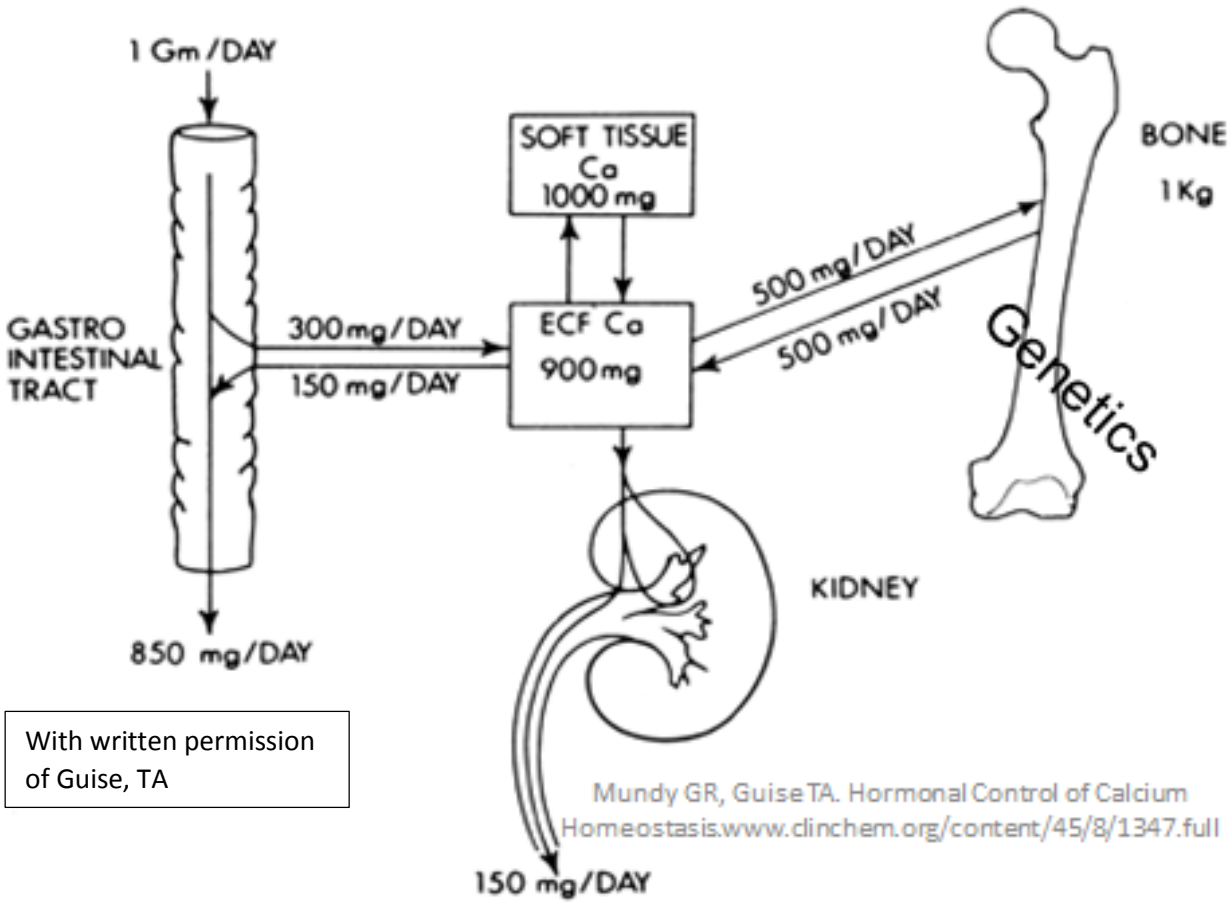
Cellular and physiological functions of calcium include intracellular signaling, nerve transmission, maintenance of skeletal integrity, muscle contraction and vasomotor regulation [23]. Pre-pregnancy calcium metabolism and homeostasis depend on four key processes: absorption from the gut, urinary losses, endogenous fecal loss and mobilization from skeletal stores. The daily quantity of endogenous fecal loss which is mainly due to losses in intestinal secretions and epithelial sloughing, has been shown to be relatively constant[36]. The other processes are primarily regulated through the activity of three hormones; parathyroid hormone (PTH), calcitriol and calcitonin [37]. PTH increases serum ionized calcium levels by increasing mobilization of calcium phosphate from skeletal stores, reducing urinary calcium excretion and elevating intestinal calcium absorption through increased activation of calcitriol. Calcitonin on the other hand reduces calcium mobilization from the bones and increases urinary excretion [37,38] .Physiological changes in these processes, which are thought to be mediated by hormonal alterations, occur during pregnancy.

Pregnancy is a state of high calcium demand with about 30g of calcium transferred for fetal development during gestation, 80% of which occurs in the third trimester [37]. Circulatory volume expansion and increased urinary excretion of calcium in pregnancy also contributes to this heightened demand. Some studies have examined the dynamic relationship between this heightened demand, maternal nutrient intake, skeletal changes, changes in calcitropic hormones and fetal outcomes. However, results have been conflicting and characterization of these relationships remain controversial. The increased calcium requirement is partly met by doubling of intestinal absorption during pregnancy. Higher calcium intake reduced loss in bone mineral in pregnant adolescents, indicating complementary role of bone mineral mobilization to meet extra demand [39]. Maternal calcium metabolic stress, indicated by elevated PTH levels during pregnancy, have been reported in different populations in Asia,

Africa and the United States, and this has been associated with delivery of babies small for gestational age in a study [40,41]. Calcitonin elevation has been reported in several studies, presumably protecting the maternal skeleton from excessive demineralization in the face of heightened physiological demand [38]. Other hormonal changes affect calcium homeostasis in pregnancy, but their specific effects are less striking. The relationship among these factors is known to be modified by maternal age and genetic factors, but the influence of these factors is yet to be well characterized.

Calcium is the most abundant nutrient in the human body with about 99% of body calcium stored in the bones. Dairy products, bony fish and leafy vegetables are the richest dietary sources of calcium. Calcium supplements and medicines such as antacids can contribute significantly to calcium intake. The U.S recommended dietary allowance for pregnant and lactating women, which is based on skeletal outcomes, is 1000mg for 19-50 year old women (UL=2500mg) and 1,300mg (UL=3000mg) for 8-18 year old females [23]. Habitual calcium intake varies widely locally and globally. It has been found to be lower than 300mg/day in some African communities and higher than 1,200mg/day in few European countries [22].

Fig 1. Normal Calcium Homeostasis



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Mundy GR, Guise TA. Hormonal Control of Calcium Homeostasis.www.clinchem.org/content/45/8/1347.full

D. Frameworks, theories and conceptual models

Frameworks are important tools for specifying the range of important variables to be considered in studying biological and social phenomena. Various frameworks can be developed for studying a particular phenomenon depending on the perspective of the researcher. However, frameworks are not directly tested in empirical research because they do not specify explicit relationships and direction of influence among specifically defined variables [42].

Theory has been defined as a set of inter-related concepts, definitions and propositions that present a systematic view of phenomena by specifying relations among variables with the purpose of explaining and predicting phenomena [43]. Theories are different from frameworks because development of a theory involves the extra step of specifying relationships among variables for the purpose of explanation or prediction. Even though a precise theoretical base has been emphasized as being important for rigorous empirical research, existing theories may not be adequate for a particular empirical research project in a specific context. Integration and adaptation of a set of theories might be needed for an adequate conceptual model.

Many have emphasized the importance of well-formulated conceptual models to the rigor of intervention research [43,44]. Besides situating a particular project within the relevant body of literature, it guides selection of appropriate variables, important relationships to be tested, and interpretation of empirical findings in a way that can be useful for coherent development and improvement of interventions. Different epistemological world views prescribe different approaches to testing theories and conceptual models ranging from logical positivism to constructivism and critical realism, among others [43,44]. Several frameworks, theories and models have been developed and synthesized for studying delivery of health interventions and use of health technologies by end-users [45,46].

E. Theories of health behavior and design of implementation research

Two groups of theories have been mostly used to explain and predict adoption and adherence to health practices and technologies by individuals: 1) Stimulant-response (SR) theories and 2) Value-Expectancy theories. The stimulant response theorists, led by Skinner, posit that behavior is determined by events that affect the '*physiological drives activating behavior'*. These events, which could be deterrents or reinforcements, are termed operants. These theories do not attach much importance to mental states and processes in explaining behavior [44]. On the other hand, value expectancy theories hold that the '*subjective assessment of outcome'* due to a behavior is the key determinant of adoption and adherence to the behavior. Most widely-utilized models in this field include some elements of both groups of theories in their formulation, but tend more closely towards value-expectancy theories.

Rosenstock's health belief model (HBM) is one of the most widely used in the field. The model explains adoption of particular health behaviors in terms of the expectations of the outcomes. The proponents of this model state that the key driver of the decision to adopt a behavior is the subjective assessment of the likelihood of avoidance of a negative outcome, by adoption of the behavior. The individual's perceptions of susceptibility to a negative outcome, severity of the outcome, efficacy of a particular behavior or technology in preventing the outcome and the individual's confidence in her ability to take action are key constructs in this model. These key constructs and the availability of cues to 'activate' the readiness to act, explain the adoption and adherence to a practice or technology according to this model [47]. In the context of this project, the health belief model predicts that a pregnant woman's supplementation behavior will be influenced by her perceptions of personal risk of hypertension, severity of hypertension and its effects, efficacy of calcium in preventing hypertension and her self-efficacy in initiating and adhering to calcium supplementation as prescribed. Environmental cues that can 'activate' the motivation for calcium administration will also improve adherence according to the

HBM. Thus, the HBM emphasizes instrumental calculations towards achieving a particular benefit i.e. avoidance of a negative health outcome, as the primary driver of behavior, in addition to self-efficacy and activation cues.

Ajzen and Fishbein's theory of planned behavior has also been influential in this sphere of research. In its current form, the theory of planned behavior (TPB) posits that initiation and adherence to a behavior can be predicted by the intention to adopt the behavior and perceived control over performance of the behavior. The intention to adopt a behavior is influenced by the nature and strength of attitude and subjective norms relating to the behavior [48]. It is important to distinguish between attitude and subjective norms towards the behavior itself rather than the object or condition towards which the behavior is directed [44]. For instance, in the context of delivering micronutrient interventions, the theory of planned behavior will predict that the key determinant of intention to initiate and adhere to calcium supplementation recommendations, will be the nature and strength of a pregnant woman's attitude (arising from her perceptions of the purpose, acceptability and appropriateness) and subjective norms (arising from her perception of the attitude of the people she cares about) towards calcium supplementation rather than towards pregnancy-related hypertension. Likewise, it will predict that healthcare workers' attitude and subjective norms about calcium supplementation will be the most important determinants of implementation intention. This intention, in addition to the perceived control over carrying out the recommendation is deemed to predict implementation behavior. It is worthy of note that while subjective attitude to a health behavior might be influenced by instrumental calculations, nature and strength of subjective norms is determined by social influences rather than instrumental calculations.

The consensus framework for the implementation of evidence-based practices was used to determine the range of variables to be included in the conceptual models in this dissertation because of its

relevance and comprehensiveness. It was synthesized as a meta-framework covering the broad literature on health psychology and implementation research by leading researchers in the field, precisely for the purpose of informing and testing theory-based interventions [45]. Being a meta-framework however, it does not specify relationships among particular variables. Therefore, two health behavior theories have been integrated with the meta-framework for more specificity. The focus of this work is not to test any of the aforementioned theories in particular, but to utilize key constructs and ideas from these theories and meta-framework to synthesize conceptual models for integrating interventions for primary prevention of preeclampsia and anemia into primary healthcare delivery in resource-limited settings. In essence, we applied the set of variables suggested by these frameworks to specify the factors to be examined and variables to be measured in our conceptual model and refined the model with our empirical findings. Such a model is useful for comprehensive organization of relevant variables. It is also useful in guiding prediction and testing of relationships among individual factors that might influence implementation.

In the following chapters, I empirically examine the development, implementation and evaluation of relevant primary healthcare and micronutrient interventions. Chapter 2 reports rationale, design, analysis, result and conclusion of a trials of improved practices study, examining socio-cultural factors influencing adoption and acceptability of calcium and iron supplementation among pregnant women in rural western Kenya. Chapter three examines design, implementation and evaluation of a district-wide program aimed at integrating strategies for primary prevention of preeclampsia and anemia into primary healthcare delivery, guided by the program impact pathway approach. Chapter 4 describes the design, analyses, results and conclusions of a cluster-randomized non-inferiority comparison of the WHO regimen and an alternative regimen, with supplement consumption and adherence as primary outcomes. Taken together, these studies provide empirical evidence regarding design, feasibility and evaluation of policies and programs to integrate primary prevention of preeclampsia and anemia in pregnancy into existing ante-natal care platforms in resource-limited settings in Africa. They also provide a model for the development of programs for integrating primary prevention of preeclampsia into existing ante-natal care platforms.

CHAPTER TWO

IS THE WHO GUIDELINE ON CALCIUM SUPPLEMENTATION FOR PREVENTION OF PREECLAMPSIA ACCEPTABLE? FINDINGS FROM TRIALS OF IMPROVED PRACTICES IN WESTERN KENYA

Abstract

Hypertensive disorders in pregnancy are major contributing factors to maternal and perinatal mortality. The World Health Organization recommends calcium supplementation to prevent these conditions, but acceptability of these recommendations has not been examined. With a mixed methods approach, we studied acceptability of the guidelines among 38 pregnant women in 6 community groups in western Kenya. We assigned participants to 3 dosage regimens representing potential trade-offs between bioavailability and acceptability. Participants selected either of two Ca products with different organoleptic properties. They were provided with supplements, counseled on the guidelines, and interviewed 4 times over 6 weeks to assess barriers and facilitators. We tracked supplement consumption with electronic monitors. We analyzed interview transcripts thematically. All participants were willing and actually tried consuming the supplements. Participants preferred the 'sweet taste' of the chewable product and liked the ability to consume it without water. Difficulties with the complex regimen included afternoon doses when women were likely to forget, and having to wait hours after supper for last dose. Use of a calendar with illustrations, keeping supplements in conspicuous locations and requesting support from relatives were identified as strategies that supported adherence. Lack of reassurance from healthcare providers and discouragement from relatives in the face of perceived side-effects were barriers. We conclude that pregnant women are likely to adopt Ca supplementation, with appropriate programmatic adaptations. Careful attention to product attributes, regimen complexity and strategies for reassuring and reminding women is needed to adapt the WHO guidelines to context.

Introduction

Hypertensive disorders in pregnancy, including pre-eclampsia, are major contributing factors to maternal and perinatal mortality [3,4], but can be prevented by calcium (Ca) supplementation in populations with inadequate dietary intake [49]. While the pathogenesis of these disorders has not been fully elucidated [50,51], populations with inadequate dietary Ca intake have been shown to be at greater risk. Systematic reviews of randomized controlled efficacy trials found Ca supplementation significantly prevents preeclampsia, reducing the risk of developing the condition by half [6]. Based on this evidence, the World Health Organization (WHO) issued a strong recommendation, urging introduction of Ca supplementation in populations with low dietary intake of calcium as part of routine antenatal care (ANC) programs, to prevent preeclampsia [49].

The current challenge is to translate the global guidelines into effective national and sub-national policies and programs[21,49]. There is little empirical evidence regarding factors that might influence implementation of the WHO guidelines at different levels of the policy and program impact pathways [28]. Understanding such factors is important to guide optimal policy-making, program design and implementation. Most studies that have examined factors affecting acceptability of micronutrient recommendations have focused on iron-folate supplementation among end-users in low-income settings[52–58] . A study in Bangladesh examined relative acceptability of different delivery vehicles for calcium supplementation among pregnant women [59] and concluded that conventional pills were more acceptable than chewable pills. However, there have been no studies comprehensively examining acceptability of the various features of the WHO guidelines on calcium supplementation, including attributes of delivery vehicle, daily regimen and other barriers and facilitators[28,49] .

The main objective of this study was to comprehensively explore acceptability of calcium supplementation for prevention of preeclampsia among pregnant women in rural communities in

western Kenya. We employed the trials of improved practices approach to elucidate factors that might influence adoption and acceptability. Specifically, we sought to answer four questions; (**i) Are pregnant Kenyan women likely to adopt calcium supplementation? (ii) How do product attributes affect acceptability? (iii) How does supplement regimen affect acceptability and adoption? (iv) What are the challenges, barriers, facilitators and strategies associated with adoption and acceptability of the guidelines among pregnant women?**

Methods

For this study, we adapted the definitions of Proctor and co-authors for adoption and acceptability [60]. Thus, we define acceptability as the perception among pregnant women that calcium supplementation, product attribute or recommended regimen is agreeable or desirable. We define adoption as the intention, initial decision, or action to consume calcium supplements.

Study design

We adapted the trials of improved practices (TIPs) approach to explore adoption and acceptability of the WHO recommendations among pregnant women. TIPS is a flexible adaptation of commercial marketing techniques, developed by the Manoff group[61] . It is a mixed-methods approach assessing the acceptability of recommended health behaviors through in-home trials during which people are asked to try new behaviors and participate in follow up interviews on their experiences and willingness to adopt the behaviors[76].

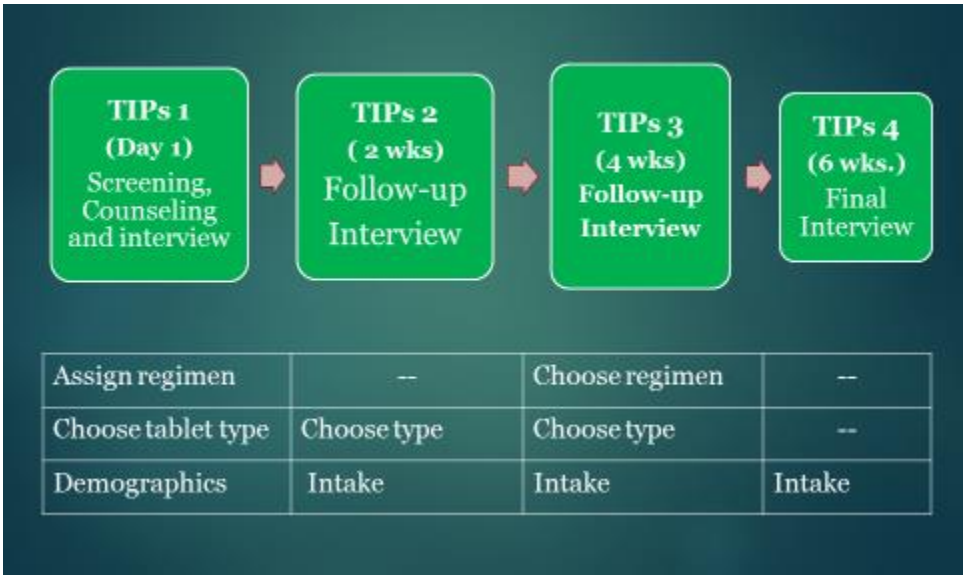
We selected six communities as study sites in Malava sub-county in western Kenya. They were purposively selected to maximize diversity based on rural/urban characteristics, proximity to healthcare facilities and accessibility of the healthcare facility in the community. During community sensitization, a list of all pregnant women in the 6 communities was compiled by the field team through door-to-door visits throughout the selected communities, with information on parity, age and educational status. A sampling scheme designed to maximize diversity based on parity, age, educational status and daily time spent away from home was prepared. Based on the sampling scheme, we purposefully selected 5-7 women from each of the communities (38 women altogether) to participate in the study. Inclusion criteria were (i) age above 15 years (ii) gestational age from 16-30weeks (iii) not having plans to relocate from the community within the next 6 weeks and (iv) inadequate daily calcium intake according to a

screening tool based on self-reported habitual consumption of common calcium-containing foods in the region and medication.

We used two calcium products with different organoleptic properties in the study: hard tablets and chewable tablets. We used the same type of iron supplements across the board. The hard Ca supplement was Ostocal Calcium and Vitamin D3 manufactured by Eskayef Bangladesh Limited. It contained 500 mg elemental Ca (as calcium carbonate) + 200IU Vit D3 in each film-coated tablet. The tablet was white, tasteless and cylindrical in shape. The chewable Ca supplement was Ideos Chewable Tablets manufactured by Helsinn Birex Therapeutics Ltd. It contained 500mg elemental Ca (as calcium carbonate) + 400IU Vit D in each tablet. The tablet was sweet, greyish white, and cuboidal. All supplements were purchased through Madawa Pharmaceuticals, Nairobi, Kenya.

We assigned the participants to three different regimens. The regimens, based on potential trade-off between bioavailability and feasibility, were (i) 4 pill-taking events, 1.5g elemental Ca (3x500mg) plus IFA taken separately, as per WHO guidelines; (ii) 3 pill-taking events, 1.5g elemental Ca (3x500mg) and IFA taken with last Ca dose; and (iii) 2 pill-taking events, 1.0g elemental Ca (2x500mg) and IFA taken with last Ca dose. Combining Ca and IFA, given the lack of evidence of significant clinical effects of interaction, was considered reasonable to reduce regimen complexity and potentially improve feasibility [28].

Fig 1. Design of household trials of calcium supplements in Kenya



We aimed to interview each respondent 4 times (T1-T4) at 2-week intervals over 6 weeks to assess barriers and motivators over time. The interviews were conducted in study participants' households by research assistants. At T1 visit, the essence of the study was explained, the respondent was screened for eligibility and written consent was sought. All selected respondents granted consent. After consent was granted, the respondent was counseled about the guidelines, including the assigned regimen. The respondent was also asked about willingness to try the recommendations, requested to choose a supplement product type after close examination of both types and provided with Ca and IFA supplements. She was then counseled on how to use the medication event monitoring systems (MEMS Aprex Corp., Fremont, Calif.). MEMS consist of pill bottles in which the calcium supplements were kept, and covers containing microprocessor monitors that recorded when the covers were opened.

At T2 visit, the participant was asked whether she had tried the recommendations and if she was willing to continue. She was asked about the facilitators, barriers and strategies that affected her experience as well as her experience with the regimen and product choice. She was then given the opportunity to change the choice of product. The T3 interview was similar to the T2 interview. In addition, however,

the respondent was given the opportunity to change the assigned regimen at T3. The T4 interview, which is the last contact with the study participant, repeated data collected at T2 and T3. If a respondent was unavailable on the scheduled interview date, the interview was re-scheduled for the earliest possible date after the initially scheduled date. The interviews were mostly conducted in Kiswahili and audio records were made. The records were later transcribed and translated to English. The MEMS electronic data were downloaded from the monitors over time by the study coordinator after interviews.

Data analysis

We analyzed interview transcripts thematically, using Atlas.ti qualitative analysis software [62]. One participant's transcripts from T1-T4 were independently coded by 2 coders to generate a preliminary code list and code book. A matrix for facilitators, challenges and barriers to supplement consumption was developed [63]. The code book was revised throughout the coding process, and emergent codes were discussed and added to the book. The coders then coded three participant transcripts from all four TIPs visits, merged the coded transcripts, compared codes and resolved discrepancies by discussion. Throughout the coding, common themes and key quotes were noted and similarities and differences across participants and between themes were constantly explored [64]. We ran queries and extracted illustrative quotes relevant to the research questions. Member checking was done by presenting the themes and quotes to a healthcare provider and research assistants from the community for review and discussion[64,65].

Quantitative data from the interviews were doubly-entered into REDCap database software[66] . MEMS data were exported from the Power view software. The datasets were cleaned in Microsoft excel 2013 and all subsequent analyses carried out in Stata 14 [67]. There were no MEMS data for 3 women that had relocated from their communities before the 1st follow-up interview or discarded the monitor after delivery.

Results

The 38 study participants contributed a total of 1,161 person-days of study participation. Participants in the study sample were mostly married women living in their matrimonial homes in rural communities and a sub-urban settlement. They were 16-37 y old, with an average age of 24 y. Parity ranged from 0-8 with an average of 3. The average gestational age was 5 mo and the participants spent an average of 5 h away from home during the day. Most respondents had completed elementary but not secondary education and had not received any antenatal care from a health facility for the index Pregnancy.

Table 1. Participant Characteristics in household trials of calcium supplementation in Kenya

Participant characteristics	
Variables	**Frequency[1]**
<=19yr old	7(18.4%)
First pregnancy	7(18.4%)
Did not complete primary education	14(36.8%)
Average time spent away from home daily> 6hrs	13(34.2%)
Attending ANC	15(39.5%)

1) Are pregnant Kenyan women willing to adopt calcium supplementation?

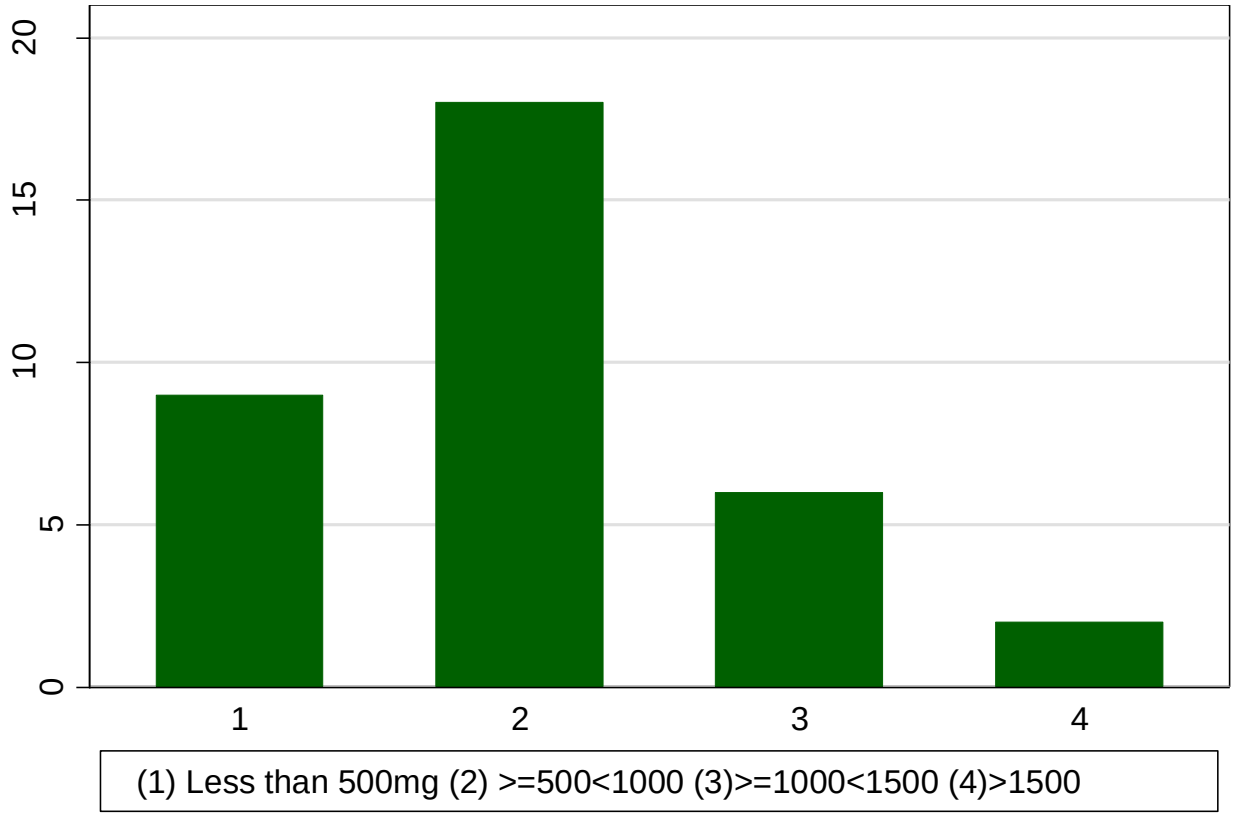
All 38 study participants accepted to try the supplements at the beginning of the study. Only 3 participants subsequently declined to continue taking the supplements at later stages. Two of them declined to continue at the end of the 1st phase (period between T1 and T2 interviews), with one participant attributing her decision to lack of monetary incentives from the field team while the other cited fear of side effects and pressure from her mother-in-law. One other participant declined to continue at the end of the 2nd phase (period between T2 and T3interviews), citing advice from her relatives and fear of side-effects.

[1] Number of participants with a particular characteristic, out of all 38 participants

In addition, 10 women dropped out of the study before T4, due to delivery and relocation but not reasons related to the recommendations. Of these 10 women, 3 dropped out in phase 1, 4 in phase 2 and 3 in phase 3 (period between T3 and final interviews), of the study.

Electronic and self-reported data show that all participants actually tried the supplements. We multiplied the total number of MEMS entries for each participant by 500 mg and divided by the number of days that the participant contributed to the study to calculate average daily consumption. We excluded interview days because of the likelihood of extraneous bottle openings. The lowest average daily supplement consumption for a participant was 77mg / d while the highest was 1577mg / d.

Fig 2. Range of Daily Ca Supplement Consumption Values among Pregnant Women in Kenya[2]



[2] Number of women whose average daily Ca consumption as calculated from MEMS data fell within indicated ranges (X-axis)

2) How do product attributes influence adoption and acceptability of calcium supplements?

Respondents were offered two products with different organoleptic properties at the beginning of the study. Three quarters (74%) of respondents chose the chewable product type after examining (observing, smelling, tasting) the organoleptic properties of both product types. Most (92%) of those that chose the chewable type never switched to the hard type, compared to half of those that initially chose the hard type.

The supplement types differed with respect to more than one attribute. The qualitative data provide insight into which characteristics likely influenced participants' choices. Those who chose the chewable type alluded to its sweet taste and the ability to consume it without water as the reasons for their decision. Participants expressed the view that not bothering about looking for water (for example, when working on the farm) was convenient, and swallowing with water is associated with nausea. Among participants that indicated preference for the hard product type, conventionality, lack of smell and relatively small size were cited as reasons. Women that changed to the hard product type mostly did so out of curiosity. These quotes illustrate the reasons why participants chose particular product types.

28 year old, multiparous respondent who chose chewable in previous phases and was offered the opportunity to change to the hard type

"Those to be taken with water (hard type) are bitter…they have bitterness… I fear taking them…. many times if I take medicine with water I feel like vomiting"

18 year old, primigravida who chose chewable in previous phases and was offered the opportunity to change to the hard type

"I don't think I should change to that one that is taken with water…… it isn't as sweet as the one for chewing…. the first one (chewable) is easy to remember to take….. I will just take it and eat it but for the second one I will have to search for water first before taking it"

However, a few individuals expressed dissatisfaction with the "smell" and relative large size of the chewable type as illustrated by the quote below.

16 year old, primigravida who initially chose the hard type and declined the opportunity to change to the chewable type

"… that (chewable) one, I am not able to take it……it gives me a bad smell…., it (chewable) cannot pass here (points to throat) because it is big……I like this (hard type) just because I can take it with water."

Taken together, the quantitative and qualitative findings demonstrate that product attributes influenced acceptability of calcium supplements by study participants.

3) What factors influence adoption and acceptability of supplement regimen?

Initially, regimen was randomly allocated, but respondents were allowed to choose a new regimen or choose to continue with the assigned regimen at beginning of phase 3 (in contrast to product types that were chosen by participants throughout the study). Among the 27[3] respondents still in the study at T3, fewer people among those assigned to the 2-dose regimen (30%, n=10) chose to change their assigned regimen compared to those assigned to 3-dose (55.5%, n=9) or 4-dose regimens (62.5%, n=8). This suggests that the 2-dose regimen was more acceptable than the alternatives.

The qualitative data explores reasons for participants' preference of the 2-dose regimen. Difficulties with the complex and simplified regimen included afternoon doses when women were likely to forget or be away from home, as illustrated by the following quote from a 28-year-old, married respondent without formal employment who spends an average of two hours away from home during the day. She had been assigned the 3-dose regimen, but chose the 2-dose regimen when offered the opportunity.

[3] 38 participants started the study. Three women had declined to continue and 7 women had dropped out due to relocation and delivery in the 2 earlier phases. 3 women dropped out in the last phase but 2 among them provided information at T3 before dropping out of the study.

"…. I decided to change because I have discovered that often times I forget to take my pill, either because I am busy or I am away from home and did not carry the tablets with me because I forgot….but it is easy to remember in the morning….it is also easy to remember in the evening because I will just be here at home"

Having to wait after supper for the last dose in the 4-dose regimen was an additional burden that limited acceptability. The 2-dose regimen was acceptable because it eliminated both of these concerns. This is illustrated by this quote from a 21-year-old married multiparous respondent, who reported spending an average of 5 hours away from home during the day; she had been assigned to the 4-dose regimen at T1, but opted for the 2-dose regimen at T3.

> "I will try the morning and the evening one (2-dose regimen)…because during the day, it is normally hard for me…this (low regimen) will give me a little relief…I mean there is an interval between morning and evening…I see this one as a bit of relief…because I will take just one in the morning….then in the evening take iron and calcium together……(if) I take calcium and then wait for two hours before taking iron (in the evening), I would easily forget….but this one, I won't forget"

4) What are the challenges, barriers, facilitators and strategies associated with adoption and acceptability of the guidelines among pregnant women?

In our analyses, themes related to hindrance or enhancement of adoption and acceptability of supplement consumption emerged. Where a hindering factor was reported to actually lead to stopping calcium consumption, it was coded as a barrier but where the hindering factor did not lead to stoppage of supplement consumption, it was coded as a challenge. We also differentiated between enhancement factors that increased the desire to consume the supplements and factors or strategies that enhanced capacity of the respondents to actualize such desire, which were coded as motivators and facilitators

respectively. We noted factors that were reported in anticipation and those that were experienced. Also some factors seem to have resulted from the study design.

Tab 2. Factors and strategies influencing adoption, acceptability and adherence to antenatal Calcium supplements among 38 Kenyan women in a household trial

Salient themes on barriers, challenges, facilitators and motivators			
	Anticipated	**Experienced**	**Study-design induced**
Challenges	• Forgetting to take pills • Side-effects • Discouragement from relatives	• Forgetting to take the pills, • Side effects (nausea, bloating, burping, stomach ache, diarrhea tiredness, loss of appetite), • Discouragement from relatives and friends, • Pill burden (especially when having additional medication), • Food insecurity, • Undesirable smell and taste of the pills	• Inability to open pill bottle Pill-bottle too large to carry around • Not allowed to put pills in any other container • Suspicion about origin of pills (not delivered through health facilities, a member of the field team is a foreigner)
Barriers	• None	• Discouragement from trusted relatives (mother-in-law and husband) • Lack of reassurance from HCWs in the face of perceived side effects	• Lack of monetary incentive from research team
Motivators	• Perceived benefits (physical and cognitive development of fetus, Less bleeding at delivery, Prevent high blood pressure)	• Relief from health concerns (headache, tiredness, dizziness, swollen legs) • Reduced eating of soil	• Knowledge that the MEMS was monitoring pill-taking activity
Facilitators	• Use of calendars, • Reminder by spouse	• Use of calendars • Reminder by relatives (husbands, children, parents, in-laws) • Placing pills in conspicuous locations (on the table, by the bedside) • Taking pills at specific times of the day (meal times, bedtime, first thing in the morning) • Administering medicine to kids	N/A

The most salient challenge for participants in the study was forgetting to take the pills and not having the pills around at the right time. This was reported both in anticipation and as experienced challenges. This was usually experienced when women were not in their households. Typical quotes from women who spent time away from home:

"….there was no problem except forgetting. I remembered when (I was already) far away that I should have carried it….the difficult thing is that I go out during the day, then I get late, and I had not carried the pills…".

"……I didn't take (the pills), not because I did not have them … but because I forgot… but I had them in the bag… because of the issue of dignitaries visiting the school (I forgot), and by the time I remembered, I found out the time had passed…. "

It is not clear from our data, the extent to which MEMS-related factors including our advice that extra pills should not be taken out of the bottles, the awkwardness of the bottle because of its large size, and difficulty of manipulating the bottle cover affected adherence.

However, women also reported forgetting to take their pills even when they were in the house, particularly when busy. Key strategies that helped to address the challenge of forgetting included the use of a calendar with illustrations, keeping the pill bottle in a conspicuous location, taking the pills at specific times of the day or in relation to specified daily events e.g meal times, reminders from relatives, usually spouses and children. Typical quotes regarding strategies for remembering include:

"…….My husband reminds me….and because I have put it (the pills) near, when I see it, I remember…..he (husband) tells me to take it every time…"

"……..I would remember every time I am eating breakfast then lunchtime, also at supper and after eating when I am going to sleep….calendar was helping me besides food…."

Some participants anticipated that unfavorable perception of the pills by relatives could be a challenge, but this did not stop any participant from accepting to try the supplements. Side-effects including nausea, bloating, burping, stomach ache, diarrhea, tiredness and loss of appetite were also reported, but this generally did not lead to stopping of supplementation. There were several women that encountered these conditions but did not discontinue the pills. Prior counseling to anticipate side-effects and reassurance about its transitory nature is likely to be responsible for their continuation of supplementation despite experiencing side effects. Typical quotes regarding side effects include:

"…… in the beginning when I started I felt headache…..but eventually it came down…….when I am going to sleep I feel the throat is so dry…and I feel like I cannot swallow saliva….that saliva, when I swallow, I feel like vomiting but the throat is dry……no, I did not stop taking the tablets…"

"….. so after the third day I started feeling pain (in the) stomach, then (I was) urinating all the time, then feeling like vomiting all the time. It even forced me to ask another nurse. I told her, this pill what does it do? Or which pill have I taken that makes me feel this way? She told me to continue taking it until it is finished….so I continued…"

Few women that actually discontinued supplementation attributed their decision to discouragement from a relative and lack of reassurance from health workers in addition to perceived side-effects. This was the main barrier identified.

"….. For the past two weeks, I haven't been using any pills … I only used it when you had visited me...then I felt pain … I decided to visit the doctor and explain it to him …… to see how it was …..I haven't yet been given the answers."

The key motivators include anticipated benefit regarding physical and cognitive health of the fetus, prevention of high blood pressure and 'low blood' in the mother and avoiding too much bleeding at delivery. These were consistent with the messages provided in counseling and printed materials given

to the women. Experienced benefits such as reduced eating of soil and relief from poor health conditions including headache, tiredness, dizziness and swollen legs motivated participants to continue supplementation.

Discussion

We examined factors influencing adoption and acceptability of the WHO guidelines on calcium supplementation for prevention of preeclampsia in a rural Kenyan population. The TIPs approach provided a rich set of mixed data to inform a complex set of research questions. To our knowledge, this is the first study to comprehensively assess multiple features of the guidelines, which might influence adoption, acceptability and adherence among pregnant women in an everyday household context.

Acceptability of Recommended Regimen

The recommended regimen in the WHO guideline involves 1.5-2.0g elemental calcium with separate administration of IFA in a total of at least 4 pill-taking events daily [49]. We have shown that the 'standard' regimen (4-dose) in the guidelines is less acceptable compared to alternative regimens. Difficulties with the 'standard' regimen (4-dose) include a) afternoon doses when women are likely to be away from home or forget to take their pills and b) having to wait after meals to take IFA separated from the Ca dose. An alternative (2-dose) regimen with lower daily recommended dose (1g) and fewer (two) recommended pill taking events was more acceptable because it avoided these two difficulties. Another alternative, the 3-dose regimen with equal daily recommended dosage, but without separation of the calcium and IFA doses was also more acceptable, as it avoided the wait for separating iron and calcium in the evening. The optimal amount of calcium supplement consumption for prevention of preeclampsia remains unknown [28]. A meta-analysis of low-dose (<1g) calcium supplementation studies found comparable efficacy to high-dose (>1g) studies, but the primary studies in the low-dose analyses were of poor quality [6]. If ongoing well-conducted randomized controlled trials demonstrate efficacy of low dose calcium supplementation in preventing preeclampsia, that might make the 2-dose option the regimen of choice, given the likelihood of higher acceptability. However, if the studies demonstrate significantly lower efficacy, 3-dose regimen might be most appropriate. It should be noted that this regimen

prescribes concomitant iron and calcium consumption. Calcium supplementation has been shown to inhibit iron absorption, however clinical effects of concomitant consumption have been shown to be minimal over time. Future studies should model the clinical implications of the balance between missed iron and calcium doses due to separation and reduced iron bioavailability due to concurrent consumption.

Product Attributes and Acceptability

Our data indicate that supplement product attributes, including being consumable without water, sweet taste, small size and being odorless are associated with higher acceptability of calcium supplements. This is consistent with prior studies that have shown that organoleptic properties of pills and supplements influence acceptability [68]. We found that the chewable product type was more acceptable than the hard product type. This is in contrast to findings in the Bangladeshi study in which conventional tablets were found to be preferable to chewable tablets [59]. There are multiple possible explanations for this contrast: a) It is possible that the differential properties between our hard and chewable product types do not correspond to the differences between the conventional and chewable tablets in the Bangladesh study; b) It is not clear that the conventional and chewable tablets were recommended in identical regimens in the study in Bangladesh. If regimen was not identical, the effect of regimen could have been confounded with the effect of product type in their study. 3) The difference might be due to socio-cultural differences between Bangladeshi pregnant women and Kenyan pregnant women, including access to water and taste preferences.

It is important to note that although the chewable product type in our study was more acceptable, it was approximately 4 times as expensive as the hard product type according to the Micronutrient Initiative's unpublished cost information. Therefore, it is likely that large-scale programs in developing countries will choose the hard product type for large-scale programming. However, we are unaware of

the drivers of differential cost. If such drivers are unrelated to the attributes related to acceptability, it might be possible to produce product types that balance cost with acceptability.

Barriers, Challenges, Motivators and Facilitators

We identified anticipated benefits to the fetus' health and cognitive development as motivating factors, alongside experienced benefits of increased strength. Less salient but also identified as a motivator was the belief that the supplements could help avoid 'too much bleeding' during pregnancy and 'body swelling' and 'pressure'. Forgetting to take the pills was the most salient challenge reported by participants in the study. Seeing a reminder calendar with illustrated regimen and messages, placing pills in conspicuous places and reminder by relatives were identified as useful strategies for addressing this challenge. This is consistent with prior findings in relation to iron supplements [53]. Gastro-intestinal side-effects were widely reported, but they did not lead to discontinuation of supplement consumption, likely because women had been counseled about side effects. This is also in contrast with the Baxter study that found low incidence of perceived side effects [59]. This might be due to the fact that participants in our study were also consuming iron supplements alongside the calcium supplements. Other studies have reported that pregnant women are likely to continue taking their iron supplements in the face of side-effects, if they have been appropriately counseled [53]. Discouragement from relatives in the presence of side effects constituted a barrier that led to stoppage of supplement consumption in some cases.

Contributions, Strengths and Limitations

This trial of improved practices, for the first time, examined multiple issues related to implementation of the WHO guidelines on calcium supplementation, among pregnant women in everyday life context. Using a mixed methods approach allowed us to apply multiple lines of enquiry to explore our research questions in rich detail, shedding light on questions of key importance to maternal and child health program managers taking steps to integrate primary prevention of preeclampsia into their programs.

Our findings should be interpreted in the context of several weaknesses. The small sample size in this study is a limitation. We did not try to rule out chance as an explanation for the findings in our analyses of regimen and product type preferences. We used qualitative analyses to provide complementary information to understand the trends noted in our quantitative analyses. Secondly, there is potential for measurement error in the study. The MEMS recordings represent electronic monitoring of bottle openings. The assumption that bottle opening represents pill-taking might be erroneous in some cases, potentially resulting in misleading conclusions about adoption. We encouraged study participants to remove one pill from the bottle at a time and only for immediate consumption, in order to minimize misreporting. Analysis of our qualitative data suggest that this instruction was mostly adhered to. Thirdly, pill-taking behavior is a socio-cultural activity and the exact nature in which culture interacts with the features of a recommendation might differ across cultures [68]. Studies with similar designs in other cultures are needed to determine the applicability of our findings across cultures. Finally, decisions about program and policy design are complex. The end-user is just one stake-holder in a complex web of interactions, albeit a really important one. Appropriate design will balance findings from our type of study with several other considerations to make optimal decisions.

Conclusion

In conclusion, we have examined factors affecting adoption and acceptability of calcium supplementation recommendations among pregnant women in a household trial in western Kenya. We find that women are likely to adopt Ca supplementation in pregnancy, with appropriate programmatic adaptations. Chewable tablets that were consumable without water and tasted sweet enhanced acceptability. An alternative regimen with 2 doses of 500mg elemental Ca, without separating calcium from iron consumption was preferred although many women also found a regimen of 3 doses acceptable. A regimen that separated IFA from Ca resulting in 4 pill-taking events per day was less acceptable. Lack of appropriate counseling and reassurance about side-effects, in the face of discouragement from relatives can constitute a barrier to adoption and acceptability. Careful attention to product attributes and cost, regimen complexity and strategies for reassuring and reminding women is needed to adapt the WHO guidelines to context.

Chapter Three

A Program Model for Integrating Calcium and Iron-Folate Supplementation for Prevention of Preeclampsia and Anemia in Pregnancy into Primary Healthcare Delivery

Abstract

Calcium (Ca) supplementation for prevention of preeclampsia can save maternal and newborn lives, but there are no comprehensive program models for its integration into antenatal care (ANC) platforms. We used a program impact pathway (PIP) model to guide the design and evaluation of integrated Ca and iron-folate (IFA) supplementation in western Kenya. We provided healthcare providers with job aids, trained them on counseling techniques and supplementation guidelines, and developed behavior change materials (calendars) for pregnant women to take home. We allocated health facilities to prescribe either 1.0 or 1.5 g / d Ca, along with standard IFA. We collected data from 16 health facilities and 990 pregnant women through facility spot-checks and client exit interviews, including pill counts. We explored the effects of supplementation on percentage of the population meeting Ca dietary reference intakes. Supplements and job aids were available during 90% of facility spot-check episodes; calendar availability was lower (78%). 91% of clients during 1st ANC visits had calendars at exit interviews, and over 80% reported being counseled with counseling guides. Over 98% of clients received Ca and IFA supplements, but only 76% received enough Ca supplements to last until return date. Among clients that still had pills by return date, adherence was 77% and 83% for the IFA and Ca regimen, respectively. When 1.5 g/d of Ca supplements were prescribed, over 75% of participants still met recommended daily allowance (RDA) in the most conservative scenario. Only 54% met the RDA when 1.0 g was prescribed in the same scenario. This program illustrates a feasible approach to integrating Ca supplementation with prenatal IFA supplementation in primary healthcare delivery, guided by a comprehensive program model. Policy makers and program planners should pay careful attention to supply chain, healthcare worker (HCW) dispensing behaviour, and appropriateness of regimen for their setting.

Introduction

A primary challenge in improving global maternal, neonatal, and child health is the sustainable and effective delivery of high impact interventions for pregnant women. Public health programs fail to achieve impact because of two main reasons: 1) lack of validity of the program theory or flawed assumptions linking program inputs and activities to the problem in a particular context; and 2) inadequate implementation of core activities in the program model[69] . Evaluating these potential causes of program failure provides unique insight into how programs achieve outcomes. It enhances validity of program evaluation, shedding light on the relevance of impact effect estimates to different contexts. Moreover, it is important in evaluation design to differentiate these two types of potential failures, because they require different interventions for effective course correction. Analytical approaches useful for guiding these types of evaluations include the logic model, logical framework, results framework, value chain analysis, and program impact pathway (PIP) analysis[70,71]. All are variants of theory-based analytical approaches for program evaluation.

Compared to other theory-based approaches applied at the project level, PIP analysis is particularly suited for evaluating implementation of the core activities in a supplementation program. This is due to its emphasis on detailed tracking of resource transfer activities among the different players in a program. Resources in this case may be material (supplements, food, posters, calendars, etc.) or non-material (knowledge, motivation, self-efficacy, etc.), and they are typically made explicit on a finer scale than other approaches, such as in a logic model. When appropriate theories in the social, behavioral and organizational sciences are employed to specify and investigate potential influences on resource transfer activities in the PIP, it can serve as a useful conceptual tool for design and evaluation of nutrition programs. The PIP has been generally defined as “the explicit representation of the pathways by which the program (activities) achieves its intended outcomes”[70]. For nutrition programs, the PIP has been specifically defined as “the flow from a nutrient’s introduction into a program to its biological

outcome"[71]. We employed the integrated behavior model to identify relevant modifying variables for investigation, during our formative research and specification of potential influences on the program impact pathway[44].

Micronutrient supplementation in developing countries has a strong evidence base but limited programmatic success [2,72] and integration of new supplementation programs into existing platforms might require more comprehensive and detailed theory-based programming and evaluation. Increased risk of maternal and child morbidity and mortality due to severe anemia, and impaired physical and neuropsychological development due to iron deficiency, is well documented. Iron supplementation has long been known to be efficacious in preventing and treating iron-deficiency anemia, and there are policies supporting iron supplementation for pregnant women in several developing countries [10]; yet iron deficiency remains a major cause of maternal morbidity globally [73]. Likewise, preeclampsia/eclampsia remains a major contributor to maternal and perinatal morbidity and mortality globally [3–5]. Systematic reviews of randomized controlled efficacy trials confirm that calcium (Ca) supplementation significantly lowers the risk of preeclampsia [6,7]. The World Health Organization (WHO) recommends Ca supplementation in populations with low habitual intake, as part of antenatal care (ANC) programs to prevent preeclampsia [49] . Because this guideline is recent, delivery of Ca supplements through ANC has hardly been evaluated, yet there are indications of potential implementation failure. For instance, a study in Brazil found that, in a sample with 210 mg / d mean Ca intake and 90% of individuals with inadequate Ca intake, only 5.1% of ANC clients received Ca supplementation prescriptions [74]. Integrating Ca supplementation into existing antenatal programs requires a comprehensive approach to reduce the likelihood of implementation failure, especially given the challenges faced by existing antenatal iron supplementation programs.

Using the PIP approach, we developed and tested a program model to integrate Ca supplementation into ANC delivery at sub-national levels. This approach involves three iterative steps. 1) developing a

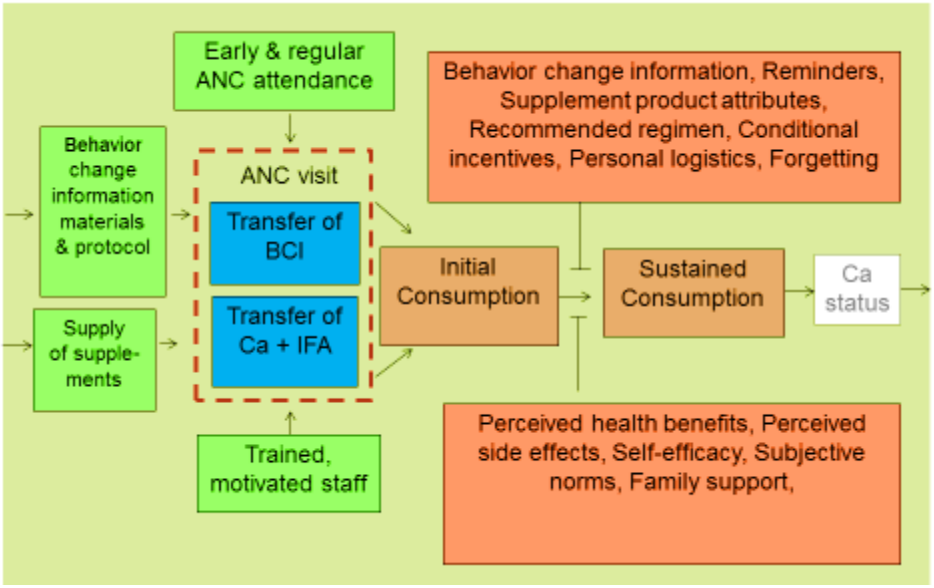
comprehensive schematic representation of flow of resources, activities, and other factors that can influence program impact (the PIP model), based on existing scientific and contextual knowledge; 2) grounding the PIP model in a particular context through formative research to develop specific programs; and, 3) empirically testing validity of key theories and assumptions as well as adequacy of implementation of core activities and flow of resources in the program, using the PIP model as a guide for data collection and analysis.

Our primary objectives in this paper are i) to describe the development of a comprehensive program model for the integration of Ca supplementation into ANC platforms using the PIP approach and ii) to determine whether Ca supplementation can be feasibly integrated with antenatal IFA supplementation in primary ANC . Most of the biological and behavioral theories linking inputs to expected impact in this program model have empirical support in the clinical and behavioral sciences literature. We collected data to test the validity of these theories and our assumptions about the transfer of non-material resources in our program context; however, that is not the focus of this paper, and those data will be reported elsewhere. This paper focuses on evaluating implementation of activities and flow of material resources only. Specifically, we address the following questions**: (i) Were nutritional supplements and other requisite materials (trained staff, job aids, behavior change materials) for program impact available at the primary healthcare facilities?; (ii) Did healthcare workers appropriately carry out activities/utilize resources requisite for program impact?; and (iii) Did ANC clients consume supplements and utilize other resources received from primary healthcare facilities?**

Study context

This study was conducted in Malava sub-county, Kakamega County in Western Kenya from September 2014 to June 2015. The Malava sub-county, located northeast of Kakamega County, is mainly rural with some sub-urban neighborhoods. Malava, the largest town in the sub-county, is the sub-county headquarters. One referral facility in Malava, and 16 primary healthcare facilities were providing prenatal care services as at the time of study design. These included 3 health centers and 13 dispensaries. The health centers had 3-5 clinical staff in addition to laboratory staff and had 24 hour opening hours. They provided emergency medical services, in-patient services, out-patient services and maternal and child health clinics. The dispensaries had 2-3 clinical staff and had 9:00 am- 5:00 pm opening hours. They provided out-patient services and maternal and child health clinics. The focus on delivery through facility-based consultations was informed by the Kenyan national policy of delivering micronutrient supplementation for control of deficiencies through facility-based healthcare providers.

Fig 1. Program impact pathway for integrating calcium supplementation into primary care delivery



Development of program impact pathway model and district-wide program

Based on literature review and consultation with experts, we developed a PIP model for the integration of Ca supplementation into primary healthcare delivery. A simplified adaptation of our PIP is in Figure 1.

We conducted formative research in western Kenya to adapt the model to the local context, the results of which are described by Martin and others [75]. In brief, ANC clients, facility-based healthcare providers and community-based healthcare workers (HCWs) were purposively selected for in-depth interviews. Key findings from the formative research include poor ANC attendance beyond 1st visit, erratic supply of IFA supplements, inadequate knowledge of IFA recommendations among healthcare workers and poor counseling of clients about benefits and side-effects. We also conducted desk review of relevant policy documents and informal interviews with policy actors. We found multiple national policy and programmatic guideline documents emphasizing routine prenatal IFA supplementation for prevention and treatment of anemia. Existing policy also emphasized delivery of supplements through facility-based healthcare workers. Following the formative study, we conducted a trial of improved practices (TIPs) study to gain deeper insight into factors that influence pill-taking behavior among pregnant women taking iron and Ca supplements (Chapter 2). TIPs is a flexible adaptation of commercial marketing techniques that is designed to explore families' response to nutrition recommendations and elucidate the implementation process [76]. In brief, we purposively selected 38 pregnant women from 6 community groups. We aimed to follow up the women with 4 visits, every two weeks over 6 weeks. Study staff counseled them on the importance of Ca supplementation, requested that they choose one of two types of Ca supplements differing in organoleptic properties, and assigned each participant to 1 out of 3 different regimens. We measured supplement consumption with electronic pill monitors and conducted interviews to assess factors associated with acceptability of the recommendations.

Based on the formative findings, we developed a district-wide program to integrate Ca supplementation into facility-based ANC and strengthen delivery of IFA supplementation. In line with the PIP, the program consisted of activities aimed to ensure that pregnant women attended ANC clinics and that supplements, behavior change resources, and well-equipped healthcare workers were consistently available in primary healthcare facilities.

Based on the formative research, we identified six intervention delivery activities: (i) training ANC providers on Ca supplementation guidelines and counseling techniques to inform, motivate and reassure clients; (ii) mobilization of pregnant women to attend ANC clinics through training and motivation of community health workers; (iii) stop-gap provision of IFA supplements to district pharmacy and distribution to all facilities to avoid stock-outs; (iv) provision of Ca supplements to the district pharmacy and distribution to all facilities to avoid stock-outs; (v) development and distribution of take-home behavior change communication materials (i.e. calendar and poster) to healthcare facilities to facilitate pregnant women's adherence to recommendations and encourage familial support; and, (vi) development and distribution of appropriate counseling guides and job aids to all facilities

We trained facility-based healthcare workers in the district on Ca supplementation recommendations and counseling techniques, during 4 training sessions that took place on 4 different days at the same venue. Each training session lasted 6-8 hrs. All sessions contained modules covering purpose, rationale, prescription regimen, benefits and side-effects of Ca and IFA supplementation as well as training on counseling techniques. The sessions were similar in content except for recommended supplementation regimen for which there were two options. The recommended regimen differed because a cluster-randomized non-inferiority trial of the impact of recommended regimen on supplement consumption was embedded in the program, the results of which are reported elsewhere (Chapter 4)[77] . The recommended regimen on each of the training sessions was consistent with the regimen allocation for invited attendees for that session. The same set of facilitators, which included 2 members of the sub-

county health management team and 2 members of the investigating team, delivered all training sessions. Make-up sessions were facilitated for 13 healthcare workers who were newly recruited by the government during the course of the program and one of the two healthcare workers who missed the original training. The make-up training sessions were also consistent with the original training protocols, but were delivered by the program coordinator and research staff. We also trained selected community health workers to track and mobilize pregnant women to ANC clinics and reinforce program-related messages. The design and logistics of the training was similar to that of the facility-based healthcare providers, but the emphasis was on mobilization of pregnant women to antenatal care visits.

We delivered Ca and IFA supplements to the district pharmacy. Study staff worked with the district pharmacy staff to design and implement a distribution and notification plan to prevent Ca and IFAs stock-outs during the study period. This involved a complementary push and pull mechanism. The healthcare facility manager was expected to notify the district pharmacy or designated study staff when stock-outs are imminent. Pharmacy staff and designated study staff were also scheduled to visit all facilities at approximately 8-week intervals to replenish facility stores. The Ca supplements used in the trial were Ostocal Calcium and Vitamin D3 film-coated tablets manufactured by Eskayef Bangladesh Limited and purchased through Madawa Pharmaceuticals, Nairobi, Kenya. All Ca products contained 200 IU of vitamin D3 per pill. The pills were hard, tasteless and white.

Job-aids (i.e counseling guide) for healthcare providers and take-home behavior change materials for pregnant women were developed to be consistent with existing IFA materials, which had been recently rolled out nationally. Ca supplementation messages were generated and integrated with existing IFA materials. The materials were pretested in focus group discussions with pregnant women and interviews with healthcare providers in 3 community groups within the district. The materials were modified based on the data from the discussions and interviews. The job-aids were delivered to healthcare facilities at the beginning of the program. Behavior change materials, which included posters and calendars with

illustrated regimen, motivating messages and spaces for tracking consumption with daily marks were periodically delivered to the healthcare facilities by study staff through the course of the program.

Methods

Data collection

Table 1. Data collection schedule for implementation analysis

Table 1. Data collection schedule					
	Data collection activity	**Timing**	**Observation unit**	**Instrument**	**Data source**
1	Spot-checks and program data	Once in two months	Healthcare Facility	Monitoring template	Administrative records
2	Training data (Knowledge assessment)	Pre and post training events	HCW and CHW	Structured questionnaire	HCW and CHW
3	HCW surveys	Midline and Endline	HCW	Structured questionnaire	HCW
4	ANC exit interviews	Initial ANC consultation and return visits	ANC client	Structured questionnaire	ANC client

Monitoring and evaluation data were collected by study staff and included: (i) unannounced spot-checks to track availability of resources at the health care facility; (ii) exit surveys with ANC clients and; (iii) midline and endline surveys with health care providers (Table 3). These were supplemented with other sources of program data including training records and assessments, facility ANC registers, and district pharmacy bin cards. We developed the instruments by generating questions and checklists or adapting existing scales and questionnaires when available. Research assistants translated and back-translated the questionnaires before pretesting in the communities and facilities. We cognitively tested data collection instruments as needed and consequently made alterations to improve reliability and validity of the instruments. We developed a template for facility tracking of Ca and IFAs inventory, ANC traffic and counseling guide use during spot checks. We also measured whether the clinician providing care had been trained on Ca recommendations using this template, altogether providing data on program fidelity at the healthcare facility level.

For the facility spot-checks, a research assistant visited each participating facility at an average of 4 times during the course of the study to collect information to fill out the facility-tracking templates.

For ANC client exit interviews, a team of 7 trained interviewers recruited ANC clients from each of the 16 participating facilities. We collected data from each participant at up to three time points when possible. Recruitment days for each participating facility were scheduled and communicated to staff and communities in advance. All ANC clients attending the facility on the designated day were screened and consent was sought from those found eligible for the study, prior to their ANC consultations. Eligibility criteria were (i) maternal age at least 15yrs (ii) gestational age 16-30wks based on self-reports and clinician judgement (iii) not planning to relocate from the community prior to delivery and (iv) inadequate habitual Ca intake as measured by a screening tool that requested information about frequency and estimated serving size of local dietary Ca sources. Consenting clients were enrolled, then demographic surveys were administered, and clients were asked to participate in exit interviews after the ANC consultations. After the exit interview, enrolled participants were requested to grant follow-up interviews at the return ANC visit approximately 4 weeks later. At follow-up interviews, we interviewed participants prior to their ANC consultations and their remaining pills were counted. We also conducted exit interviews after the ANC consultation. We collected similar data at a subsequent and final follow-up visit. Where clients did not attend on the scheduled day, arrangements were made for follow-up on the earliest possible later date.

For healthcare workers, we collected data on their characteristics, satisfaction with the training and knowledge of module contents through surveys administered before and after the training sessions. We also collected data on the experience of the health care providers in the program through midline and endline healthcare workers' survey.

Data Management and Analysis

We entered ANC exit interview data and healthcare worker surveys into REDCap electronic data management tool hosted at Cornell University. REDCap is a secure, web-based data collection tool designed to support data capture for research studies [66]. We exported the data into Stata statistical software for further processing and analysis [67]. The facility tracking data was cleaned in Microsoft Excel.

We developed a table of metrics and scoring protocols for key activities in the program impact pathway. We calculated values for the key indicators of availability of resources (supplements, counseling guides BCM) at the facility and activities of health care workers, as ratios, percentages and absolute values, using Microsoft Excel and Stata as appropriate.

We assessed adherence to IFA by calculating percentage of clients with average daily intake of 0.8- 1.2 pills / day. We assessed adherence to Ca regimen by computing average daily consumption for each group as a percentage of the recommended daily dosage for the group. We also estimated the percentage of clients in each group that consumed more than an average of 800 mg /d, 1000mg and 2000 mg / d of Ca supplements, since this approximates meeting the estimated average requirement (EAR), recommended dietary allowance (RDA) and exceeding the upper limit (UL) respectively. We excluded clients that had follow-up periods exceeding the dispensed amount of pills from the analyses, if they did not return with any left-over pills, as it was not possible to assess their consumption using pill-counts.

Results

a) Were nutritional supplements and other requisite materials (trained staff, job aids, and behavior change materials) for program impact available at the primary healthcare facilities?

As shown in table 2. Below, requisite materials were mostly available at the facilities (>90% of spot check episodes), except for the behavior change materials. Ca and IFA supplements were available during 94% and 98% of assessment spot-checks respectively, indicating regular supply of supplements. Healthcare provider counseling guides were also found in the facilities during 97% of assessment episodes. However, take-home behavior change materials were found during 78% of spot-check episodes only.

Tab 2. Availability of program materials at primary healthcare facilities in Kenya in district-wide ante-natal Ca supplementation program in Kenya[4]

Facility-level availability of resources		
Activity	**Indicator**	**Value**
Ca supplements	% spot check episodes during which Ca Supplements were available	98.1% N=53[5]
Iron-Folate supplements	% spot check episodes during which IFA Supplements were available	93.8% N=64
Take-home behavior change communication materials	% spot check episodes with behavior change materials seen at facility	78.1% N=64
Counseling guides and job aids	% spot check episodes counseling guides seen	96.8% N=63
Ca= Calcium,	IFA= Iron-Folate, N= No of Spot Check Episodes	

[4] The values indicate availability of materials (no stock-outs) at the facility and do not indicate utilization or dispensing of materials. The ideal requirement is that materials be available at all times since clients at all stages of gestation and ANC attendance continuously visit the facilities, however there is no known availability threshold for a well-functioning program.
[5] There was a total of 64 spot-checks (4 per facility), but data on availability of calcium supplements were not recorded for 11 facilities in the first wave of spot-checks.

b) Did facility-based healthcare workers (HCWs)/community Health workers (CHWs) appropriately carry out activities/utilize resources requisite for program impact?

All indicators of frontline worker activity exceeded 80%, except ANC Consultations during which the client received adequate calcium supplements. Eighty-one percent of ANC clients attended follow-up ANC visits on scheduled return dates, indicating successful mobilization by community health workers. We did not measure community coverage for 1st ANC visits. The national average for 1st ANC visits was about 96% in the KDHS 2015, however return for follow-up visits had been a bottleneck. From the sub-county administrative records in 2013, the rate of 2nd ANC visits was 71% of those that attended a 1st visit. Clients received some calcium supplements during almost all (>98%) consultations, but the amount received was sufficient in only 76% of consultations.

Table 3. Characteristics of participants providing exit interview data in district-wide ante-natal Ca supplementation program in Kenya

Characteristics	**Regimen A , n=479**	**Regimen B, n=511**
Age, mean (SD)	25.10 (5.96)	24.81 (5.72)
Adolescent, % *15-19 years*	17.39	18.38
Gestational Age, months (SD)	5.5 (1.1)	5.4 (1.1)
Education, % Completed secondary	21.98	24.58
Marital status, % Never married	11.39	11.89
Primigravid, %	24.12	26.97
HH hunger scale categories, % Severe hunger	8.16	6.40

Table 4. Program activities implemented by healthcare workers and community health workers in district-wide ante-natal Ca supplementation program in Kenya

Adequacy of HCW and CHW activities		
Activity	**Indicator**	**Value**
Dispensing Ca supplements	% ANC Consultations during which client received adequate calcium supplements	76.4%
Dispensing Iron-Folate supplements	% ANC Consultations during which pregnant women received adequate iron supplements (>=28 pills)	88.5%
Giving take-home behavior change materials	% ANC Consultations during which pregnant women received (shown to exit interviewer) posters and calendars	89.4% (poster) 91.4% (calendar)
Using counseling guides	% ANC consultations during which HCWs used Counseling guide (as reported at recruitment ANC exit interview)	82.9%
Mobilizing pregnant women by CHWs	% ANC clients that attended follow-up visits at recommended times (28 days)	81%
ANC= Ante-natal care, CHWs= Community Health Workers, HCWs= Facility-Based Healthcare Workers		

c) Did ANC clients consume supplements and utilize other resources received from primary healthcare facilities?

Participants providing exit interview data were mostly married women in 3rd and 4th decades of life, who had not completed secondary education and were in their 2nd and 3rd trimesters of pregnancy.

Overall, 77% and 83% adherence was recorded for the IFA and Ca regimen respectively. Initial mean adherence to Ca supplementation regimen at first follow-up was 90% across board, but reduced significantly at 2nd follow-up in both regimen groups.

A nationally representative survey indicated that the average daily dietary calcium intake in Kenya was 511 mg / d (95% CI= 422, 600) [78]. We explored the impact of supplementation on percentage of the population meeting calcium dietary reference intakes for pregnant women by regimen and time interval, taking dietary intake into account. In the most conservative scenario (using lower limit of 95% CI of average dietary intake estimate in Table 7) for participants prescribed 1.5 g/d, over 75% of the population would meet the daily recommended intake for pregnant women with ages 19-50 years. However, in the same scenario for participants prescribed 1.0 g/d, only 55% would meet the daily recommended intake for pregnant women with ages 19-50 years.

Table 5. Adherence and consumption of calcium supplements by prescription regimen and time interval in district-wide ante-natal Ca supplementation program in Kenya [6]

	1.0g		1.5g	
	1st interval n = 301	2nd interval n = 291	1st interval n = 319	2nd interval n = 225
Mean adherence	91.5% (29.6)	69.3% (36.3)	89.9% (24.0)	67.6% (31.8)
Average daily supplemental intake mg / d (s.d)	915 (296)	693 (363)	1349 (359)	1014 (477)
>=500 mg/d	91.43%	61.79%	96.93%	84.33%
>=1000 mg/d	29.52%	16.07%	85.89%	50%
>=1500 mg/d	4.44%	2.5%	27.30%	16.79%
> 2000 mg/d	0.00%	0.00%	2.45%	1.12%
N= No. of Respondents, 1st interval = Assessment at 1st follow-up visit 2nd interval = Assessment at 2nd follow-up visit[7]				

Tab 6. Consumption of Calcium by prescription regimen and time interval in district-wide ante-natal Ca supplementation program in Kenya, (Supplements + Average National Daily Intake for Pregnant Women in Kenya i.e 511 mg)[8]

	1.0g		1.5g	
	1st interval n = 301	2nd interval n = 291	1st interval n = 319	2nd interval n = 225
	1426 (296)	1204 (363)	1860 (359)	1525 (477)
>=800 mg / d	96.51%	85.36%	99.39%	92.54%
> =1000 mg / d	92.700.33%	62.50%	96.93%	85.82%
>=2500mg / d	0.32%	0.00%	3.07%	1.49%
N= No. of Respondents, 1st interval = Assessment at 1st follow-up visit 2nd interval = Assessment at 2nd follow-up visit				

[6] This table refers to only supplemental intake and does not account for dietary intake

[7] Each follow-up visit was scheduled for 4 weeks after the last visit. However actual follow-up intervals ranged from 3-7 weeks.

[8] This table refers to supplemental calcium with some adjustment for dietary intake. 511mg/d was added to each participant's average daily supplemental intake, because that was the average daily dietary Ca intake for Kenyan pregnant women in the national survey.

Tab 7. Consumption of calcium by prescription regimen and time interval in district-wide ante-natal Ca supplementation program in Kenya (supplements +lower limit of the 95% CI of average daily dietary intake for pregnant women in Kenya) [9]

	1.0g		1.5g	
	1st interval n = 301	2nd interval n = 291	1st interval n = 319	2nd interval n = 225
	1337 (296)	1115 (363)	1771 (359)	1436 (477)
>=800 mg / d	94.92%	78.93%	98.77%	88.43%
> =1000 mg / d	85.71%	54.64%	94.79%	76.12%
>=2500mg / d	0.32%	0.00%	1.84%	0.75%
N= No. of Respondents, 1st interval = Assessment at 1st follow-up visit 2nd interval = Assessment at 2nd follow-up visit				

Tab 8. Consumption of calcium by prescription regimen and time Interval in district-wide ante-natal Ca supplementation program in Kenya (supplements +upper limit of the 95% CI of average daily dietary intake for pregnant women in Kenya) [10]

	1.0g		1.5g	
	1st interval n = 301	2nd interval n = 291	1st interval n = 319	2nd interval n = 225
	1515 (296)	1293 (363)	1949 (359)	1614 (477)
>=800 mg / d	97.78%	92.5%	99.39%	94.40%
> =1000 mg / d	94.60%	76.43%	98.77%	87.69%
>=2500mg / d	0.32 %	0.00 %	4.39%	2.24%
N= No. of Respondents, 1st interval = Assessment at 1st follow-up visit 2nd interval = Assessment at 2nd follow-up visit				

[9] This table accounts for both supplemental and dietary intake as in the preceding table. However, 422 mg/d (lower limit of the 95%CI of average daily dietary intake), rather than 511mg/d (point estimate of average daily dietary intake) is the value added to each participant's average daily supplemental intake value.

[10] This table accounts for both supplemental and dietary intake as in the preceding table. However, 600 mg/d (upper limit of the 95%CI of average daily dietary intake), rather than 511mg/d (point estimate of average daily dietary intake) is the value added to each participant's average daily supplemental intake values.

Discussion

The WHO issued global guidelines for integration of Ca supplementation for prevention of preeclampsia with IFA supplementation programs in ANC, but there has been no program model for implementation of these guidelines. Prenatal IFA supplementation programs continue to face implementation challenges. Reports of Ca supplementation programs are rare, but a study in Brazil reported that only 5% of ANC clients received Ca supplement prescriptions in a client population where over 90% individuals had inadequate habitual intake[74]. To our knowledge, this is the first study to design and evaluate a comprehensive program model for implementing these guidelines.

Facility-level availability of requisite resources for program impact

We carried out unannounced spot-checks at the facilities to determine the extent to which nutritional supplements, counseling guides and behavior change materials were regularly available. All metrics reflecting availability of supplements and other resources at the facility level were higher, compared to availability of behavior change materials. As part of program design, we instituted a mixed push and pull mechanism for facility-level supplement forecasting and stock replenishment, but this was not extended to behavior change materials. The healthcare facility manager was expected to notify the district pharmacy or designated study staff when stock-outs were imminent. Pharmacy staff and designated study staff were also scheduled to visit all facilities at approximately 8-week intervals to replenish facility stores, irrespective of notification calls. The few supplement stock-outs that were recorded resulted from notification delays from healthcare facilities to the district pharmacy during periods of unanticipated surges in ANC attendance. These could have been prevented with shorter intervals between scheduled replenishment visits by district officials or increasing the inventory threshold at which notification by facility managers was required. The relatively high level of stock-outs for behavior change materials is plausibly due to the absence of a well-coordinated notification plan for supply and

replenishment of the materials to the facilities, but the design of this study does not permit a direct test of this hypothesis. Taken together these findings underscore importance of a well-coordinated push and pull mechanism for delivery of materials for program success.

Adequacy of HCW and CHW activities

We examined exit interview data to understand the extent to which healthcare workers counseled clients with job-aids and dispensed supplements and BCM materials during ANC consultations. Over 80% of clients reported being counseled about Ca and IFA supplementation with counseling guides.

Although over 98% of ANC clients received some Ca and IFA supplements, only 76% and 89% of clients respectively received amount of supplements needed to meet their prescriptions until scheduled return date. Prior studies and our formative research have shown limited fidelity to prescription and dispensing guidelines for pills and supplements among healthcare providers [75]. This 'rationing' is likely due to limited understanding of dispensing guidelines on the part of healthcare providers in our own study, rather than supplement stock-outs in the facilities, given the high supplement availability rates recorded during spot-checks. The lower rates of appropriate dispensing of IFA compared to Ca supplements might be due to the fact that healthcare workers had been used to dispensing IFA with different protocols prior to the study. Although our training sessions included information about prescription and dispensing guidelines, there could have been more emphasis and clarity about dispensing guidelines. Inclusion of dispensing guidelines in counseling guides and other job aids in addition to other reminders could have been helpful for reinforcement. Future studies should examine utility and impact of job aids and other tools for reinforcing dispensing guidelines.

Supplementation adherence and behavior change material utilization by pregnant women

Most clients that received BCM calendars used it. Our formative research revealed that calendars helped pregnant women remember to consume their supplements.

Cumulative supplement consumption depends on the balance between long-term adherence and recommended daily consumption. Adherence was defined as mean daily consumption as a percentage of prescribed daily consumption. Adherence to Ca supplementation reduced over time in this study. Similar findings have been reported for other pills and supplements in other settings. We found that a high proportion of (over 75%) participants were still able to meet the recommended dietary allowance, when prescribed 1.5 g / d, despite the drop in adherence. However, when prescribed 1.0 g /d the percentage of participants that met the recommended dietary allowance might be as low as 55% in the 2nd interval. Our findings provide empirical evidence suggesting that i) we can expect at least 75% of the population to meet DRIs if our program conditions are replicated in our kind of population with current WHO regimen ii) adherence to regimen reduces over time irrespective of regimen and iii) lower regimen led to fewer people meeting DRIs because both regimen resulted in comparable adherence.

Supplement Products and Regimen

Average daily dietary Ca intake in a nationally representative Kenyan sample was 511 mg / d with standard deviation 281 mg / d, in an analysis reports submitted by Healthbridge to Micronutrient Initiatives[78]. The minimal amount of Ca intake needed to prevent preeclampsia is yet to be determined. The World Health Organization recommends 1.5-2.0 g / d of supplemental Ca based on meta-analysis of randomized trials, however, comparable benefit has been reported in meta-analysis of studies administering dosages below 1.0 g /d, but the primary studies were of poor quality and relevance [6].The estimated average requirement and recommended dietary allowance for pregnant women are 800 mg /d and 1000 mg /d respectively [23]. Although these are based on skeletal end-points in a different population, it is believed that effect of Ca in preeclampsia prevention derives from filling the dietary Ca gap in populations with inadequate dietary intake [49]. Therefore, the recommended dietary allowance was used as the criterion for adequacy of supplement intake in this study and finding indicates that prescribing 1.5 g / d is likely to have higher clinical impact. However, choosing prescription regimen in national programs can be more complex. It will be considered not only in light of clinical impact, but also implications for cost and supply chain logistics in large scale programs; factors that might favor lower dosages.

Formative research revealed preference for sweet chewable Ca supplement tablets among pregnant women, however, we used hard tasteless pills in the pilot program because it costs approximately 25% as much as sweet chewable tablets. It is unlikely that large scale programs will use the chewable tablets with the current price regime. However, we are unaware of the drivers of differential cost between the pill types. This might not be related to attributes driving consumer preferences. Hence, it might be possible to produce new pill types that will balance consumer preferences with program cost thereby improving adherence and consumption. Future studies should examine this trade-off in detail.

Strengths and Limitations

This study has certain key strengths. i) It is the first study to examine programmatic design for integration of calcium supplementation with iron-folate supplementation in primary healthcare facilities, in a low or middle-income country. This is important because of high prevalence of dietary calcium inadequacy and incidence of preeclampsia in such countries globally. ii) Our program design was based on a rigorous program model grounded in established behavioral theories iii) We carried out extensive formative research that grounded the program model in the local socio-cultural and health systems context, providing us with relevant insight to interpret the findings and lessons from our study and iv) We address issues of key relevance to program planners and policy makers in several countries.

Our findings should be interpreted with caution. Firstly, our analysis of HCW activities was based on self-reported data from exit interviews. Classically, social desirability and recall problems are potential sources of bias in this situation. However, data from exit interviews in this analysis involved receipt of materials that were also directly verified during the exit interviews, except for use of job-aids by HCW during consultation. Secondly, our adherence and consumption estimates are aggregates based on pill counts. This might obscure distributional characteristics that are biologically relevant. The pill count was done after 4 to 8-week time intervals. This might obscure within-person fluctuations, such as periods of over and under-consumption by the individual. The group adherence aggregates might also obscure the influence of outlier individuals. While we are unable to rule out within-person fluctuations, graphical analysis of sub-group distributions and analysis of influence of outliers suggest that our conclusions are not driven by this factor. Thirdly, there is potential for measurement error in dietary intake values used in our study. We did not measure individual dietary intake but used averages from a national survey. Also we used the dietary reference intakes for pregnant women older than 18 years in our study, which is less than the reference intake for adolescents, but 17% of our participants were adolescents. This might bias our estimates of percentage population meeting recommended dietary intake. However, our

conclusion about relative effect of prescription regimen on the percentage population meeting recommended dietary intake is likely robust to the potential errors in our estimates, given that facilities were randomly assigned to the prescription regimens. Fourthly, socio-cultural and health system factors are complex and heterogeneous across low and middle-income countries. Further studies will delineate the inferential boundaries of our conclusions in terms of geographical, socio-cultural and health systems conditions. Fifthly, our study was well implemented over a period of over a period of 9 months. It is plausible that over time the effect of the interventions might wane. Finally, there is a broader range of factors that need be considered in national programs than we were able to examine in this study. National programs will require a sustained support system whose focus transcend operational bottlenecks that we investigated in the delivery system, but also work with managers to address organizational and political economic constraints[79]. Our study is a first step in elucidating key program delivery issues, further research and programmatic experience will refine our conclusions.

Conclusion

In conclusion, this study illustrates a comprehensive approach to integrating primary prevention of preeclampsia and anemia into ante-natal care delivery, guided by a program impact pathway model. Availability of requisite resources at primary healthcare facilities, activities of healthcare workers and community health workers, and adherence behavior among antenatal care clients were mostly adequate. Policy makers and program planners should pay careful attention to supply chain, HCW dispensing behavior and appropriateness of regimen and supplement products for their settings.

Chapter Four

Impact of Dosing Regimen for Antenatal Calcium and Iron-Folate Supplementation on Supplement Consumption: A Cluster-Randomized, Non-Inferiority Trial in Western Kenya

Abstract

Background: To prevent pre-eclampsia, the World Health Organization (WHO) recommends ante-natal calcium (Ca) supplementation in populations with inadequate habitual intake. The WHO guideline recommends 1.5-2.0 g /d with a dosing regimen that might require 4-6 pill-taking events when combined with iron and folic acid (IFA) supplements. We hypothesized that simpler regimens with lower daily dosages might lead to higher adherence, and therefore yield the same population calcium intake while costing less.

Methods: We examined the impact of Regimen A, a 3-dose regimen (500mg X 3, per WHO guidelines), compared to Regimen B, a lower 2-dose regimen (500mg X2), on average daily supplement intake, using a parallel, cluster-randomized non-inferiority trial in 16 primary healthcare facilities in rural Kenya. We enrolled 990 pregnant women between 16 to30 weeks gestational age. The primary outcome was average daily amount of Ca supplement consumed (mg/d), measured by pill counts assessed at 2 time points, 4wks and 8wks after recruitment. We carried out intention-to-treat analysis using mixed effect models, with regimen as fixed effects, using a non-inferiority margin of 125 mg/d.

Results: Participants from facilities assigned Regimen A consumed 388 mg/d (95%CI = 341, 434) more supplemental calcium than those assigned regimen B. Participants with Regimen B

Conclusion: We conclude that recommending a lower and simpler 2-dose regimen led to lower impact on calcium intake than the WHO recommended dose. Further studies are needed to evaluate the cost-effectiveness of lower and simpler regimens in large-scale programs under routine delivery conditions.

Trial Registration: NCT02238704

Background

Hypertensive disorders in pregnancy, including pre-eclampsia, are major contributing factors to maternal and perinatal mortality. While the pathogenesis of these disorders has not been fully elucidated [14], populations with inadequate dietary calcium (Ca) intake have been shown to be at greater risk . Systematic reviews of efficacy trials have established that Ca supplementation reduces the risk of preeclampsia [6,7].

Based on this evidence, the World Health Organization (WHO) strongly recommends the introduction of Ca supplementation in populations with low habitual intake as part of existing antenatal care (ANC) programs [49](WHO 2013). Many ANC programs are already implementing daily iron-folic acid (IFA) supplementation, therefore addition of Ca will require an integrated prescribing and counseling protocol.

To optimize bioavailability and efficacy, the WHO recommends 1.5-2.0 g of elemental Ca in 3 divided doses, preferably taken with food. This regimen should begin at 20 weeks of gestation and continue through delivery. To alleviate concerns about negative effects of iron-calcium interaction on iron absorption, separating administration of Ca and IFA supplements is suggested . However, there is evidence that the interaction has a transient and clinically insignificant impact over time [27]. A combined regimen will favor adherence and the overall benefit might outweigh the negative impact of the interaction [28].

Integrating Ca and IFA supplementation while taking the two types of supplements at different times adds up to 4-5 separate pill-taking events daily of 3-4 Ca pills and 1-2 IFA pills. (If the woman is anemic, 60 mg twice daily administration of iron supplements is the recommended therapy). This complex regimen, while consistent with dosages tested in existing efficacy trials, does not account for such factors as client adherence, dietary patterns, motivation and satisfaction, which were not the focus of the efficacy trials and meta-analyses, but are relevant for effectiveness in public health programs. Earlier

commentators have called for reexamination of the suggested prescription in the WHO guidelines, on the basis that lower supplemental intake might be sufficient for efficacy and safer, or simpler regimens with lower daily calcium load might be equally effective in improving supplemental intake in large-scale programs and might be more cost-effective [6,28]. Implementation of public health programs with high dosages faces higher cost and logistic complexities, given the cost and weight of supplements [6]. Previous research has shown that medication adherence decreases with an increase in regimen complexity and pill burden [24]. Removing the recommendation to separate Ca from IFA administration, given minimal clinical implication of interaction, would be a reasonable approach to reduce regimen complexity and its potential effects on adherence and supplement consumption [28].Formative research suggested that a 2-dose regimen was more acceptable to pregnant women than a 3-dose or 4-dose regimen (Chapter 2). We hypothesized that this preference would translate to better motivation and adherence to the extent that supplement consumption in a simpler regimen would be as high as with a higher dose regimen. If indeed adherence was greater with the lower dose regiment, public health programs recommending the 2-dose regimen would have the same impact on calcium status and implicitly population risk of preeclampsia, while saving program resources.

Objectives

The objective of this trial was to determine the impact of a lower Ca dosing regimen (Regimen B) compared to a dosing regimen consistent with the WHO guidelines (Regimen A), on supplement consumption among ANC clients in rural Kenya. Specifically, we compared Regimen B comprising 2 Ca pills +1 IFA pill daily to Regimen A that comprises 3 Ca pills (per WHO guidelines) + 1 IFA pill daily. We sought to determine whether Regimen B will lead to non-inferior average daily Ca supplement consumption, and by extension comparable impact on calcium status and population risk of preeclampsia, due to higher regimen-specific adherence.

Outcome

The primary outcome was average daily amount of Ca supplement consumed (mg/d). We assessed supplement consumption at follow-up visits at 4 weeks and 8 weeks post-recruitment. We compared average amount of Ca supplements consumed per day between women in facilities assigned the Regimen A (higher-dose) and Regimen B (lower-dose).

Hypothesis

We tested the hypothesis that Regimen B would lead to average daily Ca supplement consumption that is not inferior to the average daily Ca supplement consumption in Regimen A, because of higher adherence rates in Regimen B. Our margin of inferiority was 125mg /day. Ideally, this margin would correspond to the minimal difference in calcium intake that is clinically meaningful for prevention of preeclampsia. However, the minimal amount that is clinically meaningful remains unknown [21,28]. Given the high absolute amount of daily calcium prescribed in both regimens, we deemed 125 mg / d to be a conservative (i.e. small) margin a priori [77]. This is summarized as:

Ho: A-B ≥ 125mg / d, (B is inferior to A, by at least 125 mg / d)

Ha: B -A < 125mg / d, (B is not inferior to A, within a margin of 125 mg / d**)**

Methods/Design

Study design

The study was a parallel, cluster-randomized, non-inferiority trial comparing two Ca + IFA dosing regimens. Regimen A, consistent with current WHO recommendations, prescribed 1.5g elemental Ca (as calcium carbonate) in 3 pill-taking events (500mg Ca/pill) and IFA (60mg Fe + 400microgram folic acid) taken with the evening dose. Regimen B prescribed 1.0 g elemental Ca (as calcium carbonate) in 2 pill-taking events (500mg Ca/pill) and IFA (60mg Fe + 400microgram folic acid) taken with the evening dose. Supplement consumption was assessed during up to two follow-up visits at 4 and 8 weeks after enrollment. Cluster-randomization was deemed appropriate because of the health facility-based nature of the intervention. In public health programs, regimen guideline decisions are made at a higher level than the individual clinician. Randomization at the level of clinician or ANC client would also have increased the risk of contamination, given the high levels of social and communal interactions among pregnant women in the study communities. We chose a non-inferiority hypothesis, rather than superiority or equivalence hypotheses because we did not deem it plausible that pregnant women will consume more supplements with lower recommended doses.

Setting

This study was conducted in Malava sub-county, Kakamega County in Western Kenya. The target population consists of pregnant women receiving antenatal care services and healthcare workers providing such services in healthcare facilities. The county headquarters, Kakamega town, is located 52 km north of Kisumu. Malava sub-county, located northeast of Kakamega with a population of over 220,000, is primarily rural, and its headquarters is located in the largest town, Malava. ANC services were provided by one sub-county referral facility in Malava town, 3 health centers providing ambulatory preventive and curative services, and 13 smaller dispensaries providing preventive health services.

Randomization, treatment allocation, and masking

Treatment was randomly allocated at the level of cluster, considering each primary healthcare facility in Malava sub-county as a potential cluster. There were 17 healthcare facilities providing antenatal primary care services in the sub-county at the time of cluster selection. All healthcare facilities with at least 60 first ANC visits according to the 2013 sub-county administrative data were selected to participate in the study. Based on this criterion, one healthcare facility in the sub-county was excluded. Prior to treatment allocation, we received commitment from the county and sub-county health management teams that all selected facilities would participate in the study and none of the selected facilities opted out.

To allocate treatment, the Cornell Statistical Consulting Unit (CSCU) generated a roster of 16 numbered units randomly allocated to two different groups, A and B. Group A units had been pre-designated as Regimen A and group B as Regimen B. A member of the collaborating team in Kenya was requested to assign serial codes 01-16 to the selected participating facilities, prior to receipt of the randomization roster from CSCU. The randomization roster was matched to the serial numbers to determine facility treatment allocation by the project coordinator.

This study was open-label. Research assistants, healthcare providers and participants were all aware of the allocated prescription regimen. The specific study hypotheses were however not disclosed to research assistants until data collection had been completed.

Study Participants

Recruitment of study participants commenced on September 22, 2014, and respondent follow-up was completed on June 12, 2015. Study participants were recruited among women attending regularly scheduled ANC visitations, on days that had been designated as recruitment dates at each participating primary care facility. Women 16-30 wks gestational age were considered for inclusion. Gestational age was assessed primarily by self-reported last menstrual period (LMP) but where self-reported LMP differed from clinician assessment during the ANC consultation, clinician assessment was accepted. Exclusion criteria were: age <15 years old, adequate dietary or medicinal consumption of Ca (assessed with a dietary and medicinal Ca consumption screening tool developed for the study), and intention to leave the study community before 8 weeks from date of recruitment interview. This was similar to the exclusion criteria in many of the prior studies that examined clinical efficacy.

Intervention

This cluster-randomized trial occurred within a pilot demonstration of the implementation of the WHO Ca supplementation guideline within the primary healthcare system in Kenya. The study team worked with the sub-county health management team to integrate Ca supplementation into ANC services at all facilities in Malava sub-county. Aside from the regimen assignment, all other interventions were similarly delivered across all healthcare facilities in the sub-county, irrespective of participation in the cluster-randomized trial or the study arm within this trial. These "blanket interventions" were: a) direct provision of Ca supplements to all facilities to avoid stock-outs; b) direct stop-gap provision of iron-folic acid supplements to all facilities to avoid stock-outs; c) community mobilization of pregnant women to attend ANC clinics through training and motivation of community health workers; d) training ANC providers on Ca supplementation and counseling techniques; e) development and distribution of appropriate counseling guides and job aids to all facilities; and f) development and distribution of take-home behavior change communication materials (i.e., calendar and poster) to healthcare facilities to facilitate pregnant women's adherence to their recommended regimen and encourage familial support. Health care workers from the study facilities were trained during 4 identical one-day training sessions that took place on 4 different days at the same venue. All training sessions contained modules teaching the purpose, rationale, prescription regimen, benefits and side-effects of Ca and IFA supplementation as well as training on counseling techniques. The 4 training sessions were identical in content except for the dosing regimen for Ca supplementation, which was determined by randomized group. Almost all (40/42) healthcare workers who provide ANC in the sub-county attended a session in which the prescription regimen reflected the treatment allocation of their cluster; the remaining did not attend any initial session. The same set of facilitators, which included 2 members of the sub-county health management team and 2 members of the investigating team, delivered all training sessions. Make-up training sessions were facilitated for 13 healthcare workers who were newly recruited by the

government during the course of the study and one of the two healthcare workers who missed the original training. The make-up training sessions were also consistent with the treatment allocation for the health workers' facilities.

The Ca supplements used in the trial were Ostocal Calcium and Vitamin D3 film-coated tablets manufactured by Eskayef Bangladesh Limited and purchased through Madawa Pharmaceuticals, Nairobi, Kenya. All calcium products contained 200IU of vitamin D3 per pill.

Sample size

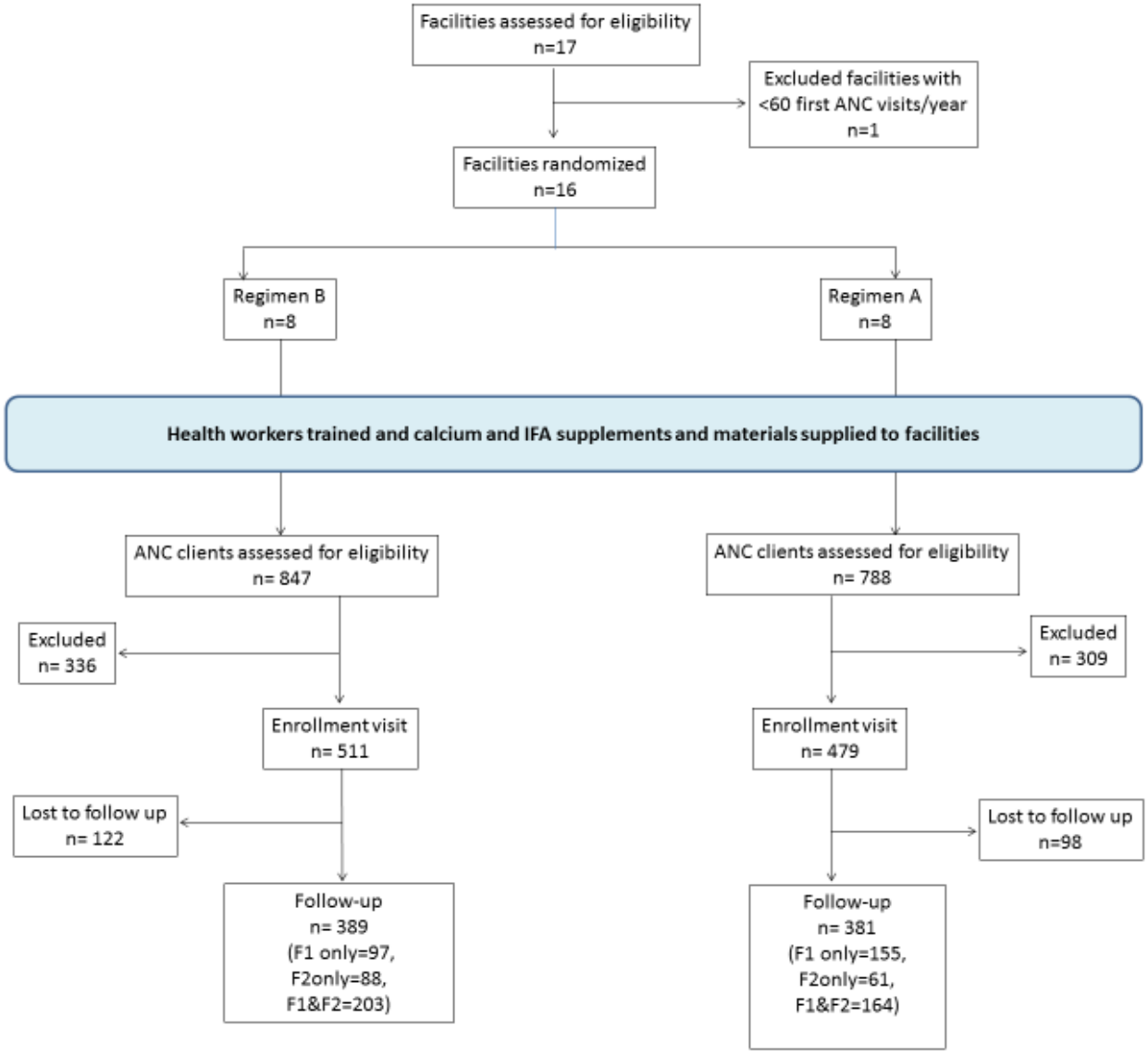
The primary outcome of this study was supplement consumption. The inferiority margin was a mean difference of 0.25 pill (125 mg) consumption per day i.e the null hypothesis of inferiority of the lower-dose regimen will be rejected if the upper border of the 95% confidence interval around the mean difference in average daily calcium consumption between the two study arms is below 125 mg / d. Based on preliminary data from formative research in the same study site, the standard deviation of daily supplement consumption was expected to be 0.9 pill/day. A sample size of 194 women per group would allow rejection of the null hypothesis that Regimen B led to reduced average daily consumption of Ca (by >0.25 pill) than the Regimen A, assuming a standard deviation of 0.9 pill /day, for a one-sided test with alpha of 0.05 and power of over 0.80 and loss to follow up of 10%. We assumed an intra-cluster correlation of 0.02 and an average cluster size of 60 participants from each of the 16 eligible facilities, therefore we used a design effect of 2.18. We aimed to recruit 423 women/group in this clustered sample to achieve the same power as 194 women/group in a randomized design in which all observations are independent. We recruited 990 participants, and were able to collect primary outcome data for 771 (80% of enrolled) women. The number of participants per cluster ranged from 70-99 women.

Measurements and Data management

A team of six trained interviewers recruited participants and administered survey questionnaires. All survey questionnaires were translated into Kiswahili and translated back into English to verify translation quality and content. The contextual appropriateness and understanding of the questions were assessed during pre-testing of the instruments. Data were collected from each participant at up to three time points. Recruitment days for each participating facility were determined and communicated to staff and communities in advance. At the enrollment visit, all ANC clients attending the facility on the designated day were screened and consent was sought from those found eligible for the study, prior to their ANC consultations. Consenting clients were enrolled, a demographic survey was administered, and clients were asked to participate in an exit interview after the ANC consultation. After the exit interview, enrolled participants were requested to return for follow-up visits, 4 and 8 weeks later. Actual follow-up intervals were variable (3-12 weeks), because some participants missed their return visits and were rescheduled.

At follow-up visits, participants were interviewed prior to their ANC consultations and their remaining pills were counted and retrieved. During an exit interview after the ANC consultation, newly-received pills were counted. After the first follow-up interview, participants were requested to return for a second follow-up visit, with similar data collection activities, approximately 4-6 weeks later. This was the final visit before exit from the study. Participants that missed follow-up visits were tracked to their homes for supplement counts to be conducted, when traceable. Exit interviews at each visit were used to assess health care provider fidelity to the intended protocol. These interviews sought information about whether or not ANC clients received an adequate number of supplements, as well as accurate and complete information about their dosing regimen, the purpose, benefits, and side-effects of Ca and IFA supplementation. Data was entered into REDCap data capture software with double entry by data entry clerks to limit entry errors.

Fig 1. Participant Flow Chart for Cluster-Randomized Trial of Impact of Regimen on Supplementation Adherence and Consumption among Preganant Women in Kenya[11]



Regimen A, 3-dose regimen (500mg X 3, per WHO guidelines)

Regimen B, lower 2-dose regimen (500mg X2)

[11] F1 only-outcome data only for 1st visit, F2 only-outcome data only for 2nd visit, F1 &F2-outcome data at both time points

Statistical Analysis

Analysis was based on statistical methods that accounted for the hierarchical structure of the data. Supplement consumption assessed as average number of pills consumed/day was the primary dependent variable. Each pill contained 500mg elemental calcium. This continuous outcome was modeled using a 3-level linear mixed effects model using the xtmixed command in stata 14, to account for measurements at 2 different time points for participants nested within health facilities. The treatment (Regimen A vs. Regimen B) was the fixed effect while the random effects were the cluster and unique client identifiers (health facility and client code). The null hypothesis of inferiority would have been rejected if the upper bound of the confidence interval of the fixed effect coefficient was <125 mg/day. Analysis was done on intent-to-treat basis. Statistical analysis was done using *Stata Statistical Software: Release 14* [67]. We ran unadjusted models and then included participant characteristics as covariates (age, education, marital status, primigravidity, follow-up interval and hunger). Inclusion of the covariates did not change our substantive conclusions.

Ethical Aspects

This study was reviewed and approved by the Institutional Review Board at Cornell University and Kenyatta National Hospital and University of Nairobi Ethics and Research Review Committee. All respondents were given detailed information about the objectives and purpose of the study and written informed consent was obtained from each respondent before enrolment. This trial is registered as NCT02238704.

Results

The characteristics of enrolled women were similar across study arms at baseline suggesting that the randomization of health facilities resulted in similar groups.

Table 1. Characteristics of study participants by Treatment Arm[12]

Characteristics	**Regimen A , n=479**	**Regimen B, n=511**
Age, mean (SD)	25.10 (5.96)	24.81 (5.72)
Adolescent, % *15-19 years*	17.39	18.38
Gestational Age, months (SD)	5.5 (1.1)	5.4 (1.1)
Education, % Completed secondary	21.98	24.58
Marital status, % Never married	11.39	11.89
Primigravid, %	24.12	26.97
HH hunger scale categories, % Severe hunger	8.16	6.40

We examined baseline characteristics of respondents that had follow-up data and those with missing data across both study arms to assess the likelihood of differential mechanisms for missing data across study arms and introduction of selection bias. The values of the covariates were similar across the two groups irrespective of whether outcome data was available or not.

[12] This is baseline data for all participants, including those without outcome data.

Tab 2. Characteristics of study participants by treatment arm and availability of outcome data in the MICa trial

	Regimen A		Regimen B	
Covariates	**No pill count n=98**	**Have pill count n=381**	**No pill count n=122**	**Have pill count n=389**
Age, mean (SD)	24.81(5.68)	25.16 (6.02)	24.31 (5.22)	24.95 (5.84)
Adolescent, *% 15-19 years*	17.98	17.14	17.01	17.46
Gestational Age, months (SD)	5.7 (1.1)	5.3 (1.1)	5.8 (1.0)	5.5 (1.1)
Education, % Completed secondary	21.98	21.99	23.21	24.94
Marital status, % Never married	14.29	9.57	13.51	10.98
Primigravid, %	27.47	23.40	32.14	25.59
HH hunger scale categories, % Severe hunger	7.69	8.26	7.00	6.23

Tab 3. Mean adherence and consumption by regimen (Unadjusted) in the MICa trial

Outcome	**Regimen A, n=381**	**Regimen B, n=389**
Consumption, mg / d (SD) overall	1198 (448)	810 (347)
Consumption, mg / d (SD) 1st interval	1349 (359)	915 (296)
Consumption, mg / d (SD) 2nd interval	1014 (477)	693 (363)
Adherence, % *overall*	79(0.30)	81(0.35)
Adherence, % *1st interval*	90(24)	92(30)
Adherence, % *2nd interval*	68(32)	69(36)

When we modeled the relationship between adherence and regimen using a 3-level mixed effects model, contrary to our expectation, there was no significant difference in adherence. Participants with Regimen A were 1.1% (95%CI= -4.8, 2.4) less adherent than those prescribed regimen B in unadjusted models. After we included relevant covariates (age, education, marital status, gestational age, primigravidity, severe hunger on the household hunger scale, length of follow-up interval in days and type of follow-up visit i.e 1^{st} vs 2^{nd} visit) in the model, participants with Regimen A were 3.6% (95%CI= -9.1, 1.7) less adherent than those prescribed regimen B in unadjusted models.

We also examined the relationship between consumption and regimen using similar models. Contrary to our hypothesis, Regimen B was inferior to Regimen A. Participants with Regimen A consumed an average of 388 mg / d (CI= 341, 434) more than those with regimen B in unadjusted models. When the same covariates were added to the model, there was no remarkable change in difference in consumption, with adjusted coefficients being 420 mg/d (95% CI=352,487) as shown in table 4. Taken together these findings indicate inferiority of Regimen B.

Tab 4. Adjusted Model for the Impact of Regimen on Ca Supplement Consumption in the MICa trial

	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
Regimen*	419.6934	34.3744	12.21	0.000	352.3208	487.066
Age	1.5861	2.4872	0.64	0.524	-3.2887	6.4610
Education	48.1043	30.988	1.55	0.121	-12.6311	108.8397
Interval**	-2691582	32.1707	-8.37	0.000	-332.2116	-206.1049
Interval # Regimen***	-88.4647	45.6753	-1.94	0.053	-177.9866	1.0573
Int1[&]	-8.3473	3.4545	-2.42	0.016	-15.1181	-1.5766
Int2[&&]	-5.2527	1.7685	-2.97	0.003	-8.7188	-1.7866
Gestational age	2.2568	2.8772	0.78	0.433	-3.3823	7.8960
Marital status	50.1375	42.2001	1.19	0.235	-32.5732	132.8482
Gravidity	-18.7348	37.3452	-0.50	0.616	-91.9300	54.4604

*****Regimen B was the reference. Hence this indicates that participants with regimen A had significantly higher supplement consumption.

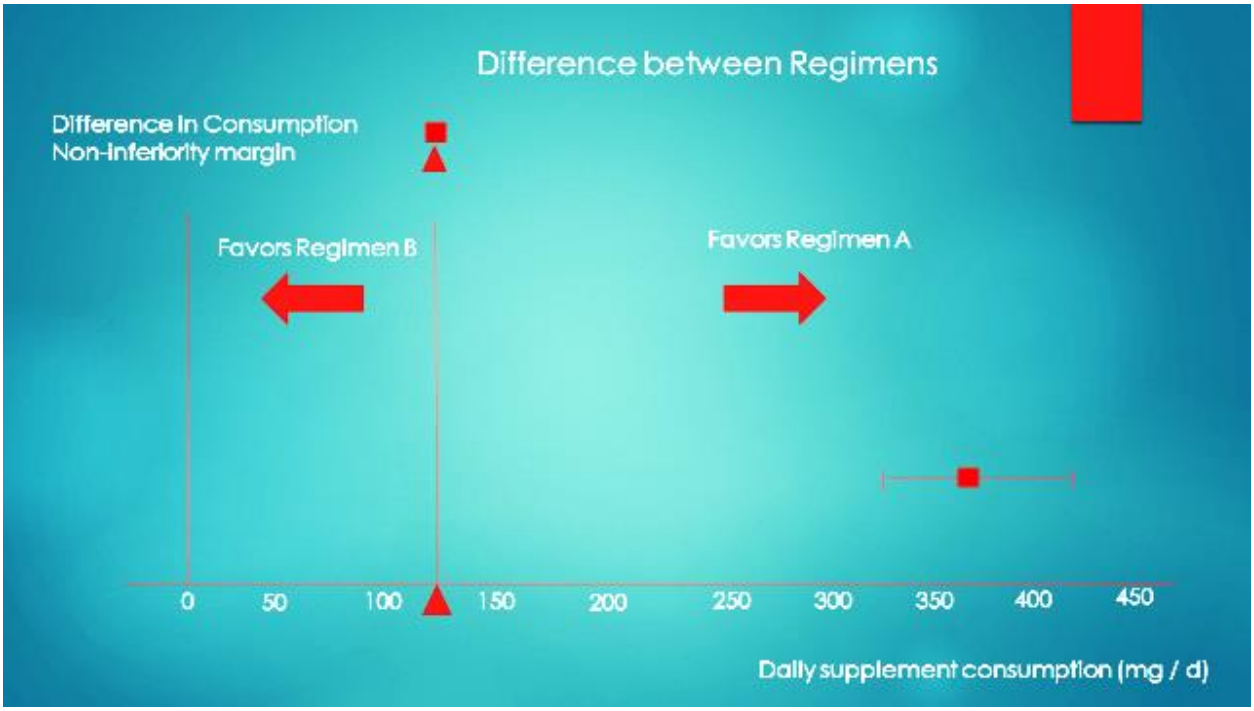
******This indicates whether the data was collected at 1st or 2nd follow-up. 1st follow-up was the reference, meaning that consumption dropped significantly at second follow up

******* This indicates the difference in difference in consumption between follow-ups across regimens. Regimen B was the reference, indicating that the drop in consumption over time was worse in Regimen A. Although the p-value is not significant, the width and boundaries of the confidence interval suggest that lack of significance is due to limited power.

& Number of days in before 1st follow up

&& Number of days between 1st and 2nd follow-up interviews

Fig 2. Difference in Consumption between Regimen A and Regimen B in the MICa trial



Discussion

In this cluster-randomized non-inferiority trial, we tested the hypothesis that a 2-dose regimen would not be inferior to a 3-dose regimen, to improve average daily calcium intake among pregnant women. Contrary to our hypothesis, we did not find differences in adherence and we found the 2-dose regimen to be inferior to the 3-dose regimen. This is the first study designed to examine relative impact of a simpler regimen with lower daily calcium load, in the context of the WHO guidelines on calcium supplementation in pregnancy. This question is important because a 2-dose regimen would have the advantage of saving cost and programmatic resources, in addition to potentially increasing client satisfaction. Pregnant women, served by a well-supported public health program, were more willing and able to take multiple Ca pills daily than we had expected.

Studies with other pills have demonstrated lower adherence to complex regimen. Indeed, our formative research showed that a simpler and lower 2-dose Ca regimen was more acceptable to pregnant women than a 3-dose or 4-dose regimen. Nonetheless, when implemented by health workers at scale, adherence did not differ by regimen. The unexpected finding from our randomized trial might result from the extent of relative complexity. The difference between our regimens is a single dose. The 3-dose regimen might not have sufficiently high relative complexity and low acceptability to translate to significant differences in adherence and consumption.

Our findings should be generalized with caution. Our trial was embedded in a demonstration project that was better implemented than many routine ante-natal supplementation programs (Chapter3). It is possible that good counseling and improved clinician-client interaction, had differentially supportive impact on adherence to the WHO regimen, thereby attenuating the difference in adherence that would have been apparent in a poorly functional program.

It is also important to note that our study did not measure clinical outcomes. We worked with the assumption that supplement consumption improves calcium status and calcium status is related to

reduction in preeclampsia risk, within our studied range. These assumptions could not be directly verified in our study. Although meta-analyses of clinical trials within comparable dosage ranges provide some support for this assumption [6], the clinical implications of our study finding is not straight-forward. The functional form of the dose-response curve for population calcium intake and preeclampsia risk is not completely resolved. There are still debates about the existence of a threshold level of calcium intake at which preeclampsia risk is impacted as well as the value of such threshold. It is not known whether any shift of the population distribution to the right confers benefit, and whether the further the shift to the right, the higher the level of preeclampsia risk protection conferred, until the upper limit is reached.

Another limitation of our study is the lack of outcome data for 20% of participants recruited into the study. This could have introduced selection bias into our analyses if the mechanism of missing data was differential across study arms and related to consumption. The common reasons for missing outcome data were complete loss to follow up, failure to return for follow-up in due time or failure to return with pill bottles for left-over pill counts. Baseline characteristics of participants without outcome data were similar across study arms, and also to characteristics of those with outcome data. When we added baseline covariates to our model to examine sensitivity of our conclusions to potential selection bias, our substantive conclusions did not change. Although this suggests robustness of our conclusion, selection bias can still not be completely ruled out.

Conclusion

In conclusion, contrary to our hypothesis, we found Regimen B (500 mg elemental Ca X 2 with IFA taken with the last Ca dose) to be inferior to Regimen A (500 mg elemental Ca X 3 with IFA taken with the last Ca dose) in terms of average daily Ca supplement ingestion. The more complex Regimen A was not associated with lower adherence. The 3-dose regimen might be more effective than simpler and lower-dose regimens in meeting program goals when consistent supplement supply, good clinician counseling skills and high quality behavior change materials have been established.

CHAPTER FIVE

CONCLUSION

In summary, this dissertation examines three related papers concerning integration of strategies (micronutrient supplementation and counseling) for prevention of preeclampsia and anemia in pregnancy, into primary healthcare delivery in rural Kenya. Taken together, this work demonstrates feasibility and provides a program model for integrating prevention of preeclampsia into primary healthcare delivery.

In the first paper, I explored end-user perspectives about factors that will influence adoption and acceptability of calcium and iron-folate supplementation recommendations using mixed methods. I also explored strategies that supported adherence. I found that participants in our sample were willing to adopt the recommendations. They all accepted to try the recommendations and took action to consume the supplements. I also demonstrated that alternative regimens were more acceptable to participants, compared to the WHO-recommended regimen. Difficulties with the WHO-recommended regimen included a) forgetting to take the middle dose because pregnant women were usually away from home during the day and b) having to wait for hours after supper to separate the last calcium dose from the iron dose. Moreover, I found that attributes that favored adoption and acceptability of calcium supplement products included being consumable without water, sweet taste, lack of odor, small size and conventionality. Forgetting to take the pills was the main challenge for adherence. Strategies useful for remembering included use of a daily calendar, placing the pill container in a conspicuous location and having a relative serving as a regular reminder. Although participants widely reported side effects, this did not lead to stoppage of supplement consumption. However, when there was pressure from relatives to discontinue supplementation in the face of side effects and there was no reassurance from healthcare personnel, this became a barrier.

The study design in this first paper allowed me to focus on pregnant women in their households and explore multiple factors that will be worth considering in future program design. I circumvented several steps that a pregnant woman would need to take under routine conditions to access supplements in

most settings. Focused support and counseling was also provided to participants. This limits the confidence with which the conclusion about adoption can be extrapolated to routine conditions.

The sampling technique in this paper was purposive. I took steps to ensure sample extensiveness by ensuring diversity based on factors that were assumed to influence pill-taking behaviors. It is not possible to confirm whether there were more important sampling characteristics that deserved more attention, or even whether the characteristics I focused on were particularly relevant in the study population. While this sampling approach provides the opportunity to identify diverse factors that influence adoption and acceptability, the study population is not representative of any known population, and the analytical techniques based on frequency of codes related to particular themes, limit the rigor with which relative importance of the identified factors, relative strength of preference for product attributes and regimen characteristics can be determined.

This paper's key contribution is in demonstrating that multiple contextual factors deserve attention and need be tweaked in program design to foster adoption of these guidelines. It also identifies a set of effective strategies and key factors in our population, providing a springboard as the first study of these guidelines, for future studies to build more rigorous and elaborate theories about drivers of adoption of these guidelines across populations. Future studies should examine the relevance of the identified influencing factors and preferences in study populations with theoretically relevant contextual differences, to extend knowledge about and confidence in the identified determinants of adoption.

The second paper examined design and implementation of a district-wide program to integrate the preventive strategies into routine primary healthcare delivery, guided by the program impact pathway approach. I specifically asked the following questions: (i) were nutritional supplements and other requisite materials (trained staff, job aids and behaviour change materials) for program impact available at the primary healthcare facilities? ; (ii) did healthcare workers appropriately carry out activities/utilize

resources requisite for program impact? ; and (iii) did ANC clients consume supplements and utilize other resources received from primary healthcare facilities?

I found relatively high fidelity of implementation, in that materials requisite for program impact were mostly available at the primary healthcare facilities. Healthcare workers and community health workers appropriately carried out counseling and mobilization activities that were necessary for program impact and ANC clients consumed their supplements and utilized the calendars they received as a cue to action.

This study focused on specification of the pathways to impact and demonstrated that a reasonably well-functioning ante-natal care program can successfully integrate primary preventive measures for preeclampsia and anemia in pregnancy into routine practice. Many ante-natal care programs in developing countries are not functioning properly. The study design and focus of this paper precluded analysis of factors upstream to adoption of recommendations at the sub-national level and delivery of commodity to healthcare facilities. More careful analyses and deeper engagement with socio-cultural, organizational and political economic factors shaping delivery of ante-natal care is necessary, for the knowledge of specific impact pathways and operational interventions focused on addressing bottlenecks in those pathways, to translate into broad and sustained public health impact.

The key contribution of this paper is its demonstration of the feasibility of shifting calcium intakes of a high percentage of pregnant women to being consistent with the dietary reference intakes, with a comprehensive program model. It also specifies key features of a comprehensive program model that can serve as starting points for program planners in various contexts. Future studies should examine the relevance of these program features in other theoretically relevant contexts. Validity of the findings in long-term programs require further research. Novel strategies for motivating appropriate dispensing behavior among healthcare workers need to be developed and tested.

The third paper examined the impact of recommended regimen on supplement consumption, and by extension the calcium status of the study population and population risk of preeclampsia. I hypothesized that a 2-dose (500 mg X 2) regimen with higher acceptability as demonstrated in the first paper, would lead to better adherence and consequently comparable supplement consumption as a 3-dose regimen (500 mg X 3, per WHO-guidelines). Using a cluster-randomized, non-inferiority trial, I found that the 2-dose regimen was inferior to the 3-dose regimen in shifting population calcium intake distribution to the right, suggesting that higher acceptability did not in fact lead to higher adherence. The key contribution of this paper, is that it provides a rigorous empirical test of the hypothesis that a lower regimen is not inferior to the WHO recommendation, in shifting population calcium intake towards the DRI. We find the lower regimen to be actually inferior. There are other important implications of regimen and dosing strategy, that should also influence decisions about maintaining or changing current WHO regimen guidelines. However, this study provides empirical evidence against the argument that equivalence of impact on calcium intake due to poor adherence to the WHO regimen should be a basis for changing current WHO recommendations to lower doses, particularly in the context of a comprehensive program.

The clinical implications of this finding is however not straight-forward. The functional form of the dose-response curve for population calcium intake and preeclampsia risk is not completely resolved. There are still debates about the existence of a threshold level of calcium intake at which preeclampsia risk is impacted as well as the value of such threshold. It is not known whether any shift of the population distribution to the right confers benefit, or whether the further the shift to the right, the higher the level of preeclampsia risk protection conferred, until the upper limit is reached.

The relationship between acceptability on one hand and feasibility or adherence on the other merits further rigorous theoretical and empirical explication. That was not a core objective of this dissertation. It is plausible that preferred actions and options should be more feasible and higher adherence to such actions can be reasonably expected. Higher adherence to less complex recommendations is well

documented. Our findings suggest that this relationship might not be invariant. Further research should identify conditions under which these relationships might not hold, particularly exploring the programmatic context, nature of the recommendation and strength of relative preference.

Finally, it is worthy of note that there are other approaches beyond supplementation that I have not examined, but will be integral for a comprehensive program to prevent preeclampsia and anemia in pregnancy in resource-limited settings. Food-based approaches, such as biofortification, nixtamalization and other food systems interventions should be seriously considered as long term strategies for improving population-level iron and calcium status, because of their potential sustainability.

Low-dose aspirin has also been recommended by the WHO for primary prevention of preeclampsia, and there is need to examine how primary healthcare delivery platforms can safely deliver this intervention. Strengthening preeclampsia surveillance in ante-natal care, timely patient transfer and delivery, in addition to adequate care of children born too soon all have to be considered in crafting an integrated strategy for prevention of preeclampsia and anemia in pregnancy in resource-limited settings[80].

References

1. Mbuya MNN, Jones AD, Ntozini R, et al. Theory-Driven Process Evaluation of the SHINE Trial Using a Program Impact Pathway Approach. *Clin Infect Dis*. 2015;61 Suppl 7(suppl 7):S752-S758. doi:10.1093/cid/civ716.

2. Darnton-Hill I, Mkparu UC. Micronutrients in pregnancy in low- and middle-income countries. *Nutrients*. 2015;7(3):1744-1768. doi:10.3390/nu7031744.

3. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, et al. Global, regional, and national levels and causes of maternal mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet (London, England)*. 2014;384(9947):980-1004. doi:10.1016/S0140-6736(14)60696-6.

4. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Heal*. 2014;2(6):e323-e333. doi:10.1016/S2214-109X(14)70227-X.

5. Hodgins S. Pre-eclampsia as Underlying Cause for Perinatal Deaths: Time for Action. *Glob Heal Sci Pract*. 2015;3(4):525-527. doi:10.9745/GHSP-D-15-00350.

6. Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane database Syst Rev*. 2014;6:CD001059. doi:10.1002/14651858.CD001059.pub4.

7. Imdad A, Bhutta ZA. Effects of calcium supplementation during pregnancy on maternal, fetal and birth outcomes. *Paediatr Perinat Epidemiol*. 2012;26 Suppl 1:138-152. doi:10.1111/j.1365-3016.2012.01274.x.

8. World Health Organization. Guideline: Calcium Supplementation in Pregnant Women. 2013.

9. World Health Organization. *THE GLOBAL PREVALENCE OF ANAEMIA IN 2011*. Geneva; 2015.

10. Stoltzfus RJ. Iron interventions for women and children in low-income countries. *J Nutr*. 2011;141(4):756S - 762S. doi:10.3945/jn.110.128793.

11. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood*. 2013;123(5):615-624. doi:10.1182/blood-2013-06-508325.

12. Duley L. Pre-eclampsia, eclampsia, and hypertension. *BMJ Clin Evid*. 2011;2011. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3275298&tool=pmcentrez&rendertype=abstract. Accessed March 14, 2016.

13. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: a systematic review. *Lancet*. 2006;367(9516):1066-1074. doi:10.1016/S0140-6736(06)68397-9.

14. Cudihy D, Lee R V. The pathophysiology of pre-eclampsia: current clinical concepts. *J Obstet Gynaecol*. 2009;29(7):576-582. doi:10.1080/01443610903061751.

15. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertens An Int J Women's Cardiovasc Heal*. 2014;4(2):97-104. doi:10.1016/j.preghy.2014.02.001.

16. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet (London, England)*. 365(9461):785-799. doi:10.1016/S0140-6736(05)17987-2.

17. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi J-M. Pre-eclampsia: pathophysiology, diagnosis, and management. *Vasc Health Risk Manag*. 2011;7:467-474. doi:10.2147/VHRM.S20181.

18. Belizán JM, Villar J. The relationship between calcium intake and edema-, proteinuria-, and hypertension-getosis: an hypothesis. *Am J Clin Nutr*. 1980;33(10):2202-2210. http://www.ncbi.nlm.nih.gov/pubmed/6999886. Accessed June 16, 2016.

19. Belizán JM, Villar J, Repke J. The relationship between calcium intake and pregnancy-induced hypertension: up-to-date evidence. *Am J Obstet Gynecol*. 1988;158(4):898-902. http://www.ncbi.nlm.nih.gov/pubmed/3284363. Accessed June 16, 2016.

20. Gillon TER, Pels A, von Dadelszen P, MacDonell K, Magee LA. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. *PLoS One*. 2014;9(12):e113715. doi:10.1371/journal.pone.0113715.

21. Cristina P, Jean-Pierre P-R. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems : RHL commentary (last revised: 1 February 2010). *WHO Reprod Heal Libr Geneva*. 2010. http://apps.who.int/rhl/pregnancy_childbirth/antenatal_care/nutrition/cd001059_penasrosaspj_com/en/. Accessed June 6, 2016.

22. Lee SE, Talegawkar SA, Merialdi M, Caulfield LE. Dietary intakes of women during pregnancy in low- and middle-income countries. *Public Health Nutr*. 2013;16(8):1340-1353. doi:10.1017/S1368980012004417.

23. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington DC; 2011.

24. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *J Behav Med*. 2008;31(3):213-224. doi:10.1007/s10865-007-9147-y.

25. World Health Organization. *Guideline: Daily Iron and Folic Acid Supplementation in Pregnant Women*.; 2012.

26. Hallberg L, Rossander-Hulthén L, Brune M, Gleerup A. Inhibition of haem-iron absorption in man by calcium. *Br J Nutr*. 1993;69(2):533-540. http://www.ncbi.nlm.nih.gov/pubmed/8490006. Accessed June 16, 2016.

27. Lönnerdal B. Calcium and iron absorption--mechanisms and public health relevance. *Int J Vitam Nutr Res Int Zeitschrift für Vitamin- und Ernährungsforschung J Int Vitaminol Nutr*. 2010;80(4-5):293-299. doi:10.1024/0300-9831/a000036.

28. Omotayo M, Dickin K, O'Brien K, Neufeld L, De-Regil LM, Stoltzfus R. Calcium supplementation to prevent preeclampsia: translating guidelines into practice in low-income countries. *Adv Nutr*. 2016.

29. World Health Organization. *WHO | Task Shifting: Global Recommendations and Guidelines*. World Health Organization; 2011.

30. The Calcium and Pre-eclampsia (CAP) study. https://pre-empt.cfri.ca/calcium-and-pre-eclampsia-cap-study-who-collaboration. Accessed June 16, 2016.

31. Jarjou LMA, Sawo Y, Goldberg GR, Laskey MA, Cole TJ, Prentice A. Unexpected long-term effects of calcium supplementation in pregnancy on maternal bone outcomes in women with a low calcium intake: a follow-up study. *Am J Clin Nutr*. 2013;98(3):723-730. doi:10.3945/ajcn.113.061630.

32. Li K, Kaaks R, Linseisen J, Rohrmann S. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition

study (EPIC-Hei. *Heart*. 2012;vol: 98((12)):pp: 920-925.

33. Hanzlik RP, Fowler SC, Fisher DH. Relative bioavailability of calcium from calcium formate, calcium citrate, and calcium carbonate. *J Pharmacol Exp Ther*. 2005;313(3):1217-1222. doi:10.1124/jpet.104.081893.

34. Heaney RP, Dowell MS, Bierman J, Hale CA, Bendich A. Absorbability and cost effectiveness in calcium supplementation. *J Am Coll Nutr*. 2001;20(3):239-246. http://www.ncbi.nlm.nih.gov/pubmed/11444420. Accessed June 16, 2016.

35. Heller HJ, Stewart A, Haynes S, Pak CY. Pharmacokinetics of calcium absorption from two commercial calcium supplements. *J Clin Pharmacol*. 1999;39(11):1151-1154. http://www.ncbi.nlm.nih.gov/pubmed/10579145. Accessed June 16, 2016.

36. Mundy GR, Guise TA. Hormonal control of calcium homeostasis. *Clin Chem*. 1999;45(8 Pt 2):1347-1352. http://www.ncbi.nlm.nih.gov/pubmed/10430817. Accessed July 18, 2016.

37. Kovacs CS. Calcium and bone metabolism in pregnancy and lactation. *J Clin Endocrinol Metab*. 2001;86(6):2344-2348. doi:10.1210/jcem.86.6.7575.

38. Fudge NJ, Kovacs CS. Pregnancy up-regulates intestinal calcium absorption and skeletal mineralization independently of the vitamin D receptor. *Endocrinology*. 2010;151(3):886-895. doi:10.1210/en.2009-1010.

39. O'Brien KO, Nathanson MS, Mancini J, Witter FR. Calcium absorption is significantly higher in adolescents during pregnancy than in the early postpartum period. *Am J Clin Nutr*. 2003;78(6):1188-1193. http://www.ncbi.nlm.nih.gov/pubmed/14668282. Accessed June 17, 2016.

40. Young BE, McNanley TJ, Cooper EM, et al. Vitamin D insufficiency is prevalent and vitamin D is

inversely associated with parathyroid hormone and calcitriol in pregnant adolescents. *J Bone Miner Res*. 2012;27(1):177-186. doi:10.1002/jbmr.526.

41. Scholl TO, Chen X, Stein TP. Maternal calcium metabolic stress and fetal growth. *Am J Clin Nutr*. 2014;99(4):918-925. doi:10.3945/ajcn.113.076034.

42. Walt G, Shiffman J, Schneider H, Murray SF, Brugha R, Gilson L. "Doing" health policy analysis: methodological and conceptual reflections and challenges. *Health Policy Plan*. 2008;23(5):308-317. doi:10.1093/heapol/czn024.

43. Kerlinger F. *Foundations of Behavioral Research, (3rd Edition, Revised)*. 3rd Editio. NY: Holt, Reinhart and Winston, Inc; 1973.

44. Glanz K, Rimer B, Viswanath K. *Health Behavior and Health Education: Theory, Research and Practice*. 4th Editio. (Glanz K, Rimer B, Viswanath K, eds.).

45. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A. Making psychological theory useful for implementing evidence based practice: a consensus approach. *Qual Saf Healthc*. 2005;14(1):26-33.

46. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci*. 2009;4:50. doi:10.1186/1748-5908-4-50.

47. Rosenstock I, Strecher V, Becker M. Social learning and the health belief model. *Health Educ Q*. 1988;15(2):175-183.

48. Ajzen I. Perceived Behavioral Control, Self-Efficacy, Locus of Control, and the Theory of Planned Behavior. *J Appl Soc Psychol*. 2001;52(1):27-58.

49. *Guideline: Calcium Supplementation in Pregnant Women*. World Health Organization; 2013. http://www.ncbi.nlm.nih.gov/pubmed/24006556. Accessed June 16, 2016.

50. Pennington KA, Schlitt JM, Jackson DL, Schulz LC, Schust DJ. Preeclampsia: multiple approaches for a multifactorial disease. *Dis Model Mech*. 2012;5(1):9-18. doi:10.1242/dmm.008516.

51. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet (London, England)*. 2015. doi:10.1016/S0140-6736(15)00070-7.

52. Galloway R, McGuire J. Determinants of compliance with iron supplementation: supplies, side effects, or psychology? *Soc Sci Med*. 1994;39(3):381-390. http://www.ncbi.nlm.nih.gov/pubmed/7939855. Accessed June 17, 2016.

53. Galloway R, Dusch E, Elder L, et al. Women's perceptions of iron deficiency and anemia prevention and control in eight developing countries. *Soc Sci Med*. 2002;55(4):529-544. http://www.ncbi.nlm.nih.gov/pubmed/12188461. Accessed June 17, 2016.

54. Aguayo VM, Koné D, Bamba SI, et al. Acceptability of multiple micronutrient supplements by pregnant and lactating women in Mali. *Public Health Nutr*. 2005;8(1):33-37. http://www.ncbi.nlm.nih.gov/pubmed/15705243. Accessed June 17, 2016.

55. Young SL, Ali SM. Linking traditional treatments of maternal anaemia to iron supplement use: an ethnographic case study from Pemba Island, Zanzibar. *Matern Child Nutr*. 2005;1(1):51-58. doi:10.1111/j.1740-8709.2004.00002.x.

56. Dairo MD, Lawoyin TO. Demographic factors determining compliance to iron supplementation in pregnancy in Oyo State, Nigeria. *Niger J Med*. 15(3):241-244. http://www.ncbi.nlm.nih.gov/pubmed/17111751. Accessed June 17, 2016.

57. Seck BC, Jackson RT. Determinants of compliance with iron supplementation among pregnant

women in Senegal. *Public Health Nutr*. 2008;11(6):596-605. doi:10.1017/S1368980007000924.

58. Tessema J, Jefferds ME, Cogswell M, Carlton E. Motivators and barriers to prenatal supplement use among minority women in the United States. *J Am Diet Assoc*. 2009;109(1):102-108. doi:10.1016/j.jada.2008.10.013.

59. Baxter J-AB, Roth DE, Al Mahmud A, Ahmed T, Islam M, Zlotkin SH. Tablets are preferred and more acceptable than powdered prenatal calcium supplements among pregnant women in Dhaka, Bangladesh. *J Nutr*. 2014;144(7):1106-1112. doi:10.3945/jn.113.188524.

60. Proctor E, Silmere H, Raghavan R, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Adm Policy Ment Health*. 2011;38(2):65-76. doi:10.1007/s10488-010-0319-7.

61. Manoff Group. Trials of Improved Practices: Giving Participants a Voice in Program Design. http://www.manoffgroup.com/approach_developing.html. Accessed July 7, 2016.

62. ATLAS/ti. Version 4.2. (1999) Berlin,. 1999.

63. Lofland J, Lofland L. *Analyzing Social Settings: A Guide to Qualitative Observation and Analyses*. 4th ed.; 2006.

64. Creswell J. *Research Design: Qualitative, Quantitative, and Mixed Methods Approaches*. 4th ed. Sage Publications; 2014.

65. Morgan D. *Focus Group as Qualitative Research*. Sage Publications; 2002.

66. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.

doi:10.1016/j.jbi.2008.08.010.

67. StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP. http://www.stata.com/support/faqs/resources/citing-software-documentation-faqs/. Accessed March 29, 2016.

68. Young SL, Blanco I, Hernandez-Cordero S, Pelto GH, Neufeld LM. Organoleptic properties, ease of use, and perceived health effects are determinants of acceptability of micronutrient supplements among poor Mexican women. *J Nutr*. 2010;140(3):605-611. doi:10.3945/jn.109.113498.

69. Mbuya MNN, Jones AD, Ntozini R, et al. Theory-Driven Process Evaluation of the SHINE Trial Using a Program Impact Pathway Approach. *Clin Infect Dis*. 2015;61 Suppl 7:S752-S758. doi:10.1093/cid/civ716.

70. Kim S, Habicht J-P, Menon P, Stoltzfus R. How do programs work to improve child nutrition? :: IFPRI Publications. http://ebrary.ifpri.org/cdm/ref/collection/p15738coll2/id/124932. Accessed March 29, 2016.

71. Habicht J-P, Pelto GH. From biological to program efficacy: promoting dialogue among the research, policy, and program communities. *Adv Nutr*. 2014;5(1):27-34. doi:10.3945/an.113.004689.

72. Palacios C P-RJ. Guideline: Daily Iron and Folic Acid Supplementation in Pregnant Women. *WHO Reprod Heal Libr Geneva*.

73. Kassebaum NJ. The Global Burden of Anemia. *Hematol Oncol Clin North Am*. 2016;30(2):247-308. doi:10.1016/j.hoc.2015.11.002.

74. Camargo EB, Moraes LFS, Souza CM, et al. Survey of calcium supplementation to prevent preeclampsia: the gap between evidence and practice in Brazil. *BMC Pregnancy Childbirth*.

2013;13:206. doi:10.1186/1471-2393-13-206.

75. Martin SL, Seim GL, Wawire S, Chapleau GM, Young SL, Dickin KL. Translating formative research findings into a behaviour change strategy to promote antenatal calcium and iron and folic acid supplementation in western Kenya. *Matern Child Nutr*. 2016. doi:10.1111/mcn.12233.

76. Dickin, K.; Griffiths, M.; Piwoz, E.G. Designing by Dialogue: A Program Planners' Guide to Consultative Research for Improving Young Child Feeding; Academy for Educational Development: Washington, DC, USA, 1997. - Open Access Library. http://www.oalib.com/references/9079992. Accessed March 29, 2016.

77. Omotayo MO, Dickin KL, Chapleau GM, et al. Cluster-Randomized Non-Inferiority Trial to Compare Supplement Consumption and Adherence to Different Dosing Regimens for Antenatal Calcium and Iron-Folic Acid Supplementation to Prevent Preeclampsia and Anaemia: Rationale and Design of the Micronutrient . *J Public health Res*. 2015;4(3):582. doi:10.4081/jphr.2015.582.

78. HealthBridge C. *Report on the Dietary Data of the Kenya National Micronutrient Survey*.; 2014.

79. Meyers DC, Katz J, Chien V, Wandersman A, Scaccia JP, Wright A. Practical implementation science: developing and piloting the quality implementation tool. *Am J Community Psychol*. 2012;50(3-4):481-496. doi:10.1007/s10464-012-9521-y.

80. Omotayo M, Dickin K, Stolzfus R. Perinatal Mortality Due to Pre-Eclampsia in Africa: A Comprehensive and Integrated Approach Is Needed. *Glob Heal Sci Pract*. 2016;4(2):350-351. doi:10.9745/GHSP-D-16-00054.