Effect of Prenatal Zinc Supplementation on Malarial Morbidity, Pregnancy Anaemia and Birth Weight

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ABSTRACT

Anaemia and malaria are two related problems of public health significance in malaria-endemic countries including Ghana that continue to impact negatively on pregnancy outcomes, despite interventions being put in place to address them. The reasons for the apparent lack of efficacy of routine iron supplementation in reducing the risks of preterm and other adverse pregnancy outcomes are not clearly established in Ghana. It is not also known whether all pregnant women benefit from iron supplementation and whether there are some other factors that limit the effectiveness of prenatal iron supplementation. This study tested the primary hypothesis that 'prenatal zinc supplementation in combination with malaria prophylaxis and an iron and folic acid intervention package in a zinc-deficient and malaria-endemic population will increase mean birth weight.

A prospective double-blind, randomised controlled trial (RCT) was therefore conducted in Ghana from September 2005 to November 2006. The intervention group received combined 40 mg zinc as zinc gluconate and 40 mg elemental iron as ferrous sulphate supplement. The Control Group received 40 mg elemental iron as ferrous sulphate. Both groups received also malaria chemoprophylaxis, with sulfadoxine pyrimethamine (SP) and 400 µg folic acid.

The effect of iron-zinc supplementation on mean birth weight, geometric mean plasma zinc concentrations, mean Hb change and geometric mean serum ferritin concentrations at 34-36 weeks of gestation was masked by a strong interaction between supplement type and the iron status of participants.

Overall, prenatal iron-zinc supplementation resulted in no detectable difference in mean birth weight and length of gestation between iron-zinc supplemented group and the group that received standard routine antenatal services. However, among anaemic women (Hb <9.0 g/dl) and/or iron deficient women (serum ferritin <35µg/L), adjusted mean birth weight of babies born to women in the Iron-zinc Group was 131g higher than the adjusted mean birth weight of babies born to women who received the standard treatment (3223 g versus 3092 g), $F(1, 121) = 4.210$, $p = 0.042$.

Joint iron and zinc supplementation together with SP was protective of malaria parasite build-up during pregnancy, compared to iron and SP (the standard malaria prophylaxis). Iron-zinc supplementation resulted in a significant difference in adjusted malaria parasite densities, $F (1, 20) = 4.744$, $p = 0.042$.

Prenatal iron-zinc supplementation improved zinc status and had no adverse effect on iron status indicators. In spite of the presence of a strong inhibitory effect of high maternal iron status on iron utilisation, iron and zinc provided in the ratio of 1:1 prevented a significant depletion in maternal iron stores of pregnant women. The geometric mean serum ferritin was significantly higher in the iron-zinc, compared to the standard treatment groups (22.9 µg/L versus 16.9 µg/L), $F (1, 153) = 6.336$, $p = 0.013$.

The data of this study do not support current practice that all pregnant women seeking antenatal services in Ghana be given iron supplements. The evidence further suggests combined iron and zinc supplementation is a better option than iron alone supplementation. Iron-zinc supplementation for iron deficient pregnant women deserves consideration by health policy makers in order to avoid the needless negative impact of iron and zinc deficiencies.

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CHAPTER 1
INTRODUCTION

1.1 Background

Malaria and maternal anaemia are common and continue to be significant public health problems in pregnancy especially in developing countries (World Health Organization, 1992c; Menendez et al., 2000). Despite interventions being put in place to substantially reduce the burden of these problems in Ghana, they continue to impact negatively on pregnancy outcomes. The fact that these interventions are not achieving the desired results implied more could be done in this regard. To prevent problems such as maternal anaemia, adverse pregnancy outcomes and neural tube defects, iron and folic acid supplements are routinely given to pregnant women who attend antenatal services. The World Health Organization (WHO) recommends a daily iron supplementation (60 mg/d) for all pregnant women of reproductive age in countries where the prevalence of anaemia is more than 40% (Stoltzfus & Dreyfuss, 2000). In line with these recommendations regarding anaemia control, the policy in Ghana is that 60 mg of elemental iron and 400 µg folic acid are prescribed for all pregnant women who attend antenatal services.

However, a National Nutrition Anaemia Survey reported 64.4% prevalence of anaemia among pregnant women (Nutrition Unit of Ghana Health Service (GHS), 1995). Analysis of birth weight data collected from major hospitals in the Upper West Region of Ghana in 2003 showed the incidence of low birth weight (LBW) ranged from 15.0% to 29.1% (Upper West Regional Health Directorate, 2004). The reasons for the apparent lack of efficacy of routine iron supplementation in reducing the prevalence of anaemia, risks of LBW and other adverse pregnancy outcomes were not clearly established. It was also not known whether all pregnant women benefit from iron supplementation and whether there are some other factors that limit the effectiveness of iron supplementation.

Chemoprophylaxis, previously with chloroquine but now with sulfadoxine pyrimethamine (SP), is also prescribed for preventing malaria. Malaria continues to impact on the Ghanaian population, as an estimated 13.8% of pregnant women reporting ill at health institutions and 9.4% of all deaths in pregnant women being attributable to malaria (Yeboah-Antwi & Marfo, 2004). Used alone, SP may be safe and effective in preventing malaria during pregnancy. However, when administered together with other nutrients as pertains in Ghana, there may be some problems regarding interaction, of which little was known prior to this study.

1.1.1 Study Location

The study was carried out in the Upper West Region of Ghana, where there are high levels of LBW (Table 1.1). In Ghana, malaria is hyper-endemic, predominantly caused by *Plasmodium falciparum*, though *P. malariae* and *P. ovale* can also be found (Brown et al., 2000). Birth weight data collected from major hospitals in the Upper West Region in 2003 showed LBW was a problem at all of them (Table 1. 1) (Upper West Regional Health Directorate, 2004). A prevalence of LBW of more than 15% usually indicates a major public health problem of child and maternal nutrition. A Sentinel nutrition surveillance report in 2001, showed 34% of the under five children surveyed were chronically malnourished, 16% suffered from acute malnutrition, and 28% were underweight (Upper West Regional Health Services, 2001)

Table 1.1 Prevalence of LBW in Upper West Region of Ghana

Hospital	Total Births	LBW % (n)
WA	1,678	15.0 (252)
JIRAPA	607	21.4 (130)
NANDOM	515	29.1 (150)
LAWRA	322	17.4 (56)
TOTAL	3,122	18.8 (588)

The high levels of LBW and the prevalence of stunting, wasting, under weight babies and anaemia in the Upper West Region made it an appropriate place for conducting this study.

The Republic of Ghana is located on the West Coast of Africa (Fig 1.1) and occupies an area of 238,537 km2. Ghana is bordered by the Republic of Togo to the East, La Cote d'Lvoire to the West, Burkina-Faso to the North and to South by the Gulf of Guinea. It gained its political independence from Britain on 6th March 1957. The population according to a census in 2000 was 18.8 million with a growth rate of 2.4%. Some other development indicators of Ghana are shown in the Table 1.2.

Ghana is divided into ten administrative regions; the most recently created being the Upper West Region. This study was carried out in this region because it is the most deprived in terms of resources and has one of the highest rates of malnutrition. The Upper West Region, which is situated in the North-Western part of Ghana, lies between longitude $1^{o}25''$W and $2^{o}45''$ and latitudes $9^{o}30''$N and 11^{o}N. It covers a geographical area of 18,476 km^2, which constitute 12.7% of the total land area of Ghana. Using this Region's population growth rate of 1.7% and the 2000 Population and Housing Census, the Upper West Region had a projected population of 616,802 for 2004 (Upper West Regional Health Directorate, 2004).

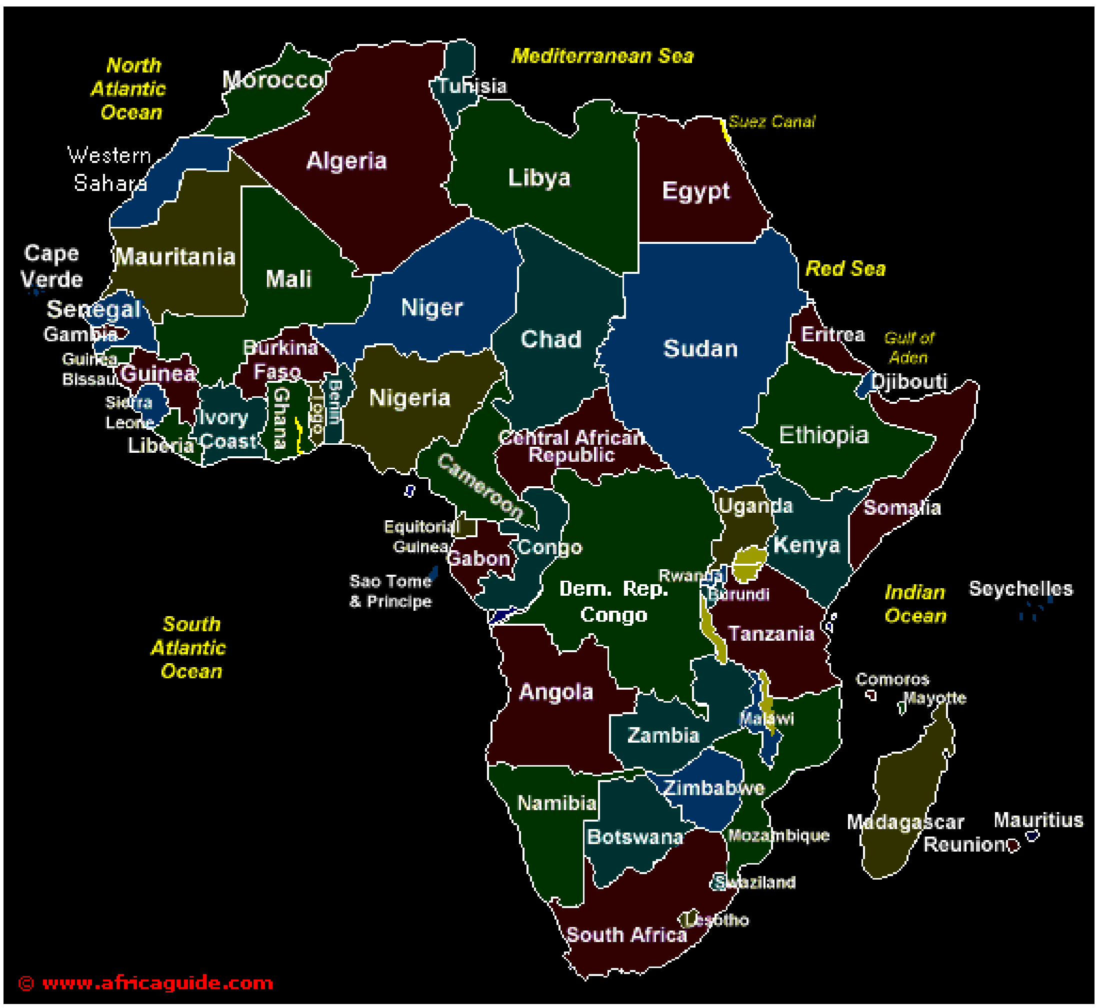

Figure 1.1 Map Africa showing countries in Ghana located on the West Coast of Africa (courtesy: Africa Guide)

Table1.2 Basic Socio-demographic Indicators of Ghana

INDICATOR	Value
Population in 2005	22.1 Million
Age structure: 0-14 years 15-64 years 65 years and above	41.8% 55.3% 3.47%
Life expectancy (2005) in years	57.5
Human Development Index (HDI)	129 out of 175 countries
Per capita National Income (GNI) for 2005 (US$)	450.0
Child malnutrition (underweight) in 1999	24.9 %
Infant mortality (2005)	68/1000
Under 5 mortality (2005)	112/1000
Neonatal Mortality rate (MMR) (2004)	43/1000 live births
Maternal Mortality (1985-2001)	210/100,000 live births
Adult literacy rate (2006)	57.9%

Source: (Ghana Website, 2004; UNDP, 2004; World Bank Group, 2005)

1.2 Justification for the Study

LBW constitutes a major public health problem worldwide especially in less developed countries. It is estimated that 16.0% of babies in developing countries (or 17.0 million infants annually) are born with LBW at term (ACC/SCN, 2000). Healthy growth and development of every child is dependent to some extent on his/her foetal growth. LBW is reported to be the most important risk factor for infant mortality and morbidity (McCormick, 1985; Kramer, 1987b; Villar et al., 1990; Balcazar & Haas, 1991). LBW has also been linked to the high prevalence of stunting seen in developing countries and may be implicated in the etiology of chronic dietary diseases in adulthood (Barker, 1998; ACC/SCN, 2000; Barker & Fall, 2000).

In the Year 2000, it was estimated that 32.5% of children aged less than five years in developing countries were stunted (ACC/SCN, 2000). The persistent high rates of LBW and stunting are sources of worry to health and human development advocates. It is known women born with LBW and those of short stature tend to give birth to LBW babies, thereby perpetuating an intergenerational cycle of under nutrition (Klebanoff et al., 1989). This cycle needs to be broken if any headway is to be made in the fight against child malnutrition.

LBW is a manifestation of intrauterine growth restriction (IUGR), preterm birth or an interaction both of these factors. In order to reduce the prevalence of LBW, its underlying determinants need to be identified and addressed. Though there are multiple etiologies of IUGR, maternal under-nutrition including anaemia, malarial infection and low gestational weight gain are key determinants in many developing countries (Kramer, 1987b; Standing Committee on Nutrition (SCN), 2000; Steketee, Nahlen, Parise & Menedendez, 2001). Maternal under-nutrition in early pregnancy can result in poor expansion of plasma volume and inadequate development of maternal tissues that support foetal growth. Gestation is a critical period that involves rapid cell division, protein synthesis and organ development. Adequate maternal nutrition is therefore essential for normal foetal growth (Carmichael & Abrams, 1997).

The important role of some specific nutrients in foetal growth has also been well documented. In particular, iron and zinc requirements are high during pregnancy. Furthermore, empirical evidence suggests iron and zinc deficiencies often occur together (Yokoi et al., 1994; International Zinc Nutrition Consultative Group (IZiNCG), 2004a). Adequate iron status during pregnancy, especially in early pregnancy, is crucial for reducing the risk of IUGR, preterm birth, LBW and perinatal mortality (Scholl & Hediger, 1994; Allen, 1997; Ronnenberg et al., 2004). Other studies have shown that maternal anaemia contributes independently to LBW through IUGR (Brabin & Piper, 1997; Ismail et al., 2000; Verhoeff et al., 2000).

Malaria is an infection of the red blood cells caused by a protozoan of the genus *Plasmodium.* Malaria is usually transmitted from infected individuals by the bite of an *Anopheles* mosquito. Malarial infection in pregnancy is particularly critical because it increases placental accumulation of the malaria parasites, thus obstructing free exchange of nutrients and oxygen between the placenta and the foetus and this can lead to LBW (Garner & Brabin, 1994; Steketee, Nahlen, Parise & Menedendez, 2001). Malaria causes a decrease in iron absorption (Wilcox et al., 1985; Molyneux et al., 1989), sequestration of iron (Abdalla, 1990) and it is also known to cause hemolytic anaemia by destroying the red blood cells (Weatherall & Abdalla, 1987).

Malaria and maternal under-nutrition including anaemia are therefore important challenges requiring effective public health strategies. In particular, interventions that address these problems concurrently are urgently needed to prevent impaired foetal growth.

Zinc, by virtue of its unique properties, is one particular essential nutrient, which in combination with other interventions has the potential to ameliorate the effects of some of the major etiological factors of IUGR. Zinc deficiency often co-exists with other nutrient deficiencies in malaria-endemic countries and it is estimated approximately 82% of pregnant women worldwide are likely to suffer from zinc deficiency (Sandstead, 1991; Caulfield et al., 1998). Zinc deficiency impairs the immune function and resistance to infections (Black & Sazawal, 2001). Zinc-deficient pregnant women resident in malaria-endemic areas may therefore be more predisposed to delivering IUGR babies because of reduced resistance to malarial infections. Apart from its involvement in foetal growth, zinc is reported to be a carrier of nutrients across the placenta to the foetus (Lira et al., 1998). By implication, zinc deficiency may impair the transport of nutrients with the resultant consequence of foetal under nutrition. The significant role zinc has on foetal growth made it an obvious point of interest for this study. Zinc deficiency can also lead to anorexia (Prasad 1983; Golden, 1988), and the associated reduced food intake can negatively affect weight gain during pregnancy which is a key determinant of birth weight (Carr-Hill & Pritchard, 1985; Miller, 1989; Yang, 1989). Prenatal zinc supplementation may correct anorexia associated with zinc deficiency and thus enhance maternal weight gain during pregnancy.

Dietary zinc intake alone is most unlikely to meet the increased zinc requirement during pregnancy, thus zinc supplementation may be necessary. However, available evidence is mixed with regards the benefits of zinc alone supplementation on foetal growth, preterm delivery and length of gestation. Meta-analyses and the systematic reviews of randomised clinical trials (RCT) that evaluated the efficacy of nutritional interventions including maternal zinc supplementation showed no evidence of a differential effect on foetal growth, LBW and mean birth weight (Gulmezoglu et al., 1997; Merialdi et al., 2003; Villar, Merialdi, Gülmezoglu et al., 2003). Consequently, the public health justification for including zinc as an antenatal supplement has not been appreciated. This is partly due to the fact that its role in improving pregnancy outcomes is still not entirely clear, as there are conflicting research findings.

For further research in the area of maternal zinc supplementation, these reviews recommended among others the following:

- the need for a continuous search for solutions to adverse pregnancy outcomes;
- the need to identify new outcomes and evaluate their biological and clinical relevance;

- evaluate a combination of interventions; and
- an accurate assessment of the causes of outcomes.

The question of whether zinc should be included as an ante-natal supplement in the search for solutions to the problems of maternal anaemia, malaria and IUGR is salient and merited further research especially in malaria-endemic countries such as Ghana. Available evidence also suggested that a combination of interventions is likely to reduce a multi-faceted problem such as IUGR (de Onis, Villar et al., 1998). Though iron and zinc deficiencies are known to occur together, there are a few supplementation studies that have addressed this concurrently in pregnancy. Consequently, information regarding their joint efficacy on the outcomes stated in the beginning of this paragraph and the interactions/antagonism of these two vital nutrients is scanty in the literature.

The safe and efficient use of zinc as a supplement with other nutrients is critical and deserves attention because of possible adverse interactions. Some research findings have reported some interactions between zinc and other nutrients including iron and copper that could have a negative impact on health (Simmer et al., 1987; Davidsson et al., 1995; Tamura & Goldenberg, 1996). Some other questions that needed to be answered before zinc could possibly be recommended for routine supplementations in a malaria-endemic country include the following:

- Can zinc supplementation reduce the effect of malarial infection (that is, malaria rate and parasitemia)?
- Can zinc supplementation reduce maternal anaemia?
- What pregnancy outcome differences are associated with combined zinc and iron supplementation?
- Can the use of iron and zinc supplement in a 1:1 ratio minimize interaction effects?
- How frequently should zinc supplements be taken to maximize efficacy?
- Is the usual dietary zinc intake of pregnant women adequate to prevent the adverse effects of zinc deficiency on pregnancy outcome?
- Do all pregnant women need iron and zinc supplements?

It is within the context of answering these questions that the present study was timely and relevant.

1.3 Problem Statement

Malarial infection, iron-deficiency anaemia and LBW continue to remain significant public health problems, despite various interventions being put in place to ameliorate them. In order to reduce these problems in Ghana, pregnant women who attend ante-natal services are given malaria chemoprophylaxis together with iron and folic acid but without zinc supplements. Proxy indicators, which reflect zinc deficiencies strongly, suggested the risk of zinc deficiency in Ghana may be high.

Improved maternal zinc status may boost naturally acquired immunity against malarial infection during pregnancy and thereby reduce its adverse consequences on foetal growth. This is strengthened by some research which suggested childhood zinc supplementation may reduce the effect of malaria morbidity in children (Bates et al., 1993; Shankar et al., 2000). The extent to which zinc supplementation may protect against the effect of *Plasmodium falciparum* infection in pregnancy did not, however, appear to be known and therefore merited further research. Furthermore, there has been only limited research on the combined effect of iron and zinc supplementation on foetal growth, maternal anaemia and malaria.

1.4 Aim and Objectives of Study

The aim of this study was to explore whether there are benefits associated with the addition of zinc to the routine malaria chemoprophylaxis, iron and folic acid intervention package for pregnant women in Ghana.

The specific objectives were to evaluate the effect of combined iron and zinc supplementation in a malaria-endemic environment on:

a. gestational maternal anaemia, iron and zinc status;

b. malaria rate and parasitemia in pregnancy;

c. mean birth weight;

d. incidence of LBW, IUGR and preterm delivery; and

e. length of gestation.

1.5 Hypotheses

The primary and secondary hypotheses to the study are stated below.

1.5.1 Primary Hypothesis

Prenatal zinc supplementation, in combination with a malaria prophylaxis, iron and folic acid intervention package in a zinc-deficient and malaria-endemic population, will increase mean birth weight.

1.5.2 Secondary Hypotheses

Prenatal iron-zinc supplementation as an adjunct to chemoprophylaxis with SP (SP) will:

a. reduce malaria rate and parasitemia;

b. reduce prevalence of maternal anaemia;

c. reduce incidence of LBW, IUGR and preterm delivery; and

d. Increase length of gestation.

1.6 Significance of the Study

Findings of the study are expected to be useful in various ways. Firstly, it is anticipated the results may clarify the potential effect of joint iron and zinc supplementation on foetal growth in malaria-endemic areas and thus contribute to the body of knowledge on zinc nutrition, especially its impact on birth weight. The findings could also serve as a practical guide for introducing zinc as an antenatal supplement and as a basis for further research including the linkages between iron and zinc supplementation programs.

The potential users of the findings will include local health authorities in Ghana and in other developing countries, non-governmental organisations (NGOs) working on micronutrient control programs, research institutions, and pharmaceutical organisations.

1.7 Conceptual Framework

LBW results mainly from preterm birth or IUGR. In a malaria-endemic environment in which the population is likely to be zinc-deficient, important hormonal and immune processes that require zinc may be compromised. In particular, the concentration of insulin-like growth factor-1 (IGF-I) may be reduced (Bauer et al., 1998; MacDonald, 2000; Low et al., 2001) and consequently, affect foetal growth. Increased susceptibility to malarial infections can lead to reduced supply of oxygen and nutrients to the fetus. It is therefore hypothesized in this study that increased maternal zinc intake through zinc supplementation in zinc-deficient malaria-endemic populations may enhance cellular growth, reduce the effect of malarial infection, prevent anorexia in pregnancy and thus improve birth weight. The possible pathways through which this could occur are shown in Fig. 1.2. The main mechanisms of effect may be through zinc promotion of cell division, hormone metabolism and enhanced immunocompetence.

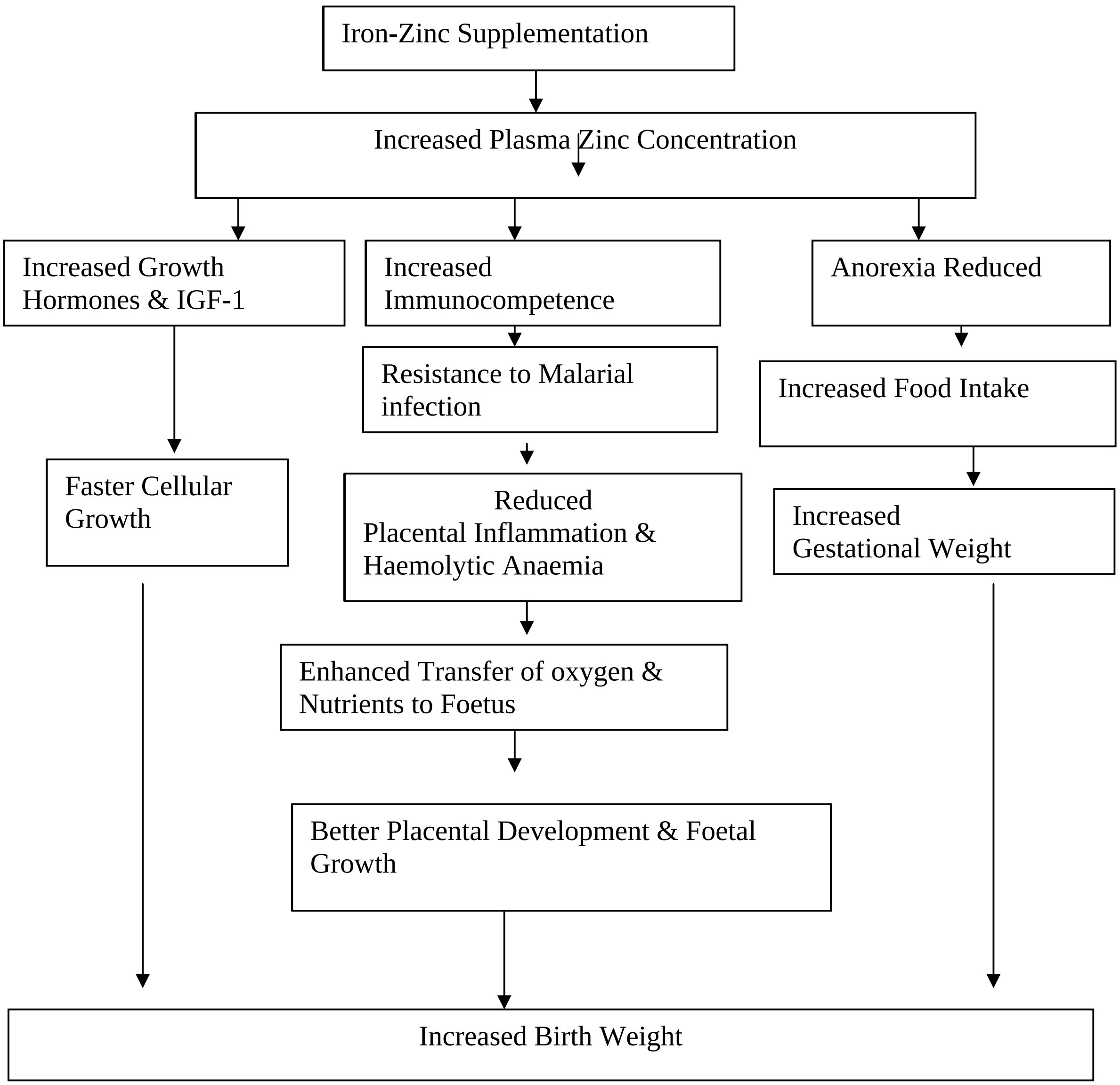

Fig. 1.2 Potential outcomes of prenatal zinc supplementation

1.8 Chapter Summary

In this chapter, the research problems were identified and justified. The hypotheses including specific objectives of this study were presented. The location where the study was conducted was described.

The rest of this thesis covers literature review which give greater details of what has already been done and what needed to be done in the research area. Furthermore, a detailed description of the research methodology and results are reported.

1.9 Operational Definitions of Terms and Concepts

The definitions of some of the terms used in this document are as follows:

- LBW is defined as a birth weight less than 2500 grams irrespective of gestational age (World Health Organization, 1992b).
- IUGR is a term that refers to a condition in which a foetus is constrained to achieving its genetically endowed potential size. Operationally, it is defined as birth weight below the 10^{th} percentile of the recommended gender-specific foetal weight for gestational age reference curves (Williams et al., 1982; WHO, 1995).
- Classification of the severity of anaemia was based on WHO guidelines (World Health Organization, 1992c).
- Iron deficiency anaemia was defined as anaemia with concurrent low serum ferritin concentrations < 12.0 µg/L (DeMaeyer & Adiels-Tegman, 1985).
- Iron deficiency was defined as serum ferritin concentrations (SF) <35.0 µg/L (Puolakka, 1980).
- Iron-replete status (that is Hb =11.0 g/dl and SF >20 µg/L) (Institute of Medicine, 1993).
- Malaria chemoprophylaxis consisted of administration of sulfadoxine-pyrimethamine (1,500 mg sulfadoxine and 75 mg pyrimethamine) on three occasions starting from the 16 weeks of gestation.
- Intention-to-treat analysis: the method of including all data from randomised subjects according to original treatment assignment, regardless of compliance.
- Malarial infection is defined as the presence of asexual forms (trophozoites and schizonts) of *P. falciparum* parasite in a thick smear of peripheral blood.

CHAPTER 2
LITERATURE REVIEW

Malaria and maternal anaemia are common and continue to be of significant public health problems in pregnancy especially in developing countries (World Health Organization, 1992c; Menendez et al., 2000), despite various interventions being put in place to address them. One of the major consequences of malaria and maternal anaemia is LBW. This literature review covers three main areas including:

a) The epidemiological evidence of the magnitude, determinants and consequences of LBW.

b) An assessment of the efficacy of iron and zinc supplementation on maternal anaemia, malaria and adverse pregnancy outcomes.

c) Identification of further research directions.

2.1 Low Birth Weight: A Public Health Problem

Birth weight is reported to have a significant influence on a child's growth and development (Olinto et al., 1993; Arifeen et al., 2000; Kalanda et al., 2005; Motta et al., 2005). Unfortunately, LBW continues to affect a large proportion of infants in developing countries and may therefore contribute to the high prevalence of chronic child under nutrition in these countries (de Onis, Blossner et al., 1998). It is further estimated 16.0% of babies in developing countries (or 17.0 million infants annually) have LBW at term (ACC/SCN, 2000). In the Year 2000, it was estimated 32.5% of children aged less than five years in developing countries were stunted (ACC/SCN, 2000). This is a major human developmental problem with profound consequences for individuals, communities and whole populations.

Several studies have identified LBW as an important risk factor for neonatal and infant mortality and impaired postnatal growth (McCormick, 1985; Kramer, 1987b; Barker & Fall, 2000). Apart from its impact on child growth and mortality, LBW is reported to contribute substantially to child morbidity such as diarrhea and pneumonia (Bukenya et al., 1991; Fonseca et al., 1996; Lira et al., 1996). LBW infants are also more likely than those of normal birth weight to suffer from intellectual impairment (Harvey et al., 1982; Grantham-McGregor, 1998; Barker & Fall, 2000).

The consequences of LBW are reported to continue through to adulthood. It has been suggested the long-term consequence of LBW is an increased risk of adult chronic diseases, including cardiovascular disease, obesity, hypertension and adult-onset diabetes (Curhan et al., 1996; Barker, 1998). Thus, the persisting high incidence of LBW, along with a world-wide increase in obesity, may contribute to an epidemic rise of cardiovascular disease and Type II diabetes in developing countries (Fall, 2001; Yajnik, 2001). Emerging evidence however, indicates the problem of Type II diabetes may affect very high birth weight as well. One recent meta-analysis examined the relationship between birth weight and the risk of Type II diabetes and reported that high birth weight was equally a source of concern as it was associated with increased risk of Type II diabetes in later life to the same extent as LBW (Harder et al., 2007).

The role LBW plays in the prevalence of childhood stunting, morbidity, mortality and adult chronic disease patterns justifies the need for research to identify effective primary prevention strategies to minimise the prevalence and effects of LBW. Despite its documented adverse outcomes, there appears to be uncertainty about how best to reduce the incidence of LBW (Martorell et al., 1998). In order to reduce the prevalence of LBW, the underlying determinants need to be identified and addressed.

2.2 Determinants of LBW

LBW results mainly from either preterm birth (that is, before 37 weeks of gestation) or intra-uterine growth restriction (IUGR) (Kramer, 1987a). It has been reported that LBW in developing countries is largely due to IUGR, while LBW in the developed countries is mostly due to preterm births (Villar & Belizan, 1982; Sachdev, 1997; Ashworth, 1998). In developing countries, an estimated 30 million infants are born every year with IUGR, representing 24% of all newborn babies (Philip, 2000). Many factors are reported to affect length of gestation and foetal growth and subsequent birth weight. Kramer (1987a) considered the major determinants of LBW in developing countries to include:

- low pre-pregnancy body mass index (BMI);
- low gestational weight gain;