RELATIONSHIP BETWEEN INFANT BIRTH WEIGHT ≤2000GMS. AND MATERNAL ZINC LEVELS AT MUHIMBILI NATIONAL HOSPITAL, DAR-ES-SALAAM TANZANIA

By

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A dissertation submitted in partial fulfillment of the requirements for the degree of Master of Medicine (Paediatrics and Child Health) of the University of Dar-es-Salaam.

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October 2003

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the University of Dar-es-Salaam a dissertation entitled: Relationship between infant birth weight ≤ 2000gms and maternal zinc levels at Muhimbili National Hospital, in partial fulfillment of the requirements for the degree of Master of Medicine (Paediatrics and Child Health).

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ACKNOWLEDGEMENT

I convey my sincere gratitude to Professor Karim Manji and
Dr. Emmanuel Munubhi who tirelessly supervised this Dissertation.
I wish to thank the staff of the Department of Paediatrics and Child Health for constructive criticisms, constant encouragement and material assistance throughout the period.
I also thank labour ward staff especially Mrs. Festa Mwambungu and Joyce Mndolwa who assisted me in collection of specimens; Mr. Joseph Phillip of Department of Biochemistry, University of Dar-es-Salaam for the tiresome work of analyzing zinc concentration of samples; Mrs. Rose Mpembeni of Department of Public Health-MUCHS for statistical data analysis.
I am indebted to the mothers who consented to participate in this study and to their babies without whom this work would not have been possible.
Lastly special acknowledgements go to my family who gave me moral support, bearing with patience my long absence from home in order to complete this work.

DEDICATION

To my late mother Ma Elesi Ezekiel, my father Alhaji Ab-Bakari Galiatano, my beloved husband Laurian and to my daughter Dalila and my son Ian.

ABSTRACT

Background

The incidence of Low Birth Weight (LBW) in Tanzania is among the highest in the world. It accounts for more than 16% of all deliveries. Despite efforts by the Ministry of Health (MOH) using different intervention measures to reduce it, there are no improvement as shown by the data of 1979 (15%), 1990 (16%) and on recent estimates of 2000 and 2001 (18%). LBW is a reliable indicator of (risk of death, growth failure, neurodevelopment problems, recurrent infections and hospitalization). There is a need to reduce the incidence of LBW. Maternal zinc deficiency has been noted in a number of settings to impair growth and development of the fetus.

In Tanzania, there is little information on zinc deficiency and its effect on birth weight of infants. However, based on dietary intakes of many communities, it is likely that zinc deficiency is a problem.

Study objective

To determine the relationship between infant birth weight ≤ 2000gms and maternal zinc status.

Study design

Unmatched case control.

Study Setting

The study was conducted at Muhimbili National Hospital (MNH) in labour ward, from July to September 2002.

Study population

The study population consisted of infants with birth weight of ≤2000gms and their mothers as cases and infants with birth weight of ≥3000gms and their mothers formed the control group. Enrolled were 81 and 84 infants and their mothers as cases and controls respectively who consented for the study.

Methodology

The study used convenient sampling technique. The first mother with an infant weighing ≤2000gms who consented was recruited as a case and the consenting mother who had a normal birth weight infant was recruited as a control. Subsequently all eligible subjects were recruited until the estimated sample size was reached.

Maternal and infants cord blood samples were taken after delivery. Plasma zinc was analyzed using Atomic Absorption Spectophotometry method. Data were analyzed using Epiinfo version 6. Logistic regression was used to assess the contribution of other risk factors on infant birth

weight. Data were converted to STATA format and logistic regression analysis was done using STATA program version 8.

Results

The results showed that there is significant relationship between infant birth weight and maternal zinc levels. Mothers with low zinc levels were two and half times more at risk of having an infant weighing ≤2000gms compared to those with normal zinc levels (OR 2.62 CI 1.36-5.73). The association was statistically significant (p value = 0.002).

Cord blood zinc concentration was significantly lower in LBW compared to control babies. Infants with low zinc levels were almost three times more at risk of being born with birth weight ≤2000gms compared to those with normal zinc levels (OR 2.79 CI 1.36-5.73). The relationship is statistically significant (p value= 0.0016).

Conclusions

- This case-control study indicated that there is a relationship between low infant birth weight ≤2000gms and maternal zinc deficiency.
- There is a relationship between infant birth weight and infant zinc levels
- Maternal age of ≤19 years is associated with low infant birth weight and low maternal zinc levels.
- Plasma zinc levels in mothers correlated with plasma zinc levels in their offspring.

Recommendation

- A community based survey is needed to determine if the relationship between maternal zinc and LBW is a public health problem in Tanzania and therefore initiate zinc supplementation.

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ABBREVIATIONS

AAS – Atomic Absorption Spectrophotometry.

DNA – Deoxyribonucleic acid.

EDTA – Ethylene Diamine Tetra Acetic Acid.

EPH – Edema Proteinuria and Hypertension.

GA – Gestational age

Ig - Immunoglobulins

IUGR – Intrauterine growth retardation

IQ – Intelligence quotient.

LBW – Low birth weight

MNH – Muhimbili National Hospital

MOH – Ministry of Health

MUCHS – Muhimbili University of Health Sciences and Health.

OR- Odds ratio

OFC – Occipital Frontal Circumference

REZP – Readily exchangeable zinc pool

RNA – Ribonucleic acid

SGA – Small for gestation age

SVD – Spontaneous vaginal delivery

TFNC- Tanzania Food and Nutrition Centre

μmol/l – micromol per litre

UNICEF- United Nations Children Fund

Wt – Weight

WHO – World Health Organization

Zn – Zinc

DEFINITIONS

For the purpose of this study:

- Low birth weight was considered to be birth weight ≤ 2000gms, and normal weight to be ≥ 3000gms.
- Plasma zinc level was considered low if it was below 9.9μmol/l for mothers and below 7.6μmol/l for infants.

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 Low birth weight baby (LBW)

Low birth weight baby refers to an infant weighing less than 2500g at birth. Low birth weight can either be due to intra uterine growth retardation, premature delivery or both. Intra uterine growth retardation (IUGR) is associated with medical conditions that interfere with placental perfusion, development or growth of the fetus, and the general health and nutrition of the mother. Premature birth whose low birth weight is appropriate for gestational age is generally associated with medical conditions. These include inability of the uterus to retain the fetus, premature separation of placenta, or stimulus to effective uterine contractions prior to term.[1]

1.2 LBW a public health problem

Low birth weight affects 20.5 million or 16.4% of newborns in the world per year.[2] The incidence of LBW in Tanzania is 16%.[3] The internationally recommended cut-off levels for triggering public health action is the incidence of LBW > 15%.[2]

Low birth weight is a reliable indicator of the risk of death, growth failure, neurodevelopment problems, recurrent infections and hospitalization. Nutritional deficiency during fetal life compromises

immune functions, leading to higher neonatal morbidity and mortality in LBW infants. The smaller and the earlier the infant is born, the greater the risk. In a study done in Dar es Salaam, LBW carried three folds increased morbidity and seven folds increased risk of mortality[3]. This problem has been addressed in other countries.[4,5] Those who survive frequently fall ill and get trapped in the under nutrition-infection vicious cycle, retarding both their physical and mental development. They have lower Intelligent Quotients (IQs) than those of normal weight infants, with an average of 5 IQ points difference.[6] Approximately 50% of infants with birth weight below 750gms require education support. The risk of developing a major handicap is approximately 5% in all infants with birth weight below 1500gms and 20%-30% in infants below 750gms.[7]

The process of becoming stunted starts in utero and extends throughout the life cycle of the child. This increases the likelihood of damage to future generations, through further fetal growth retardations.[8] LBW girls, who survive, may grow up to produce LBW babies who have a lower chance of survival than normal birth weight babies. During adulthood they have reduced working capacity thus ending in poor socioeconomical status. These factors make a LBW infant to be a family, public health, social and economic problem.

1.3 Strategies to reduce incidences of LBW

Efforts have been aiming at reducing the incidences of LBW and improvement of child survival. These are reflected through improved medical care, improved Antenatal care (ANC) coverage, and immunization against preventable infectious diseases. In Tanzania, basing on clinical observations there has been no improvement as shown by the data of 1979 (15%),[9] 1990 (16%)[3] and on recent estimates of 2000 and 2001 (18%)[10]

Maternal nutritional status with respect to both macro and micronutrients is a known important determinant of fetal development. It has been noted to influence the infant birth weight in a number of settings.[9,11] Poor maternal nutrition contributes to LBW, so it has been targeted as a starting point of the battle against LBW. Improving early nutrition should be emphasized. In field research in Gambia, it was shown that LBW could be reduced by about 40% and infant mortality by 50% through improved food intake during pregnancy.[12]

Other factors have been known to influence infant birth weight. These are maternal age, parity, socioeconomic status, education and maternal pathologies[9,11,13] In one way or another these factors contributes to poor maternal nutritional status.

At a workshop held in Singapore to review the evidence available on the possible benefits of multiple micronutrient supplementation and safe motherhood. It was noted that diets of women in developing countries are lacking a wide variety of micronutrients, possibly endangering pregnancy conditions. Improving nutrient intake was urgently recommended. It was agreed that zinc (Zn) should be considered and be included in a new multi-micronutrient supplementation and pregnant mothers were focused as a potential target group.[13]

A recent meta-analysis on nutrition supplementation trials during pregnancy suggested that measures for combating LBW should involve provision of a balanced protein/energy supplementation. The contribution of zinc and other micronutrients should be considered. Programs for prevention of LBW should begin before conception and continue to be enhanced during prenatal visits.[14]

1.4 Government commitment

The government of Tanzania is committed to reduce LBW. This commitment is reflected in a pilot project to reduce LBW initiated in 3 districts of Magu, Mbarali and Hai. This is going on through a cluster of interventions involving control of key infections of malaria, helminths and syphilis, and the provision of multiple micronutrient

supplementations including zinc. Other efforts involve promoting maternal caring practices by reducing women workload, improved diet and antenatal care.[15] In cooperation with UNICEF, the government has negotiated with the Adult Morbidity and Mortality Project (AMMP) team to incorporate the context of Early Childhood Care for Survival, Growth and Development (ECC-SGD) in their programmes. The 3 districts where the LBW prevention project is being implemented are among the 7 districts incorporated in AMMP demographic surveillance.

1.5 Zinc- an essential micronutrient

Maternal nutrition has been focusing mostly on the risks of the mother and infant from maternal iron deficiency anemia during pregnancy. However, zinc as a micronutrient is also important for maternal and infant survival.

Zinc was first recognized as an essential micronutrient for microorganisms more than 125 years ago. Despite this knowledge, researchers remained with a dilemma of whether there is a possibility of zinc deficiency in humans because of its abundance in the environment. Evidence of human zinc deficiency began to emerge when cases of zinc responsive dwarfism and delayed sexual maturation were first reported among Egyptian adolescents.[16] Furthermore, clinical studies in children

with acrodermatitis enteropathica, an inborn error of zinc metabolism resulting in poor zinc absorption and subsequent severe zinc deficiency, confirmed the critical role of zinc in physical growth.[17] Thereafter, the convincing evidence for its importance has come from zinc supplementation trials that have produced positive growth responses and improvement in pregnancy outcome.[18-20]

1.6 Role of zinc in the human physiology

1.6.1 Zinc metabolism

The human body contains about 2-3gms of zinc. There are no known specific storage sites for zinc, so regular zinc supply in the diet is required. The small intestine plays a central role in zinc metabolism and maintenance of whole body zinc homeostasis. Zinc absorption takes place mainly in the proximal small intestine. Only 20% of dietary zinc is actually absorbed by the body. Endogenous zinc secreted from pancreas and other gastrointestinal secretions, is reabsorbed. Excess zinc is excreted in faeces, urine and skin.[21] Absorption of exogenous dietary zinc and intestinal reabsorption of endogenous zinc are the two major mechanisms regulating whole-body zinc homeostasis and maintaining zinc balance. During pregnancy it has been shown that there is increased absorption and retention of zinc in order to meet the increased demand for fetal growth, uterus and placental mass. [22]

1.6.2 Readily exchangeable zinc pool (REZP)

This represents the amount of zinc available in pools that exchanges with zinc in plasma. It is important for maintaining zinc–dependent functions of human biological systems. REZP consists of 10% of total body zinc. The rest, 90% is found intracellulary, particularly in muscles, bones, liver, and other organs. Zinc in the intracellular space is not readily available for metabolism.[23] Zinc is not stored, however it can move into and out of the plasma compartment within a period of about 2-3 days. Thus it depends on recent dietary zinc intake.[23] Zinc homeostasis process works to maintain the amount of REZP. In blood, 80 % of zinc is in the red blood cells,[24] this can affect the mass of plasma zinc when there is haemolysis and give false high levels. In neonates zinc levels are about half of the adult, with levels progressively increasing until about 12 years of age.[24] Pregnant mothers have lower zinc levels as compared to non pregnant mothers, probably due to increase in plasma volume.[25]

1.6.3 Zinc and immunity

Zinc affects several aspects of the immune system, from the barrier of the skin to the gene regulation within lymphocytes. Zinc is crucial for normal development and function of cell mediating non-

specific immunity such as neutrophils and natural killer cells. Zinc regulates macrophage function such as intracellular killing of microorganisms and phagocytosis. It activates lymphocyte growth, cytokine and antibody production, particularly Immunoglobulin(Ig) M, IgA and IgG. Apoptosis is potentiated by zinc deficiency. [26]

The effect of zinc on modulating immunity has been shown in a number of studies. In one study it was found that 5mg Zn/day improved immune function and thereby reduced morbidity.[27]

In a study on the effect of zinc supplementation in infants born full term but small for gestational age, there was substantial reduction in infectious disease mortality.[28]

A 93 days old girl fell acutely sick with watery diarrhoea and herpes-like vesicular skin eruptions that progressed to severe dermatitis. No bacteria could be isolated from vesicle liquid and DNA polymerase chain reaction (PCR) for herpes simplex virus and varicella zoster virus were negative. Serum zinc level was 1.0μmol/l. Serial zinc concentrations in mother's milk sample were decreasing from 31.2μmol/l to 7.4μmol/l on day 129. The baby's symptoms were assumed to result from zinc deficiency. When zinc treatment was initiated, it resulted in the healing of skin eruptions and diarrhoea stopped within 4 days.[29]

In a study done in Dar es Salaam on the effect of zinc supplementation in children recovering from severe Protein Energy Malnutrition, the decrease of morbidity and relapse rates was one of the main outcomes.[30]

1.7 Factors leading to zinc deficiency

1.7.1 Poor diet

Bioavailability of zinc influences absorption. Zinc is absorbed efficiently from meals containing animal products and considerably less from phytate containing meals. The presence of specific inhibitors affects zinc absorption. The major inhibitor of zinc absorption is myoinostosil hexaphosphate (phytate), which is present in many plant foods especially cereals and legumes. Phytate irreversibly binds zinc forming a highly insoluble complex, which the body cannot absorb. This markedly decreases the bioavailability of zinc from food.[21, 31]

To estimate the absorption of zinc from diets, a phytate-zinc molar ratio of a food is considered. Phytate-zinc molar ratio is calculated as a phytate content of food per six hundred and sixty divided by zinc content of food per sixty five point four in milligrams. (660 and 65.4 are molecular weights of phytate and zinc respectively). Diets with a phytate-zinc molar ratio of more than 15 have poor zinc bioavailability, 5-15 have medium, while less than 5 have both good and high zinc

bioavailability. 45% -55% of zinc is absorbed from high zinc bioavailability diets, 30% - 35% from medium zinc bioavailability diets and 10% - 15% from low zinc bioavailability diets.[32]

Zinc is present in a wide variety of foods, particularly proteins. Organs and flesh of mammals and fish are the richest food sources of zinc. These foods do not contain phytate, therefore, they are particularly good sources of absorbable zinc. Eggs and dairy products have a slight lower content of zinc but are free from phytate. Most legumes like beans, lentils, yeast, nuts, seeds and wholegrain cereals have intermediate levels of zinc, but their higher phytate content reduces the amount of zinc available for absorption. Rice, starch roots and tubers have lower zinc contents. Fruits and vegetables are not rich in zinc and their bioavailability is uncertain.[31,32]

In Tanzania, Dar-es-Salaam in particular, diets are mainly plant based such as maize flour, starchy roots and tubers which are poor in zinc content, but high fiber diets rich in phytates. Foods of animal origin such as red meat and fish that are rich sources of zinc are not readily available or affordable, so they are eaten in very low amounts. The embryos of grains are often removed during processing. A study done in preschool children in Pemba, reflecting on Tanzania local diets, revealed that 63% had zinc levels below normal.[33] In Malawi where their staple

diet is the same as in Tanzania, the study revealed a high prevalence of sub optimal zinc status. Median daily intake of zinc was low and poorly available. Sixty one percent (61%) were provided with cereals and 20% by fresh food. Women consuming diets with phytate- zinc ratio>17 (the median) had lower zinc concentrations.[34] Another study assessed dietary zinc in a population, it showed that in most African countries the food Phytate- Zinc molar ratio is high.[35]

1.7.2 Infections

In response to infections or injury, monocytes and macrophages secrets cytokines such as interleukine-1 (IL-1) and tumor necrotic factor-alpha (TNF_{α}). IL-1 stimulates secretion of IL-6 and glucocorticoids. IL-6 and glucocorticoids activates hepatic synthesis of metallothionein (MT), an intracellular zinc binding protein.[36] Injection of IL-1 in rats showed increased uptake of zinc by the liver, bone marrow and thymus and decreased uptake by intestine and skin.[37]

Zinc deficiency has been associated with higher rates of infectious diseases, including skin infections, diarrhoea, respiratory infections, malaria, and delayed wound healing.[17, 27-30, 34]

1.7.3 Zinc interaction with other micronutrients

Interaction with other micronutrients such as vitamin A and iron impairs zinc absorption. Mechanism of interaction has been studied and it has been suggested that there is competition on the absorption process where by the minerals displace one another on the molecule necessary for their uptake from the lumen into the intestinal cell. Secondly, there is competition for pathways through the mucosal cell into the blood circulation. Third, interaction with one another, may form an insoluble complex, in this way impair the absorption of minerals involved. [38]

Trials on multiple micronutrients supplementations have considered this challenge by increasing the dose of zinc to the maximum daily-recommended dose. [14,39]

1.7.4 Pregnancy

Zinc levels decrease substantially during pregnancy. This is due to an increased requirement from accelerated cell multiplications involved in the enlargement of the uterus, development of placenta and growth of the fetus. It is estimated that the additional need for zinc in a pregnant woman is ≈ 1540umol or ≈ 100mg. This represents ≈5-7% of body zinc of a non-pregnant woman.[22] A study done on serial maternal zinc levels

and pregnant outcome, showed that there was a significant decrease in zinc levels in pregnant women as compared to age matched non-pregnant women.[22, 40]

However in a normal pregnancy, there is physiological adjustment in maternal zinc utilization. There is increased intestinal absorption and retention in order to meet the demand.[22] Conditions that could interfere with adjustments in zinc absorption and therefore, leading to zinc deficiency include poor maternal nutrition and lack of foods with optimum zinc bioavailability. Zinc deficiency could further be aggravated by cereal-based diets that have high phytate and fibre content, known to inhibit zinc absorption.

1.8 Zinc and pregnancy outcome

Reproductive functions related to zinc status are fetal growth, duration of pregnancy and efficiency of labour and delivery. Maternal zinc deficiency is associated with increased incidences of fetal growth retardation, spontaneous abortions, stillbirths and congenital malformations. Zinc is involved in the structural integrity of protein metabolism. It is essential for the functions of over 50 metalloenzymes including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)

polymerases. These have a range of functions including the synthesis of nucleic acids and specific proteins such as hormones.

Fetal growth is affected by zinc deficiency through impairment of DNA synthesis and mitotic activity of individual cells. Deoxyribonucleic acid and RNA polymerases responsible for growth are zinc dependant metalloenzymes. When zinc is depleted, these enzymes cannot function optimally. This reduces formation of DNA and RNA, thus slowing the replication of cells and decreasing metabolic processes involved in tissue growth, repair and maturation.[26]

On the review work by Laura et al showed that zinc deficiency decrease uterine estrogen receptors. Estrogen receptors contain zinc finger protein. The effect of zinc on the duration of pregnancy reflects the role of zinc in Estrogen-dependent gene expression. Therefore, apart from fetal growth, zinc deficiency can affect the birth weight through shortening the duration of pregnancy.[41]

Zinc deficiency is associated with fetal congenital malformations. This can be due to structural maldevelopment due to interrupted cellular growth during embryogenesis or excessive cell death.[26.] Fetal malformations have been noted to be common in mothers with inherited disorders of zinc metabolism.[42] In another study done on women with

congenitally abnormal infants it was found that they had low zinc concentrations. The commonest malformations in that study were neural tube defects.[43]

There is considerable information from human observational studies and intervention trials that indicate maternal zinc status can influence several aspects of the reproductive function and pregnancy outcome. In one study, it was observed that there is a strong association between poor maternal zinc status and various indicators of poor pregnancy outcome. These included LBW, prematurity and abortions.[22] In another study it was found that, mothers with zinc levels less than normal in the last trimester had a higher incidence of birth weight babies below 50th percentile.[40]

A study done relating maternal nutrition to pregnant outcome in an Egyptian village, found that zinc concentration during second trimester was best predictor of infant birth weight.[44]

The Thailand study, found that maternal zinc levels during antenatal care, labour and in infants with intrauterine growth retardation was significantly lower than that in normal weight infants and their mothers ($p<0.05$). Researchers concluded that low maternal zinc concentrations in the third trimester would highly suggest mothers at risk of delivering intrauterine growth retarded infants.[45]

In another study low zinc concentration in neonates small for dates and their mothers was noted.[46] Trials on zinc supplemented mothers reported reduction in incidence of LBW.[18-20]

Putting together these data, it shows that zinc plays a role in reproductive function and predicts pregnancy outcome.

2.0 RATIONALE AND OBJECTIVES

2.1 Rationale

The incidence of LBW in Tanzania is among the highest in the world. Despite efforts by the Ministry of Health (MOH) using different intervention measures to reduce it, there are no improvement as shown by the data of 1979 (15%),[9] 1990 (16%)[3] and on recent estimates of 2000 and 2001 (18%)[10]

Zinc deficiency has been noted in a number of settings to impair growth and development of the fetus. In Tanzania, there is little information on zinc deficiency and its effect on birth weight of infants. However, based on dietary intakes of many communities, it is likely that zinc deficiency is a problem. This study was done to find out zinc status in mothers and their infants and the relationship between infant birth weight and maternal zinc status.

2.2 Hypothesis

Birth weight is not associated with maternal zinc status.

2.3 OBJECTIVES

2.3.1 Broad objective

To determine the relationship between infant birth weight and maternal zinc status.

2.3.3 Specific objectives were to determine:

1. the relationship between infants' birth weight and maternal zinc levels.
2. the relationship between infants' birth weight and zinc levels.

3.0 METHODOLOGY

3.1 Study design

Unmatched case control study was done.

3.2 Study population

The study population consisted of mothers and infants of birth weight ≤2000 gms as cases. Infants with birth weight ≥3000gms formed the control group. Both groups of infants were born at MNH during the study period.

3.3 Study site

The study was conducted in labour ward at Muhimbili National Hospital (MNH). MNH is the largest tertiary referral hospital in Tanzania located in the city of Dar-es-Salaam. It is also a teaching Hospital for the Muhimbili University College of Health Sciences (MUCHS). The study site was selected for convenience. Muhimbili National Hospital receives mothers who are at risk of LBW and other obstetric complications screened from peripheral antenatal care clinics. The hospital has one labour ward with a capacity of 27 beds. Approximately there are 40 deliveries per day. Birth weight of ≤ 2000gms accounts for 9-10% of total deliveries per year.[10]

3.4 INCLUSION AND EXCLUSION CRITERIA

3.4.1 Inclusion criteria

- Infants born by spontaneous vertex delivery (SVD) with:
  - Birth weight of 2000gm. and below.
  - Birth weight of 3000gms and above.
- Mothers of the above infants.

3.4.2 Exclusion criteria

Infants were excluded from the study if they:-

- were of multiple pregnancy.
- had birth trauma e.g. cephalohematoma, fracture, ecchymosis.
- had congenital malformations.
- were delivered by other modes of deliveries than SVD.
- were born by mothers who had features of chorioamnionitis EPH, APH or blood transfusion during pregnancy.

The above conditions were excluded because of possible confounding. The study restricted to SVD only, because other modes of delivery may be confounding by low zinc levels as they are indicated after prolonged

difficult labour. This predisposes to injury, chorioamnionitis and acute phase reaction. Infections and injury are among the factors leading to low zinc levels.[36]

3.5 Sample size estimation

Sample size was determined using the formula below.[47] Mean serum zinc value in LBW infants is 60 ± 23.1μgm/dl. and in normal birth weight infants is 65.8 ±12.7μgm/dl.[46] The following statistical formula was used to determine the sample size:-

Formula $n = \frac{(\mu + V)^2 (\sigma_1^2+\sigma_2^2)}{(\mu_1 - \mu_2)^2}$

Where:-

- μ is one sided percentage point of the normal distribution corresponding to 100%- the power. If power = 80%, μ = 0.84.
- V is percentage point of the normal distribution corresponding to the significance level. If significant level = 5%, V = 1.96.
- σ1 is SD of zinc levels among cases = 23.1.
- σ2 is SD of zinc levels among controls = 12.7.
- μ1 is mean zinc levels among cases.
- μ2 is mean zinc levels among controls.
- n is a required sample in each group.

Study power = 80%

Significant level = 95%

The difference between μ_1 and μ_2 is 9.

Using the above formula the minimum required sample size was 68 for each group. One hundred and thirty six plus 10% correction for haemolysed blood samples, giving a grand total sample size of 150.

Thus, the estimated sample size consisted of 75 cases and 75 controls. A similar number of mothers for cases and controls was investigated to determine mother's zinc levels as an independent variable.

3.6 Sampling method

Every infant born with birth weight of ≤2000gms who met inclusion criteria was eligible for the study. The study used convenient sampling technique. The first mother with an infant weighing ≤2000gms who consented was recruited as a case and consenting mother who had a normal birth weight infant was recruited as a control. Subsequently all eligible subjects were recruited until the estimated sample size was reached.

3.7.0 Recruitment

- Two trained research assistants (Nurse midwives) were used in recruiting, filling questionnaires and taking blood samples from infant's cords and their mothers from antecubital vein. Identified infants with birth weight of ≤2000gms and their mothers were cases, while infants weighing ≥3000gms and their mothers formed the control group.
- The purpose and advantages of the study were written on a piece of paper. After being invited into the study, the mother was given the paper to read or the information was read to her to get a written consent.
- Once a written consent was obtained mothers were interviewed and a structured questionnaire was used to collect data. This was done confidentially.

3.7.1 Physical examination

The investigator did a thorough physical and systemic examination of every infant recruited into the study. The infants were examined for congenital abnormalities, signs of trauma like haematomas and fractures. This was done to select infants who met the study criteria. Gestational age was assessed clinically using Dubowitz method as adopted by Cappuro.[48] To classify the infant as to whether was

appropriate or small for gestational age, Battaglia and Lubchenco birth weight for gestational age standard graphs were used.[49]

3.7.2 Anthropometric measurements

3.7.2.1 Weight

The infant's weight was taken using a seca beam balance, to the nearest 10g while completely undressed.

3.7.2.2 Length

Infants' length was taken using a wooden length board, which had a fixed head plate and a movable footplate. An infant was laid on the board in a supine position. An assistant held the infant's head in contact with the head plate. The investigator straightened the infant's legs at the knees, the feet turned upward at right angles to the legs. The footplate was brought in contact with the heels and the length was recorded to the nearest 0.1cm.

3.7.2.3 Occipital frontal circumference (OFC)

The OFC measurements were taken using a non-stretchable nylon measuring tape from the occiput, over the two-biparietal prominences and passing just above the eyebrows to the nearest 0.1cm.

3.7.3 Collecting and processing of blood specimen

3.7.3.1 Infants' blood

Five millitres (mls) of cord blood was drawn using a 5mls disposable plastic syringe with stainless needle. The blood was put into a zinc free uncontaminated EDTA polyethylene tube (vacutainer) labeled with infant's serial number.

3.7.3.2 Mothers' blood

Five mls of venous blood was taken from mothers antecubital vein after the skin over it had been cleansed with a sterile swab soaked in 70% alcohol. Blood was drawn using a 5mls disposable plastic syringe with stainless needle. Blood was put into a zinc free uncontaminated EDTA polyethylene tube (vacutainer) labeled with serial number of mothers to match her infant's serial number.

3.7.3.3 Processing of blood specimen

Immediately after collection of blood the plasma was separated using a microcentrifuge machine, which rotates at 3000 revolutions per minute (rpm), for 15 minutes. Plasma was then kept frozen at -20^{0}C. The samples were analyzed within two weeks. Zinc concentration was determined using flame Atomic Absorption Spectrophotometry (AAS) method at the Department of Chemistry, University of Dar-es-Salaam.

It uses the absorption of light to measure the concentration of atoms. Every metal absorbs light of a specific wavelength. The absorbed light length is directly proportion to the concentration of the metal.[50]

The AAS method for determining of the zinc concentration is the most reliable method available. Several studies have used this method for estimation of zinc concentrations.[29,30,40,45,46] In this study, plasma was used to estimate zinc status. From biological and epidemiological point of view plasma and serum zinc levels are similar. However, since the potential of haemolysis is higher in serum and that zinc is more concentrated in red blood cells, using plasma for zinc estimation is better because of "clean catch".[51] Zinc level was considered low if it was below 9.9μmol/l for mothers and below 7.6μmol/l for infants.[29]

3.8 Duration of the study

It took 3 months to recruit 81 cases and their controls, that is from July to September 2002 inclusive.

According to the Maternity Ward Data base Unit statistics, in the year 1999 and 2000 at MNH, there were18,162 and 18,117 total deliveries respectively. The proportion of infants with birth weight ≤ 2000gms was 9.9-10.4% of all deliveries per year.[10] giving an average of 150 such infants per month including stillbirths. From preliminary pilot study an average of 30 cases were recruited per month. This was because others

infants could not meet inclusion criteria and some were being recruited in different studies going on in the labour ward at the time of the study.

3.9 Quality assurance

- Vacutainers, syringes and needles used were tested by a Laboratory scientist, and approved to be zinc free. The procedure followed the same process as expected to be done in the collection of blood samples, that is: Distilled water which was previously tested to be zinc free was drawn by the needle, then put in the EDTA vacutainers. This was centrifuged at a rate of 3000rpm for 15min. Then some of it was taken for analysis using Atomic Absorption Spectrophotometry method to determine presence of zinc. Ten such samples of vacutainers chosen randomly were found to be zinc free. The remaining vacutainers, syringes and needles of the same batch were used for collection of blood samples.
- The accuracy of zinc levels determined was assessed using commercial Standard reagent already calibrated into a known concentration and compared to distilled water, which had no zinc at all. After every three samples, the commercial standard reagent

and distilled water were read in order to countercheck the values of the samples.

- Before undertaking the study, a pilot study was conducted in order to:-
    - assess the questionnaire and efficiency of the procedure.
    - evaluate research assistants so as to see that what they did was correct.
    - correct any mistakes done in the pilot study.
    - assess the time frame needed to complete the study.

3.10 Ethical clearance

Ethical was sought from the MUCHS higher degree ethical committee of the Research and Publications Committee.

3.11 Ethical consideration

Mothers were informed by the principal investigator or research assistants about the research and gave their written informed consent. They were informed that the information obtained from them would be used only for the purpose of research and would not be revealed to other parties. Those who refused to consent were excluded from the study.
The Questionnaire and the consent forms were written in Kiswahili, the national language in Tanzania.

Infants' cord blood was taken to avoid pricking and taking a large amount of blood from them.

Sick infants were managed accordingly at the neonatology unit, regardless of whether they were included in the study or not.

3.12 Data analysis

All the data were checked by the investigator for consistency and accuracy before data entry for analysis. Data were analyzed using Epiinfo version 6. Zinc levels were classified into two groups of low and normal zinc levels based on experiences from literature surveys. x^2 test was used to test the association between infant birth weights and zinc levels, and between infant birth weights and other variables. p-value of less than 0.05 was considered significant.

Logistic regression was used to asses the contribution of other risk factors on infant birth weight. Data were converted to STATA format and logistic regression analysis was done using this program. (STATA version 8, Texas USA: 2003)

Limitations of the study:

1. Some of the blood samples haemolyzed necessitating recruitment of another pair, thus prolonging the duration of the study.

4.0 RESULTS

During the study period between July-September 2002, the total deliveries at MNH were 4957 live infants. Out of them, 450 were born with birth weight of ≤2000gms. The incidence of deliveries of infants ≤2000gms was 9.1%. One hundred and seventy four live born infants and their mothers were recruited in this study. Nine blood samples haemolyzed and so were not included in the analysis. Analysis was therefore based on 165 samples, of which 81 were cases and 84 were controls. There were 86 males and 79 females, with a male to female ratio of 1.1:1. Thirty nine (48.1%) infants among cases were born premature. Fifty eight (71.6%) infants among cases were small for gestation age (SFGA). All infants in the control group were full term. The mean gestational age was 36.16± 2.67 for cases and 39.19±0.93 for controls. Characteristics of the study population are as shown in Table 1.

Table 1: Characteristics of the study population:

	Cases n = 81	Controls n = 84
Birth weight (gms)		
Range	900 -2000	3000 - 4100
Mean± SD	1756.42 ±31.642	3355.36 ±35.142
Sex		
Male	40	46
Female	41	38
Gestational age (wks)		
<37	39	0
>37	42	84
Mean	36.16 ± 2.67	39.19 ± 0.93
Infant Zn levels		
Low	39	21
Normal	42	63
Mean ± SD	9.485 ± 4.600	10.872 ± 4.197
Maternal Zn levels		
Low	48	30
Normal	33	54
Mean ± SD	10.007 ± 4.324	11.345 ± 3.434
Maternal age (yrs)		
≤19	37	19
20-35	42	59
>35	2	6
Mean± SD	22.81 ± 6.02	25.81 ± 5.84
Parity		
1-3	74	64
>3	7	20
Mean± SD	1.593 ± 1.070	2.548 ± 1.476

Table 2a: Relationship between maternal zinc levels and birth weight:

Maternal Zn	Cases n=81	Controls n =84	Total n=165	OR	95%CI	p-value
Normal	33	54	87	1		
low	48	30	78	2.62	1.32, 5.20	0.002

- Mothers with low zinc levels were two and half times more at risk of having an infant weighing ≤2000gms compared to those with normal zinc levels (OR 2.62). The association was statistically significant.

Table 2b: Relationship between maternal zinc levels and birth weight:

Maternal zn. (µmol/l)	Cases n=81	Controls n=84	Total n=165	OR	95% CI	p-value
≥9.9	33	54	87	1		
8.0 - <9.9	15	10	25	2.45	0.91, 6.75	0.05
6.0 - <8.0	18	12	30	2.45	0.97, 6.27	0.04
<6.0	15	8	23	3.07	1.07, 8.97	0.018

- The risk of having an infant weighing ≤2000gms baby decreases as zinc levels increase. The risk decreases as the normal zinc level is approached.

Table 3a: Relationship between infant zinc levels and birth weight

Infant Zn	Cases n=81	Controls n=84	Total n=165	OR	95%CI	p-value
normal	42	63	105			
Low	39	21	60	2.79	1.36, 5.73	0.0016

- Infants with low zinc levels were almost three times more at risk of being born with birth weight ≤2000gms compared to those with normal zinc levels. The relationship is statistically significant.

Table 3b: Relationship between stratified infant zinc levels and birth weight

Infant zn. (µmol/l)	Cases	Controls	Total			
	n=81	n=84	n=165	OR	95% CI	p-value
≥7.6	42	63	105	1		
6.0 - < 7.6	17	10	26	2.49	0.92-6.36	0.03
<6.0	22	11	34	3.14	1.29,7.72	0.007

- The risk of having birth weight of ≤2000gms decreases as zinc levels increase.
- The risk is three times more in infants with zinc levels below 6.0 µmol/l and less than two and a half times as zinc levels approach normal values

Table 4: Summary of association between infant birth weight and selected exposure variables.

Exposure variables	Cases N =81	Controls n =84	Total 165	OR(95% CI)	p-value
Maternal zn					
Normal	33	54	87	1	
Low	48	30	78	2.62 (1.33, 5.17)	0.002
Infant zn					
Normal	42	63	105	1	
Low	39	21	60	2.79 (1.39, 5.73)	0.0016
Maternal age					
>19	44	65	109	1	
≤19	37	19	56	2.88 (1.39,6.01)	0.001
Parity					
>2	12	30	87	1	
≤2	69	54	138	3.19 (1.41,7.33)	0.002
Gravidity					
>2	21	37	58	1	
≤2	60	47	107	2.25 (1.11, 4.59)	0.02
Sex					
Males	40	46	86		
Females	41	38	79	0.81(0.42, 1.56)	0.5

- Maternal and infant zinc status, maternal age, parity and gravidity were significantly related to infant birth weight. There was no statistical significant difference between infant's birth weight and sex.

- This implies that infants' birth weight ≤2000gms is influenced by many factors, and zinc deficiency is one of the contributing factors.

Table 5: Logistic regression analysis: correlation of infant birth weight with selected exposure variables.

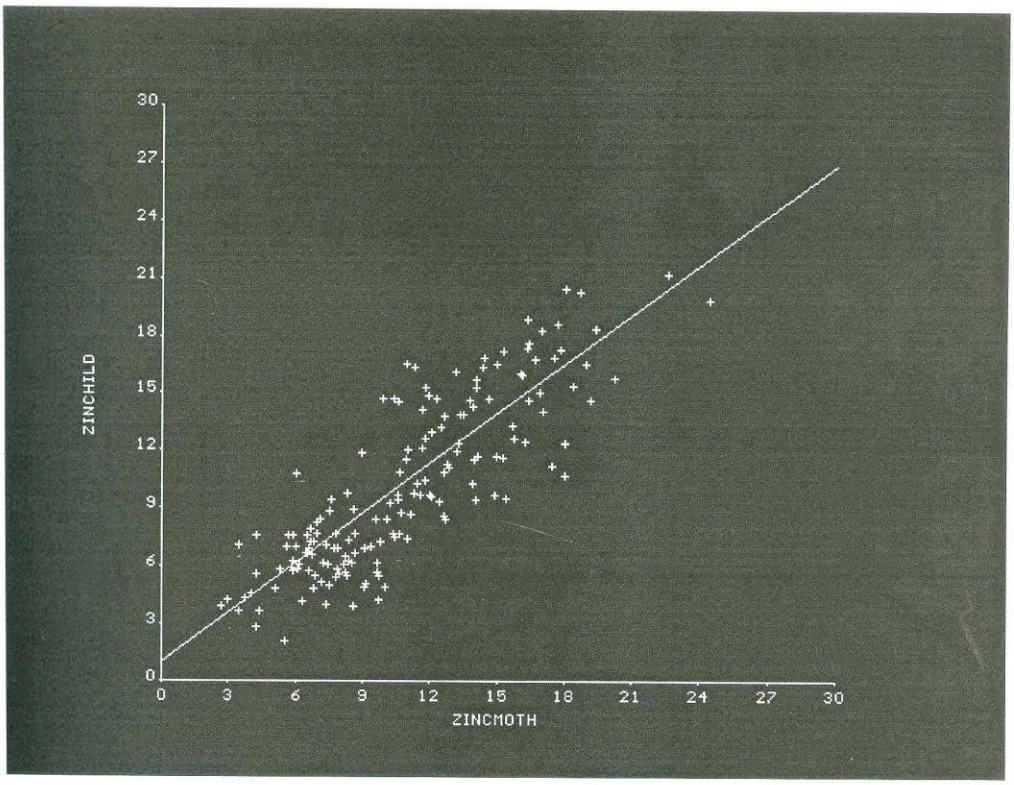
Exposure variables	β-coefficient	OR	95% CI	p-value
Maternal zn				
≥9.9μmol/L		1		
<9.9μmol/L	0.94	2.57	1.39,5.72	0.002
Maternal age (yrs)				
>19		1		
≤19	0.8415	2.32	1.8,6.5	0.001
Parity				
>2		1		
≤2	0.1	1.12	0.418,3.2	0.823
Gravidity				
>2		1		
≤2	0.124	1.132	0.421, 4.3	0.652
Sex				
Males		1		
Females	-0.013	0.984	0.408, 3.66	0.67

LR Chi square: 32.64

LR p-value: 0.000

- Table 5 indicates that there is a significant relationship between infants birth weight and maternal zinc levels.
- The crude OR between birth weight and maternal zinc was 2.62. The adjusted OR for maternal age, parity, sex and gravidity is 2.57. Crude OR minus adjusted OR divide by crude OR = 2.62-2.57/2.62=0.019, which is less than 10%, therefore, there was no confounding with maternal age ≤19 years, Parity ≤ 2, Gravidity ≤ 2 and sex of infant.
- However, there is a significant relationship between maternal age ≤19 years and maternal zinc levels below 9.9. μmols/L. Waald p-value of 0.001.
- Young mothers ≤19 years are two times more likely to have a maternal zinc of <9.9μmols/L.
- Parity, gravidity and sex were not associated with maternal zinc levels.

Fig. I: The relationship between maternal zinc levels and infant zinc levels



- Zincmoth= maternal zinc
- Zinchild= infants' zinc

r = 0.83 95% CI 0.75-0.92. This is statistically significant. Infant zinc levels are directly proportional to maternal zinc levels. With increase of maternal zinc, infant zinc levels also increase.

5.0 DISCUSSION

This study has shown a significant relationship between infant birth weight and maternal zinc levels at MNH. The difference in plasma zinc levels between mothers who delivered infants weighing ≤2000gms and mothers with infants weighing ≥3000gms was statistically significant; (OR=2.62, p-value = 0.002). This indicates that the risk of having infants weighing ≤2000gms is more than two and half times to a mother with low zinc levels relative to a mother with normal zinc levels. On evaluating the relationship between infant birth weight and different maternal zinc levels, it was found that the lower the plasma zinc levels the higher the risk of having infants weighing ≤2000gms. The risk decreased as zinc levels increased towards normal values. Similar findings were obtained on the relationship between infants' birth weight and cord blood zinc levels. The Odds ratio was 2.79, p-value=0.0016. This was statistically significant, indicating that the risk of birth weight of ≤2000gms is almost three times more in infants with low zinc levels.

Zinc has many functions including influence on growth. Zinc deficiency has been associated with impaired growth. Therefore, the low birth weight in this study might have been affected by zinc deficiency.

The results agree with findings from other studies done in developing countries.[45,46] The Thailand study, found that maternal zinc levels during antenatal care, labour and in infants with intrauterine growth

retardation was significantly lower than that in normal weight infants and their mothers.[45] A study done in India, on zinc levels in cord blood of infants and their mothers, revealed that LBW infants and their mothers had low zinc concentrations and their birth weights correlated with zinc concentrations.[46] In both studies, similar to the present, the samples were collected at labour and the same AAS method was used for determining zinc concentration. This method is accurate and the results are reliable. Several studies have used this method for zinc status estimation.

A study done relating maternal nutrition to pregnant outcome in an Egyptian village, found that zinc concentration during second trimester was the best predictor of infants' birth weight.[44]

A study on mothers with acrodermatitis enteropathica, poor pregnant outcomes of spontaneous abortion, ancephalic fetus, achondroplastic dwarf and low-birth-weight infants were observed.[42] When these patients were given sufficient zinc to maintain normal zinc concentrations throughout gestation, pregnancy outcomes were normal.[52] These data, indicates that zinc deficiency is an important determinant of poor pregnancy outcomes. These studies were carried out in countries where maternal malnutrition including micronutrients deficiency could be a problem leading to intrauterine growth retardation.

Contrary, to these findings, in a study done by Iqbal et al, found no relationship between infant birth weight and zinc status.[53] Another study on zinc supplementation and pregnancy outcome, found that increased zinc levels in zinc supplemented mothers did not improve the incidence of LBW. However researchers concluded that food intake might have contributed to the relative high zinc levels observed. Samples were taken under nonfasting conditions, but serum zinc concentration is known to vary with intake of food. Also explained that the delay of six hours between collection of blood and separation of serum may have caused an increase in zinc levels in some cases.[54] The time between blood collection and plasma separation is also known to influence zinc levels because zinc leaks from the cells into serum.[55]

In the present study, the results can be explained by the fact that all blood samples were collected shortly after delivery before mothers had been subjected to different individual foods. There were no therefore immediate factors influencing zinc concentration. Traditionally after delivery mothers take foods with good zinc bioavailability such as animal products. This could interfere with the interpretation of zinc status of an individual as zinc levels change readily with zinc intake.[23] Some studies have considered the variation of zinc concentration to immediate foods eaten. Researchers attempted to control zinc variations by collecting

blood within a specified time period in order to reduce the variation in zinc concentration due to food consumption.[43,55]

In the present study infants' blood samples taken were of venous cord blood. This has the advantage that it reflects the amount of zinc the fetus would receive from the mother. Otherwise mixed or arterial cord blood can wrongly be interpretated as having low zinc because some of it is already utilized for metabolic processes. The plasma in the present study was separated immediately after collection

A study done in Nigeria on zinc and copper in pregnant Nigerian women at term and their infants found that zinc had no effect on fetal growth.[56] Although the same methodology was used in both studies, the significant relationship observed in the present study could be explained by the bigger sample size.

In another study done on 54 women at parturition and analyzed for zinc by ASS method to determine the relationship between zinc levels and birth weight, it was found that the levels of zinc were higher in maternal blood of low birth weight babies than in those with normal weight babies.[57] Laura et al on the review of 14 studies done on evaluating association between maternal zinc levels and low birth weight conducted in developing countries, found that there were different results. Nine of the studies reported positive association between low maternal zinc level and LBW while five studies reported no association. Researchers

concluded that these differences could be due to various reasons. These include timing of the assessment during pregnancy and effect of haemodilution, variation in sample size, laboratory method and quality or the underlying zinc status of the population.[41] The present study has considered these reasons for variation. It was ensured that all blood samples were taken within the same conditions i.e. shortly after delivery. Plasma was separated immediately after collection to avoid leakage of zinc from cells. The case control study was done, meaning that all subjects have equal chances to be predisposed to immediate factors that could affect zinc levels.

It has to be considered that zinc deficiency is not the only cause of LBW. Looking at other predictors of LBW, results from different studies have shown that maternal biosocial factors like body mass index, maternal age, parity, socioeconomic status and education also influence infants birth weight.[11,12] Observations from the present study have shown that primiparity and young maternal age are associated with LBW. Using logistic regression analysis it was found that these variables are not confounding factors for infant birth weight ≤2000gms. However maternal age was significantly related to maternal zinc levels. Young mothers less than 19 years were almost three times more at risk of having a low birth weight infant compared to older mothers. The risk of having infants weighing ≤2000gms decreased with increasing age.

The significant relationship between infant birth weight and maternal age, and significant relationship between maternal age and zinc levels supports the evidence that zinc deficiency could influence infant birth weight. Adolescent girls are prone to micronutrient deficiency due to growth spurt especially during menarche. Thus, adolescent mothers may be prone to delivery of growth retarded and zinc deficient infants.[58] This is probably due to competition for nutrients between the growing adolescent and the growing fetus.

In the present study it is speculated that maternal zinc deficiency may contribute to infant birth weight of ≤2000gms due to the fact that the fetus depends on the mother for nutrients. When the maternal zinc pool is depleted this reduces the amount of zinc available to the fetus resulting in arrested fetal growth. The present study has shown that infant and maternal zinc levels are directly proportional, with a coefficient correlation of r =0.8 (Fig 1). Infant zinc levels decrease as maternal zinc levels decrease and vice versa.

Low zinc levels affect taste. [21,26] This leads to reduced food intake, and can compromise maternal nutritional status. Thus low zinc levels can affect birth weight indirectly through its negative effect on maternal nutrition. The relationship of maternal nutrition and birth weight has been addressed in a number of studies.

Besides being directly involved in the growth function, zinc is also an important carrier of nutrients from the mother through the placenta to the fetus.[27] Low zinc levels impair transport of nutrients to the fetus with consequences of fetal malnutrition and arrested growth.

Also maternal zinc deficiency may affect birth weight through shortening the duration of pregnancy. [41] This leads to premature delivery and hence LBW.

The majority of mothers with infants weighing ≤2000gms were zinc depleted. This might have contributed to low birth weight because zinc plays an important role in growth. DNA and RNA polymerase enzymes responsible for growth are zinc dependent.[26]

6.0 CONCLUSIONS

- This case-control study indicated that there is a relationship between infants' weight of ≤2000gms and maternal zinc deficiency.
- There is a relationship between infant birth weight and infant zinc levels
- Maternal age of ≤19 years is associated with low infant birth weight and low maternal zinc levels.
- Plasma zinc levels in mothers correlated with plasma zinc levels in their offspring.

7.0 RECOMMENDATION

A community-based survey is needed to determine if the relationship between maternal zinc and LBW is a public health problem in Tanzania and therefore initiate zinc supplementation.

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