THE EFFECT OF ZINC SUPPLEMENTATION ON WEIGHT GAIN IN LOW BIRTH WEIGHT NEONATES

BY

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A THESIS IS SUBMITTED TO THE UNIVERSITY OF DHAKA FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN PEDIATRICS (NEONATOLOGY)

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"..... No tasks nobler than giving children a better future"

Dedicated to All My teachers

and

Those Who Take Care of

Ailing Children

DECLARATION

I do here by humbly declare that this thesis entitled "The Effect of Zinc on Weight Gain in Low Birth Weight Neonates" based on the research work carried out by me. No part of it was presented previously for any higher degree.

The research work was carried out in the Neonatal Ward of Department of Paediatrics of Sher-E-Bangla Medical College Hospital, Barisal, Bangladesh under the Faculty of Post-Graduate Medical Science & Research, University of Dhaka, with the supervision of Prof. (Dr.) Shah Mohammad Keramat Ali. Professor of Clinical Nutrition, Institute of Nutrition and Food Science. Dhaka University, Dhaka and Prof. (Dr.) Syed Zahid Hossain, Professor and Head of department of Pediatrics, Sher-E-Bangla Medical College, Barisal. Bangladesh.

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CERTIFICATE

Thesis entitled "The Effect of Zinc Supplementation on Weight Gain in Low Birth Weight Neonates" submitted by Dr. A.K.M. Aminul Haque for the award of Ph.D in Pediatrics (Neonatalogy), is an independent research work done under the Faculty of Post-Graduate Medical Science & Research, University of Dhaka, Bangladesh with our supervision. This thesis was not been used as the basis for the award of any degree or fellowship.

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ABSTRACT

Introduction. Low birth weight (LBW) neonatal rate is high in Bangladesh. Which is the main cause of neonatal mortality and morbidity. The LBW neonates may be zinc deficient and this might adversely affect their postnatal growth. Zinc supplementation is known to help weight gain in LBW of course, evidence for an effect of zinc supplementation on growth in very young infant in developing countries is scarce and inconsistent. We therefore, tried to examine the effect of zinc supplementation during neonatal period. So, a prospective randomized, double blind, placebo-treated controlled trial study was carried out during the period from May '05 to May 2007 to evaluate the role of zinc on weight gain in low birth weight neonates. The study was carried upon ethical clearance obtained from Bangladesh Medical Research Council.

HYPOTHESIS: Zinc supplementation enhances more weight gain in low birth weight neonates.

Objective : To assess the effect of zinc supplementation on weight gain in low birth weight neonates.

Materials and Methods: The study was carried out using a pre-tested standard questionnaire in the neonatal ward of Department of Paediatrics of Sher-E-Bangla Medical College, Barisal, Bangladesh, during the period from May '05 to May '07. One hundred low birth weight neonates were included in group A and another one hundred in group B matched for birth weight, sex, types of low birth weight and feeding pattern.

Each LBW Neonate was given an identification number and randomly assigned into one of the two groups following a computer generated random number table. At the end of the trial the code was decoded and found D_1 for zinc, D_2 for placebo respectively.

In the first 28 days of life, the neonates of group A received syrup D_1 (2.5ml) and group B received Syrup D_2 (2.5ml) per day respectively. D_1 syrup (2.5ml) contained 5mg of zinc and Syrup D_2 (2.5ml) for group B contained no zinc. The two syrups were indistinguishable in taste and color. The syrups codes were kept secret with the pharmacist to maintain confidentiality.

The parents or attendants were instructed to feed 2.5ml of D_1 syrup for group A and D_2 syrup for group B every morning at 10 am to their neonates for 28 days. The researcher closely supervised the entire activities carefully.

Weights of study neonates were measured without cloth before feeding at 9a.m on 3rd day, 7th day, 14th day, 21st day and 28th day of birth and recorded in the questionnaire. Data were analyzed by using statistical software SPSS.

Result : Among the study subjects 54% were male and 46% were female, 78% were preterm, 22% were IUGR. The mean birth weight of both case and control neonates was 1789.50 + 228.89gm. After 3 days of birth, weight decreased in case neonates to 1610.50 + 255.38gms and to 1613.00 ± 215.04 gms in controls. Weight was more increased in cases than controls after 7 days of birth. Highly significant increase in weight was observed after 21 days (2261.50 + 296.14 gms) in cases than controls (2165.50 ± 243.47 gms), as well as after 28 days (2665.00 ± 331.52 gms) in cases than controls (2374.00 + 410.07 gms). So, mean weight after 21st and 28th days in cases was significantly higher ($P<0.05$) than that of control group.

Per day mean weight gain (31.37 ± 6.91 gm/day) in cases was significantly higher ($P<0.000$) than the mean weight gain (21.63 ± 5.67 gm/day) of control group. However, final mean weight of zinc group (cases) increased to 2665.00 ± 331.52 and that of placebo group increased to 2374.00 ± 410.7, which were significantly higher ($P<0.000$) when compared with mean birth weight of both groups.

Linear curve of effectiveness on weight for age z-score, it was found that increment of effectiveness in Zinc group was higher than that of placebo group. Eighty four percent of cases gained more weight than control group.

Problems like physiological jaundice, infection and convulsion were less in study group (zinc group) compared to control group.

Conclusion : Neonatal mortality in Bangladesh is high as experienced by the causes of death during neonatal period due to low birth weight. The result of the present study provided positive evidence that zinc supplementation in low birth weight neonates enhanced more weight gain and experienced less problems like infection, convulsion, jaundice. There found no adverse effect in zinc supplementation group. Therefore, we can conclude that zinc supplementation to LBW neonates is beneficial to combat curse of low birth weight.

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GLOSSARY AND ABBREVIATIONS

AGA : Appropriate for Gestational Age.

ALRI : Acute Lower Respiratory Infections.

BMI : Body Mass Index.

CHD : Coronary Heart Diseases

DNA : Deoxyribonucleic Acid.

HCL : Hydrochloric Acid.

H_2CO_3 : Carbonic Acid.

IGF : Insulin Like Growth Factor.

IGT : Impaired Glucose Tolerance.

IMR : Infant Mortality Rates.

IUGR : Intrauterine Growth Reterdation.

LBW : Low Birth Weight.

LGA : Large for Gestational Age.

NEC : Necrotizing Enterocolitis.

NIDDM : Non Insulin Dependent Diabetes Mellitus.

RBP : Retinal binding protein.

RNA : Ribonucleic Acid.

ROP : Retinopathy of pre-maturity

SFD : Small-for-date.

SGA : Small for Gestational Age.

CHAPTER 1

INTRODUCTION

1. INTRODUCTION

Zinc is essential for growth. Zinc supplementation accelerated weight gain by increases circulating insulin like growth factor (IGF-I) [1-3], appetite [4,5,6,7], improved ingestion of energy and protein [8,9,10]. IGF-I is the mediator of the growth promoting action of growth hormone. Positive effect of zinc supplementation circulating IGF-1 was reported by Payne[10], Nakamura[11]. Zinc may promote growth through changes in protein synthesis and cell replication, contributing to accumulation of lean tissue [11,12]. Zinc plays a role in nucleic acid metabolism, in many biochemical functions, hormone structure and in genetic transcription factors[13].

Zinc, which has an important immunology and growth promoting role is among micronutrients.

It is needed for diverse physiological processes and metabolic functions including many aspects of the immune system[14]. It is also important for the structure and function of membranes, the metabolism of essential fatty acid. Zinc acts as defiance against oxygen radicals. Zinc is such a critical element in human health that even a small deficiency is a disaster. Zinc supplementation is a powerful therapeutic tool in managing a long list of

illness. Zinc supplementation significantly reduces the incidence of low birth weight[15].

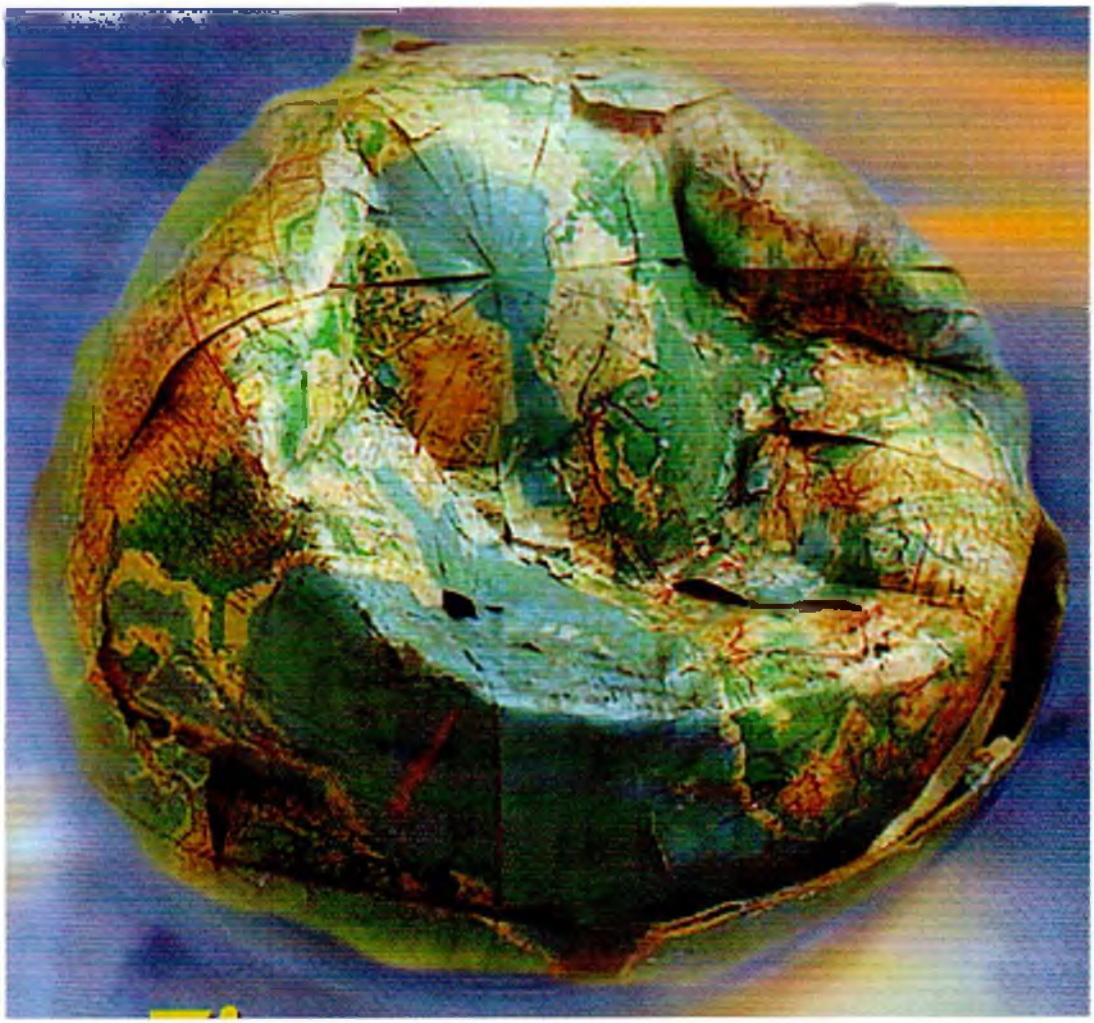


Figure 1A : Zinc deficiency affects nearly one billion people throughout the world

The deficiency of zinc is very widespread throughout the world affecting nearly one billion people[16]. Zinc deficiency impairs many cellular and

humoral (involving hormones and similar compounds) immune functions including lymphocyte number and function. Zinc deficiency in man results in dwarfism and hypogonadism (retarded genital development). There is loss of taste acuity. There is also poor growth, loss of appetite and hypogeusia in young malnourished children with subnormal hair zinc levels. The deficiency of zinc causes delayed closure of the epiphysis of the long bones. Zinc deficiency disturbs thyroid function and metabolic rate. Due to deficiency growth failure associated with infectious disease is well documented[17]. Further recent evidence suggests that fetal organs are affected by zinc deficiency. Failure to thrive, night blindness may also occur.

Zinc is an essential mineral for human cell growth, differentiation, and DNA synthesis and it is known to improve water and electrolyte absorption, accelerate the regeneration of the gut epithelium, increase the activity of brush border enzymes and enhance overall immune function.

Zinc deficiency, a prevalent condition of young children in developing countries, is associated with decreased immunocompetence and increased rates of serious infectious diseases. Recently, strong evidence for a causal relationship between zinc deficiency and childhood infections has come from randomized controlled trials of zinc supplementation in poor but not severely malnourished children in several developing countries[18].

Zinc is perhaps the most widely studied microelement in infant feeding as it is important to growth, cell differentiation, and to the metabolism of proteins, carbohydrate and lipids.

There is no simple and accurate method to measure zinc status in human. There is no zinc storage in the body for which zinc deficiency in human is quickly manifested at various magnitudes. Adequate zinc must be available in daily diet. Experimental zinc deficiency in human volunteer has shown that plasma zinc level absorption by 5th day of deprivation when subjects had low zinc intake in previous 2 weeks [19].

Zinc status in a man can be measured by plasma or serum zinc, or presences of zinc in hair, urine, saliva, leukocytes, platelets and red blood cells. Zinc status can be measure by turnover of labeled zinc. Proxy indicators such as activity of zinc metalloenzymes (alkaline phophatase, carbonic anhydrase etc), has been shown to be useful[20].

Serum Alkaline phosphatase is low in severe zinc deficiency and returns to normal and a rise in serum alkaline phosphatase after zinc supplementation.

The role of zinc in human nutrition is being increasing by highlighted after recent advances in biomedical research. Zinc as a micronutrient contributes greatly to healthy growth and development, especially in children [21-23].

Studies have demonstrated low zinc status in low birth weight neonates[24]. A zinc requirements of LBW neonates are high because of their immature

gastrointestinal tracts, which leads to both high endogenous losses and decreased absorption, an extended period of rapid growth and low body sores of zinc[25-26].

More characteristic manifestations develop after 3 months, including weight loss, failure to thrive, periorifical dermatitis, glositis, and enhanced susceptibility to infections. Zinc deficiency has been associated with poor growth and zinc supplementation in growth retarded children stimulated growth [27-32]. These studies indicate a reduced level of zinc in low birth weight neonates which might well account for growth failure in such neonate. Because there are no reliable biochemical indices for marginal zinc status, particularly for young children. It therefore convenient to use controlled supplementation, assessed by growth indices and morbidity reduction, as outcome variables[33]. Low birth weight is a major pediatric problem, accounting for 50% of all live births in a developing country such as Bangladesh[34]. This study was undertaken to assess the effect of zinc supplementation on weight gain in neonates.

Zinc intervention trial in infants and children have shown significant improvement in growth[35] and decreased morbidity, particularly from diarrhoeal disease[36] and malaria[37], although more recent studies have challenged the later finding.[38-39]

Chandra found significant improvement in immune function even in LBW supplemented with zinc.[40]

0+1.1 : Statement of the Problem

Bangladesh is an alluvial and deltoid land of 1,47,570 sq.km. She is a poor and most densely (948/sq km.) populated country in the world. Her neonatal mortality is 41. The incidence of low birth weight 30 – 50%.

The most common cause of neonatal mortality is low birth weight (24%).

According to diet counseling center, Bangladesh the prevalence of malnutrition in Bangladesh is the 2nd highest in the world. Currently 45% children and 35% women are suffering from extreme malnutrition.

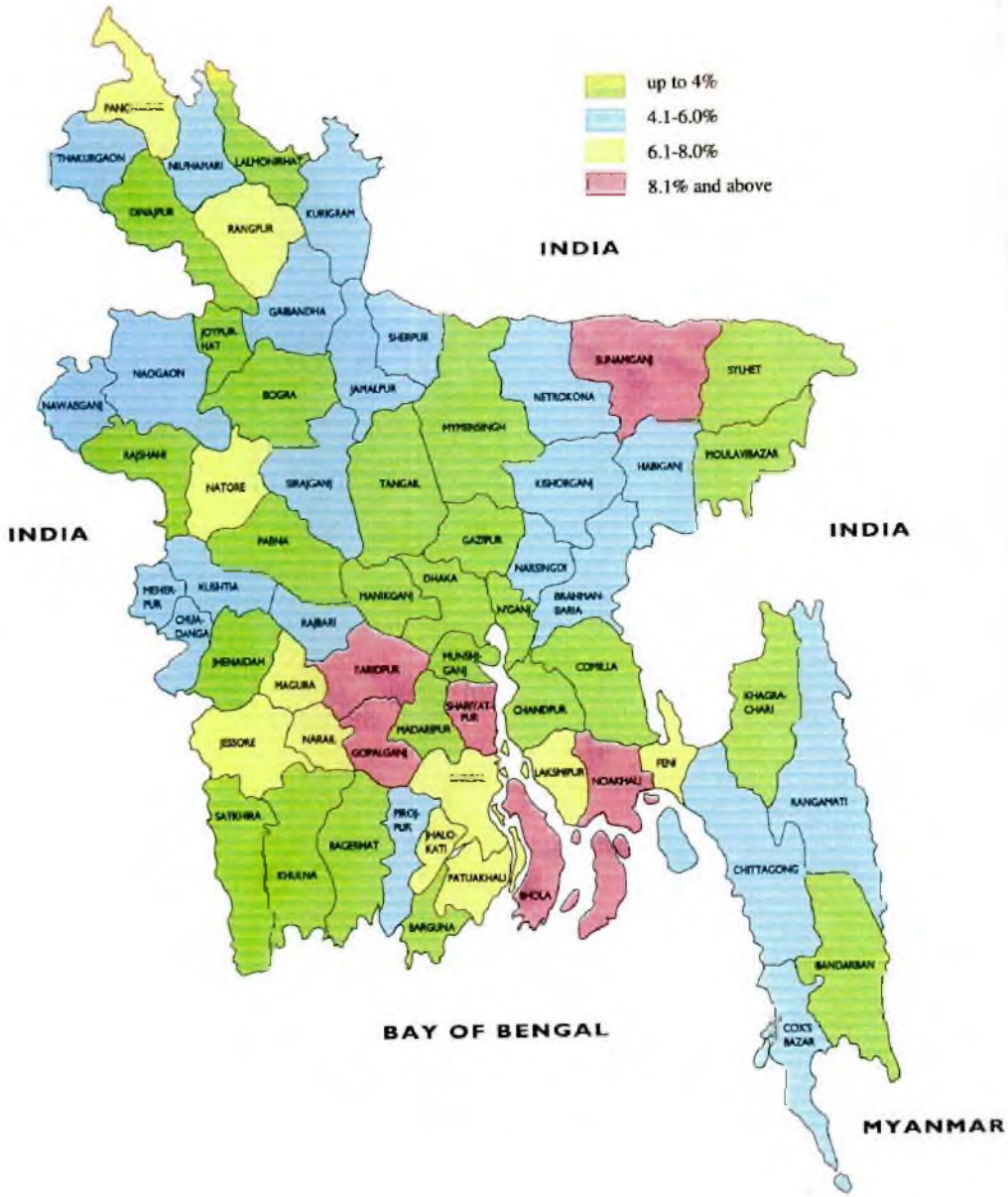


Figure: IB. Prevalence of Malnutrition (MUAC less than 12.5 cm) in Children of Bangladesh.

Source: BBS/UNICEF Multiple Indicator Cluster Survey.

The period of intrauterine growth and development is one of the most crucial in the human lifecycle.[41] The weight of an infant at birth is an important indicator of maternal health and nutrition prior to, and during pregnancy, and a powerful prediction of infant growth and survival. Infants born with low birth weight (LBW) suffer from extremely high rates of morbidity and mortality from infectious disease. Over and above under weight, stunting or wasting beginning in the neonatal period through childhood. Every year approximately 17 million infants in developing countries are born with LBW[42] and those infants who survive have little chance of fully reaching their growth potential. Moreover, evidence now shows that adults born with LBW face an increased risk of chronic diseases including high blood pressure, non-insulin dependent diabetes mellitus, coronary heart disease and stroke in adulthood[43].

The causes and effects of LBW are complex and best considered within the lifecycle conceptual framework (Figure IC). Poor nutrition often begins in utero and extends throughout the lifecycle. This amplifies risks to the individual's health and increases the likelihood of damage to future generations through further fetal under nutrition. Under nutrition, manifested by decreased maternal height (stunting), and below normal pre-pregnancy weight and pregnancy weight gain, are among the strongest predictors of delivery of a LBW infant. There are few well-defined and proven effective nutritional interventions directed at adolescent girls and women of childbearing age and during pregnancy. For those interventions proven to be scientifically efficacious (e.g., dietary supplementation during pregnancy),

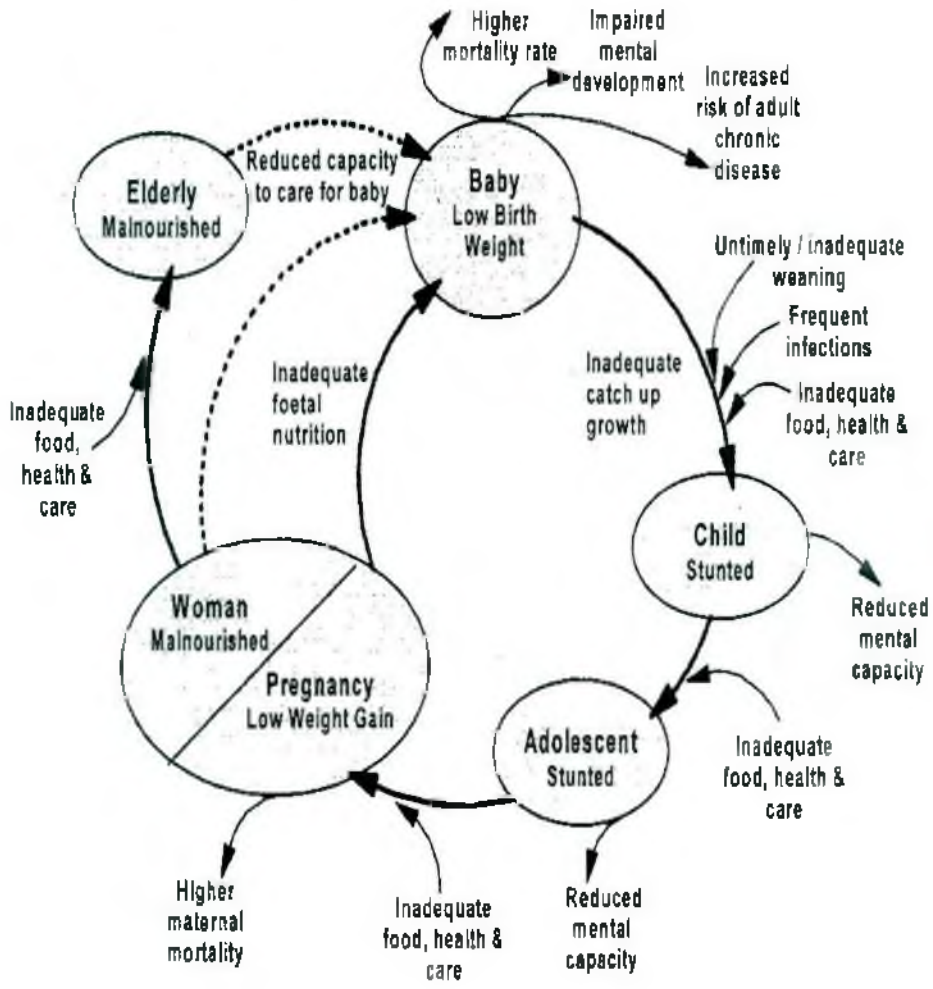
programme demands (cost, logistics of implementation) are great. Also, due to the intergenerational characteristics of the LBW problem, successful interventions will likely require substantial programme and donor commitment over a sustained, extended period of time.

There is an urgent need to answer basic and fundamental questions about the prevention of LBW and its devastating sequel. The appropriate timing, amount and characteristics of nutritional supplementation; the role of micronutrients; the impact of infection control on LBW prevention; and the full magnitude of health problems faced by adults born with LBW are all poorly understood. Answers to these questions are fundamental to understanding the potential effect of various optional biological inputs. They are, however, only a prelude to investigating the sustainable ways in which these biological effects will be promoted and actually occur through the behaviours of people in households, service setting and communities. The identification of effective and practical interventions to prevent LBW and to improve the outcome of infants born with LBW, including those with a strong behavioral change component, would have an enormous impact on the health and productivity of individuals and society, particularly in those regions where the prevalence of LBW is high.

LBW perpetuates the intergenerational cycle of poverty, under nutrition and disease. This is especially so when adolescents become pregnant before their own growth is completed, leaving little to fulfill their own or their infant's nutritional requirements. One of the nutritional goals of the 1990 World Summit for Children was to reduce the prevalence of LBW to less than 10%

by the year 2000- needless to say, LBW remains a formidable challenge for the 21st century.

Figure 1: Nutrition throughout the lifecycle



Source: Commission on the Nutrition Challenges of the 21st Century (2000) Final report to the ACC/SCN.

1.2: DEFINITIONS

Low Birth weight (LBW)- Low birth weight is defined as a body weight at birth of less than 2500 grams (g). There are two main causes for LBW: pre-maturity and intrauritering growth retardation (IUGR). LBW is often used as a proxy indicator to quantify the magnitude of IUGR in developing countries because valid assessment of gestational age is generally not available.

Preterm- The term pre-term is used for infants born before 37 weeks gestation. Most, but not all pre-term neonates weigh less than 2500g. There are many reasons for pre-term delivery, however, in many cases the cause is unknown. Reason include high maternal blood pressure, acute infections, multiple births, hard physical work, or stress.

Intrauterine Growth Retardation (IUGR)- Intrauterine growth retardation is a subtype of LBW of extraordinary importance to developing countries. IUGR is a condition where fetal growth has been constrained. An inadequate nutritional environment in utero can be one reason for this constrained growth. IUGR is usually assessed clinically when the fetus is born by relating the size of the newborn to the duration of the pregnancy using the 10^{th} percentile of a reference population. A small size for gestational age indicates IUGR, or the inability of the fetus to reach its growth potential. Infants diagnosed with IUGR may be :

(1) LBW at term (≥37 weeks gestation and <2500 g);

(2) Pre-term (<37 weeks gestation and weight less than the 10th percentile); or

(3) IUGR at ≥37 weeks gestation and weight less than the 10th percentile with a birth weight ≥2500 g.

Thus, because not all pre-term infants are IUGR, LBW among pre-term Neonates overestimates poor growth due to nutritional causes; and because some IUGR infants weigh more than 2500 g (the third classification), LBW at term underestimate the overall magnitude of the IUGR problem.

IUGR-LBW – In developing countries IUGR affects about two-thirds of infants born with LBW; the remaining one-third of these LBW infants are born pre-term, some of whom are also affected with IUGR. IUGR-LBW is used in some publications to refer only to IUGR infants who are LBW at term. IUGR infants born at term (≥37 weeks gestation) with LBW (<2500 g) are referred to in this publication as LBW at term.

Small for Gestational Age (SGA)– SGA infants have birth weights below a given low percentile cut-off for gestational age. SGA and IUGR are not strictly synonymous: some SGA infants (e.g., those born to short mothers) may represent merely the lower extreme of the "normal" fetal growth distribution, while other infants who meet the criteria for "appropriate for gestational age" may have actually been exposed to one or more growth-inhibiting factors. In individual cases, however, it is usually very difficult to ascertain whether or not the observed birth weight is the result of restricted

in utero growth; classification of an infant as IUGR is thus based, de facto, on the established cut-off for SGA.

Under nutrition- In this report the term under nutrition refers collectively to stunting, underweight, wasting, low body mass index, and fetal growth retardation- conditions of inadequate nutrition.

1.3: Neonatal Period

The neonatal period extends from birth to 28 days of age.

Perinatal period- Period from 24th weeks gestation or the time of life birth of less than 24 week's gestation to 7 days.

Early neonatal period- The first 7 days of neonatal period.

Late neonatal period 8-28 days after birth.

Classification of Newborn.

According to gestation and birth weight newborns are categorized as follows:

Gestation

Pre-term	: < 37 completed weeks of gestation
Term	: 37 to 42 weeks
Post-term	: > 42 completed weeks

Birth Weight

Normal birth weight	: 2500 g to 4000 g
Low birth weight	: < 2500 g
Very low birth weight	: < 1500 g
Extreme low birth weight	: < 1000 g

Birth weight and gestation (see Figure-ID)

Appropriate for gestational age (AGA): Birth weight between 10th and 90th centiles for that particular gestational age.

Small for gestational age (SGA) : Birth weight < 10th centile for that particular gestational age.

Large for gestational age (LGA) : Birth weight > 90th centile for that particular gestational age.

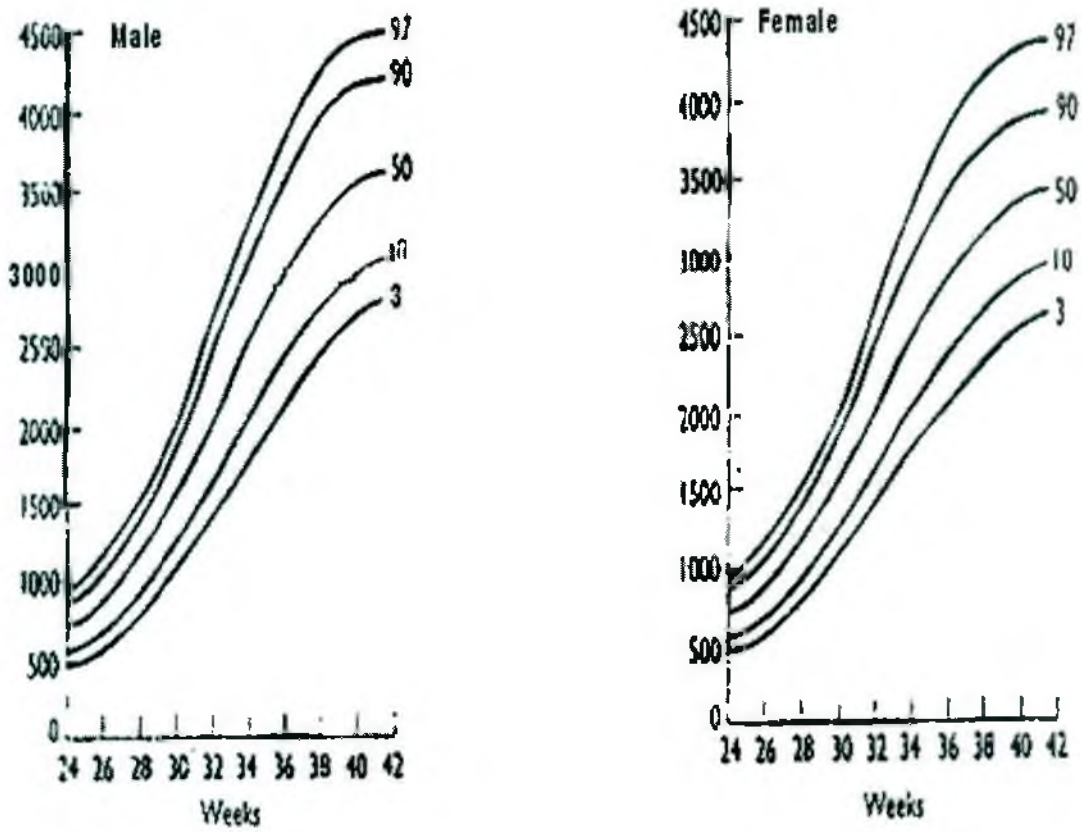


Figure: 1D. Birth weight centiles by gestational age[44].

1.4: Epidemiology, Causes and Consequences of Low Birth weight

Levels, patterns and Determinants of LBW in Developing Countries.

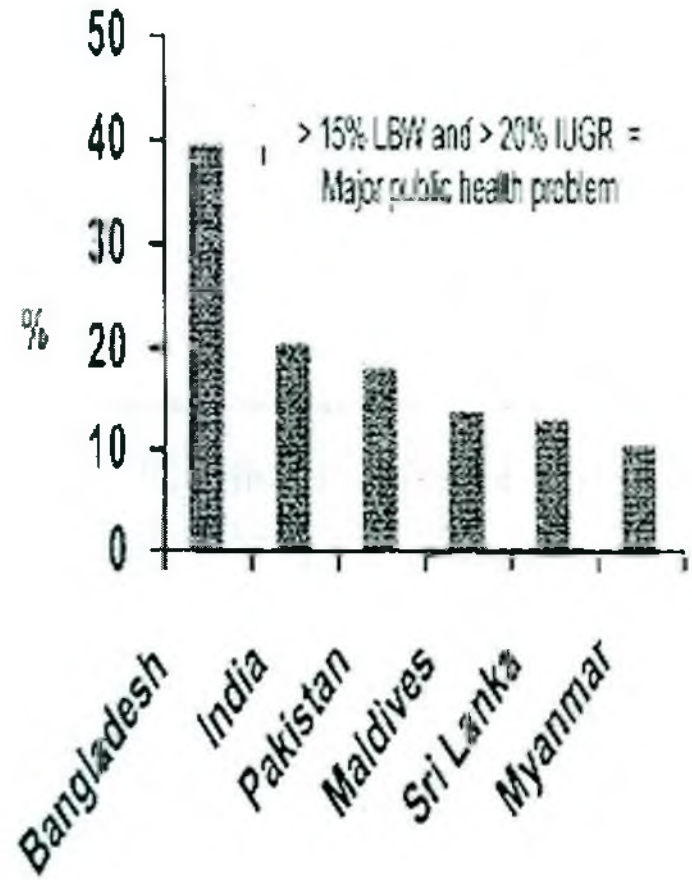
At least 17 million infants are born every year with LBW, representing about 16% of all newborns in developing countries. Nearly 80% of all affected newborns with LBW at term are born in Asia (mainly south-central Asia, with Bangladesh having the highest LBW rate in the world[45]); about 15% and 11% are born LBW at term in middle and western Africa respectively, and approximately 7% in the Latin American and Caribbean region[42]. The geographical distribution of LBW at term in selected Asian countries (Figures 1E) confirm that many developing countries exceed the internationally recommended cut-off levels which should trigger public health action. LBW rates of >15% for and >20% for IUGR indicate that LBW at term is a major public health problem. Population-wide interventions aimed at preventing LBW at term are therefore urgently required[46].

Historically, because valid assessment of gestational age is often not available in development countries, evidence of LBW has often been used as a proxy to quantify the magnitude of IUGR. The rates for LBW at term conservatively estimate IUGR because when al infants below the 10 percentile of the birth weight for gestational age reference are considered.

approximately 24% or 30 million newborns in developing countries would be affected each year. Major constraints to deriving this estimate include both the quantitative and qualitative limitations of the available birth weight data. Most of the data available from different parts of the world are from clinic or hospital deliveries, whereas, in some regions of Africa and south east Asia most infants are born at home and are not measured. There is a need to determine whether data from hospital born infants in development countries are representative of the large population born at home.

Pre-term and IUGR are the two main causes of LBW. The majority of LBW in developing countries is due to IUGR, while most LBW in industrialized countries is due to pre-term birth[47]. In many cases, the causes of pre-maturity are unknown; they may include high maternal blood pressure, acute infections, hard physical work,

Figure 1E Incidence of LBW *at term* in selected Asian countries



Source: de Onis et al. (1998) Eur J Cl Nutr 52(S1):S5.

1.5:

Box 1. Determinants of LBW in Developing Countries[48].

Maternal under nutrition-a major determinant of LBW in developing countries as evidenced by the following nutritional deficiencies;

Low gestational weight gain

Low pre-pregnancy body mass index (BMI)

Short maternal stature

Micronutrient deficiencies

Other etiologic determinants include;

Young maternal age (adolescent)

Malaria during pregnancy

Gastro-intestinal respiratory intestinal parasitosis and/or other infections

Cigarette smoking

Source: Kramer (1987) Bull WHO 65:663

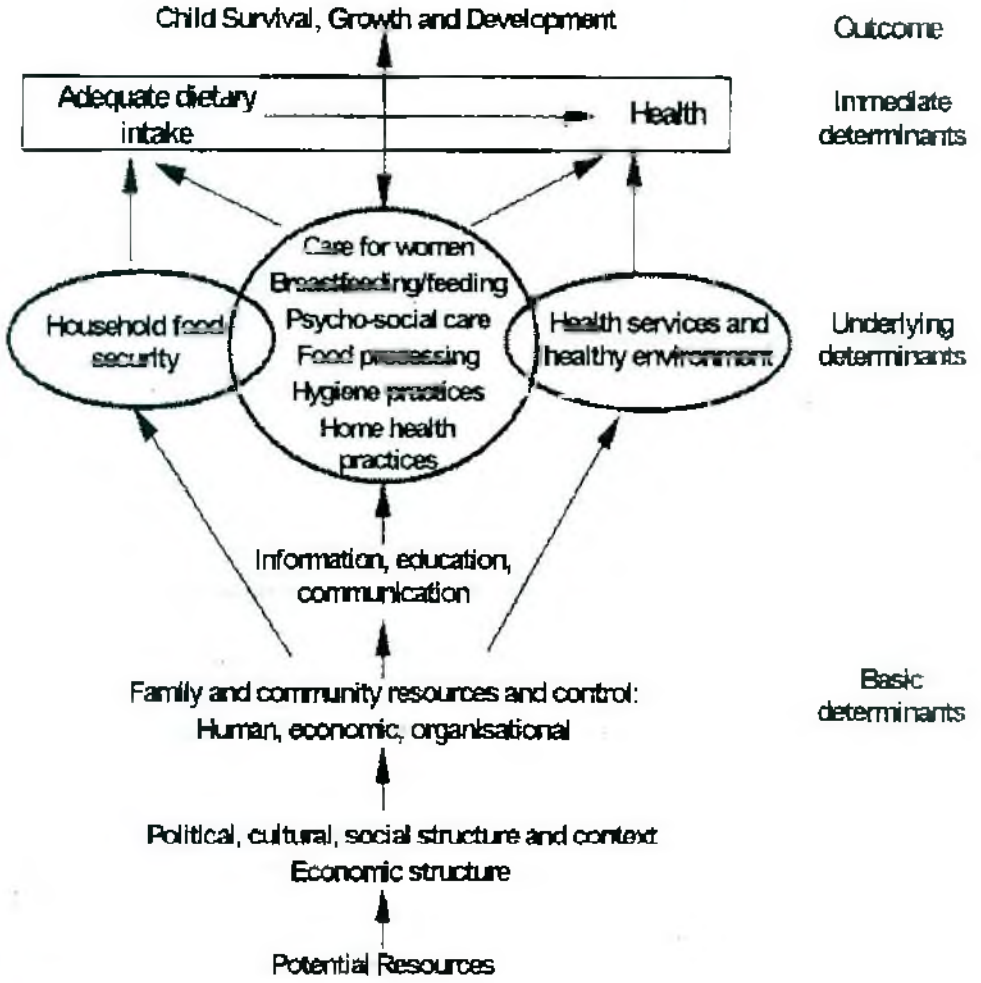
multiple births, stress, anxiety, and other psychological factors[49]. Causes of IUGR are complex and multiple, but center on the fetus, the placenta, the mother, and combinations of all three. For instance, growth will be retarded in utero if the placenta is abnormally small or blocked causing insufficient nutrients to reach the fetus. The maternal environment is the most important determinant of birth weight, and factors that prevent normal circulation across the placenta cause poor nutrient and oxygen supply to the fetus, restricting growth. These factors may include maternal under nutrition, malaria (where it is endemic), anemia and acute and chronic infections (such as sexually transmitted diseases and urinary tract infections[50]). Also associated with IUGR are primiparity multiple gestation; fetal genetic or chromosomal anomalies, as well as maternal disorders such as renal diseases and hypertension. Cigarette smoking and pre-eclampsia causes the highest relative risks for IUGR in industrialized countries, while alcohol and drug use may also restrict fetal growth[50,51].

Major determinants for LBW in developing countries, however are poor maternal nutritional status at conception, low gestational weight gain due to inadequate dietary intake and short maternal stature due to the mother's own childhood under nutrition and/or infection. Because maternal under nutrition

is a major determinant of LBW in developing countries, high rates of LBW should be interpreted not merely as an indicator of under nutrition morbidity and mortality for the newborn but as urgent public health warning that women of childbearing age are undernourished as well. Countries with higher percentages of LBW infants generally have a higher percentage of women with low body mass index (BMI) and a higher percentage of underweight children[52,53]. To address these issues successfully, the underlying and basic causes of LBW in developing countries such as household food security, maternal and child care, access to and quality of antenatal and other health services, sanitation and hygiene, education gender discrimination and poverty must be included in any long term strategies for prevention (Figure 1F)

The purpose of our study was therefore to determine whether zinc supplementation might be an effect public health intervention to increase growth.

Figure 1F. Causes of malnutrition



Source: UNICEF (1997) *The Care Initiative: Assessment, Analysis and Action to Improve Care for Nutrition*, UNICEF: NY.

1.6: Morbidity and Mortality Consequences of LBW in Neonates and Infants

LBW is generally associated with increased morbidity and mortality, impaired immune function, and poor cognitive development for neonates (newborns 1-28 days of age) and infants. Infants born LBW are at risk to develop acute diarrhoea or to be hospitalized for diarrhoeal episodes at a rate almost two to four times greater than their normal birth weight counterparts[54,55]. Infants who are LBW risk contracting pneumnonia or acute lower respiratory infections (ALRI) at a rate almost twice that of infants with normal birth weight; and more than three times greater if their weight is less than 2000 g[56-59]. LBW is also implicated as a contributor to impaired immune function which may be sustained throughout childhood[60-62].

The risk of neonatal death for infants who are LBW weighing 2000-2499 g at birth is estimated to be four times higher than for infants weighing 2500-2999 g, and ten times higher than for infants weighing 3000-3499 g[63]. In Brazil, 67% of all infants dying during their first week of life are LBW infants; in Indonesia the rate is 40%; and in the Sudan the rate is 35%. Infant mortality (less than one year of age) due to LBW was slightly lower; 47% in Brazil and 19% in Indonesia[64-66]. LBW infants during the post-neonatal period (>28 days of age) also have high mortality rates- and in some cases their risk may be greater than those for LBW infants during the neonatal period[67]. LBW accounted for 69% of the ALRI deaths in India, and it is estimated that in Bangladesh, almost half of the infant deaths from pneumonia or ALRI and diarrhoea could be prevented if LBW were eliminated[68].

1.7: Fetal and Neonatal Growth[69].

a. Fetal growth. The fetal growth rate is 5g/day at 14-15 weeks gestation, 10g/day at 20 weeks, and 30g/day at 32-34 weeks. The growth rate slows after 36 weeks gestation[69].

(1) During the first trimester, growth parameters (i.e. weight, length, head circumference) are fairly uniform in all fetuses.

(2) Variability in fetal growth during the last trimester is the result of several factors, including genetic endowment, fetal nutrition, and multiple gestation (fetal growth rate declines at 31 weeks gestation in twins and at 29 weeks gestation in triplets.

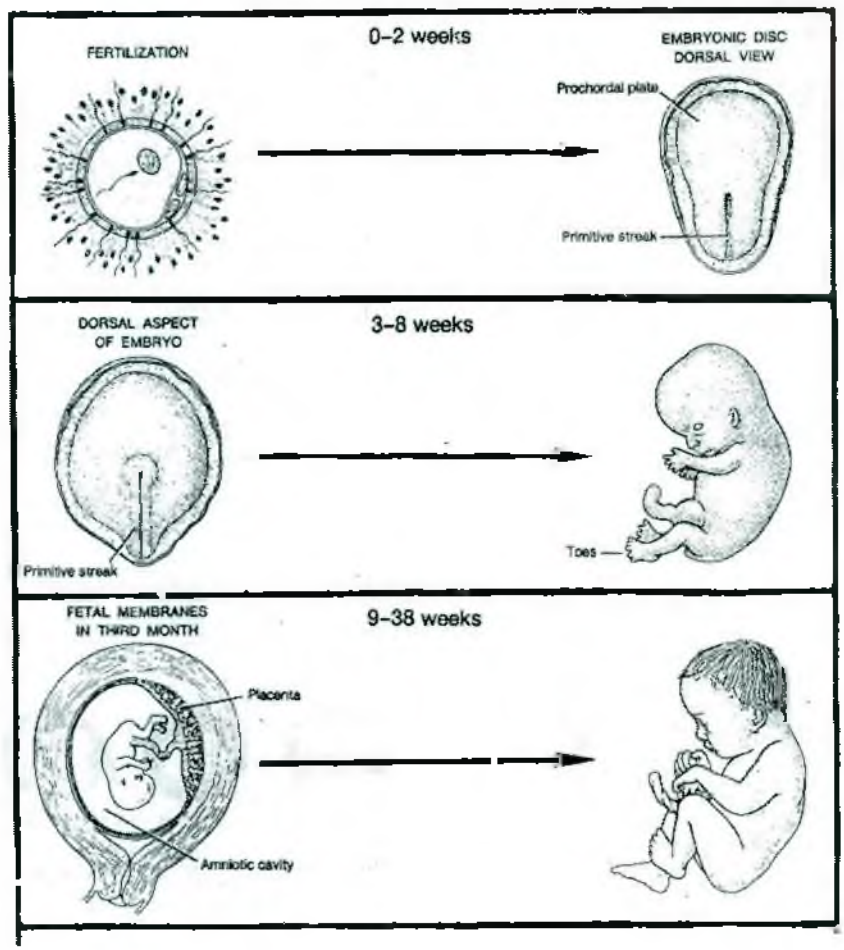


Fig. 1G : Fetal Development (0-38 weeks)

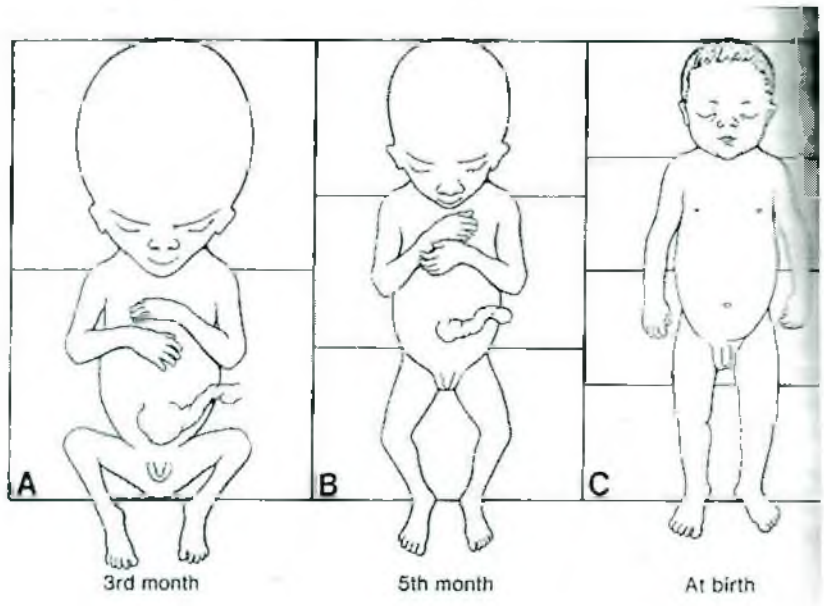


Fig. 1H : Fetal Development (3rd month - birth)

1.8: Neonatal Growth[69].

(1) After birth, there is a loss of weight due to loss of extra cellular water and sub-optimal caloric intake. Term infants lose 5% - 10% of their birth weight; preterm infants lose up to15% of their birth weight.

(2) Term infants regain their birth weight by the end of first week of life and thereafter gain 20-30 g/day.

Growth in children

Do LBW infants grow normally? What are the consequences of LBW on body size, composition, strength and cognitive development? Attaining full growth potential is especially important for women and girls in order to break the intergenerational cycle of LBW and have fewer delivery complications. Maternal height is not only a reflection of genetic make-up

but also reflects her dietary history. From societal community and individual standpoints, adolescents and adults born with LBW generally have less strength and lower lean body mass resulting in decreased work capacity and lost productivity, which may cost nations billions of dollars[70].

When growth restriction in utero occurs early in pregnancy, infants exhibit symmetrical (or proportional) growth with length weight, head and abdominal circumference all below the percentile reference for a given gestational age (stunting). When growth restriction in utero occurs late in pregnancy, the infant exhibits asymmetrical (or disproportionate) growth with a normal length and head circumference, but low weight due mainly to a lower proportion of visceral and fat tissue (wasting). Neonatal mortality rates are reported to be higher among asymmetrical IUGR infants, but if they service, they have a better prognoses for long term growth and development than that for symmetrical IUGR infants. IUGR infants catch up partially in growth relative to their appropriate birth weight counterparts during their first one of two years of life. Thereafter, IUGR children maintain their place in the distribution and neither catch up nor fall further behind. They remain about 5cm shorter and 5 kg lighter as adults. Premature infants (who are usually asymmetric LBW) who service their first year, have a much better prognosis in term of future growth than IUGR infants. Despite their earlier disadvantage, preterm children gradually catch up with their appropriate birth weight, term counterparts. Premature infants and IUGR infants should be studied as separate groups because they show different patterns of growth, morbidity and mortality. From a programmatic viewpoint these differences

have enormous implications for intervention strategies and limitations of the approach of nutritional recovery of IUGR infants in early childhood[71-77].

Neurological dysfunction is often associated with attention deficit disorders, hyperactivity, clumsiness, and poor school performance. Neurologic dysfunction, when present seems to affect IUGR boys more than girls, and children of lower socioeconomic circumstances. If IUGR infants are symmetrical and head growth is affected there seems to be more of an impact on neurological function and it is not clear whether interventions directed toward these infants will improve their outcome. For asymmetric IUGR infants, preventing asphyxia should reduce the prevalence of major and minor handicaps, especially cerebral palsy and mental impairment frequently seen in these infants[76,77]. IUGR is much larger public health problem in developing countries than in industrialized countries and the outcomes are more likely to be aggravated by obstetric complications and perinatal problems, and later by poor health and nutrition as well as psycho-social deprivation[78].

In developing countries children are exposed to poor nutrition high levels of infections, and other conditions of poverty, thus their long term development is dependent to a large extent on the quality of their environment. It is difficult to isolate the effects of IUGR from these factors in relation to cognitive development. Cognitive deficits appear to change over time. For instance when IUGR infants were examined, no differences were found during the first year of life, but differences emerged during two and three

years of age; and then differences disappeared at four to five year. Deficits have been found in children with very low birth weights, the smallest size or with early IUGR (growth restriction prior to 26 weeks gestation). Since LBW occurs more often in deprived environment, it can serve as a marker for the associated poor outcomes throughout life. A length deficits at an early age (stunting) would be the best predictor of motor and mental development deficits[79-81].

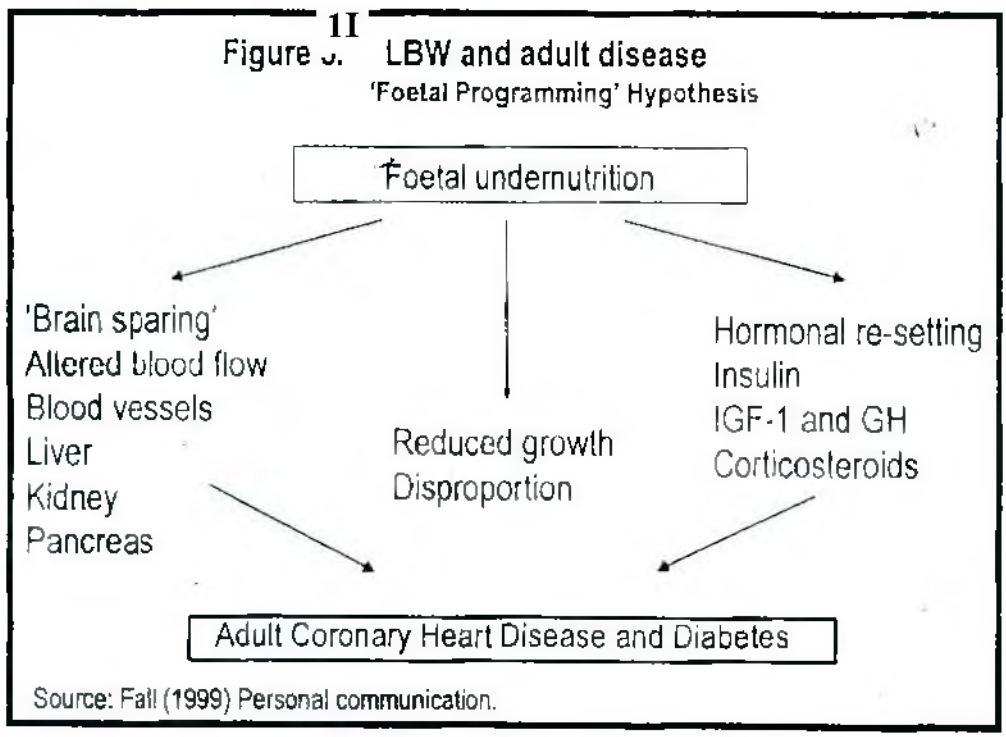
1.9: Long-term Consequences of LBW: The Fetal Origins of Disease Hypothesis

The fetal origins of disease hypothesis states that fetal undernutrition at critical periods of development in utero and during infants leads to permanent change in body structure and metabolism. These changes result in increased adult susceptibility to coronary heart disease (CHD) and non-insulin dependent diabetes mellitus (NIDDM). There is also growing evidence that those adults born with LBW suffer an increased risk of high blood pressure, obstructive lung disease, high blood cholesterol and renal damage. Thus a poorly growing foetus is an under nourished foetus prone to reduced growth, altered body proportions, and a number of metabolic and cardiovascular changes. It has been suggested that these changes are adaptations for foetal service in an inadequate nutritional environment, and that these changes persist postnatally, contributing to adult chronic disease when nutrients are plentiful.

The fetal origins of disease hypothesis, also known as the Barker hypothesis was generated by David JP Barker and colleagues of the MRC Environmental Epidemiology Unit of the University of Southampton.

Barker's group was puzzled that CHD was the most common cause of death among certain men who otherwise had low risk characteristics, i.e., they were slim, non-smokers, and had low blood cholesterol. This suggested that the etiology of CHD needed further exploration. The group speculated that fetal under nutrition during the first trimester may result in a proportionately small (symmetrical or stunted) infant prone to haemorrhagic stroke. Fetal under nutrition during the latter stages of pregnancy may result in a disproportionate (asymmetrical or thin) infant prone to CHD and an increased risk of insulin resistance or a short infant prone to CHD and thrombotic stroke[82].

The fetal origins hypothesis originated in the 1980's when Dr. Barker replicated a study from Norway which demonstrated a strong correlation between infant mortality rates (IMR) at the beginning of the century with current death rates from CHD. The author of the Norwegian study suggested that because infant mortality is a sensitive indicator of the quality of the immediate post natal environment perhaps growing up in poverty causes some sort of



deficit which result in a lifelong vulnerability to aspects of an affluent adult lifestyle such as a high fat diet. Dr Barker found a similar correlation between IMR and death from CHD in England and Wales but suggested. however that since CHD was more closely correlated with neonatal mortality than with post neonatal mortality, CHD may find some of its roots in IUGR as reflected by LBW. The historical evolution of the Southampton groups research included a move from geographical associations, to associations related to individuals than to biological risk factors. Birth records from Hertfordshire UK were first used to study mortality in relation to birth weight. The study showed that the highest death rates were in men and women who had the lowest birth weights, and death rates fell as birth weight increased. This pattern was specific for CHD and chronic obstructive lung disease. A similar pattern was found for biological risk factors (hypertension and impaired glucose tolerance (IGT) and diabetes) for CHD in men the highest rates were in men who had been small infants. More than 20% of men whose birth weights were lower than 2500 g had abnormal glucose to clearance compared with under 10% of those weighing more than 4000 g at birth. These study results have now been replicated by several groups in many different countries including to USA, Sweden, Finland, India and China.

The Barker research group also proposed a fetal programming hypothesis in which there is a brain-sparing reflex that in an under nourished fetus, diverts or conserves the blood flow to the head, while simultaneously reducing the blood flow to the liver, pancreas and kidneys. This results in a reduced

secretion of growth hormones insulin and other endocrine changes which leads to CHD and NIDDM in adulthood (Figure 1I). The Baker theory remains hypothetical since no causal relationships have yet been established, only associations. Two other explanations for the association between LBW and adult disease include the confounding explanation (Figure 1J) and a genetic explanation (Figure 1K). The confounding explanation suggests that LBW is a marker for poor socioeconomic status: poor people have smaller infants who are more likely to smoke be exposed to stress grow up with inadequate nutrition and become obese all factors which cause CHD. The genetic explanation on the other hand, suggests that if an individual has a gene for insulin resistance, this would head to LBW and the same genetic pre-disposition would lead to an increased risk of adult diabetes and CHD.

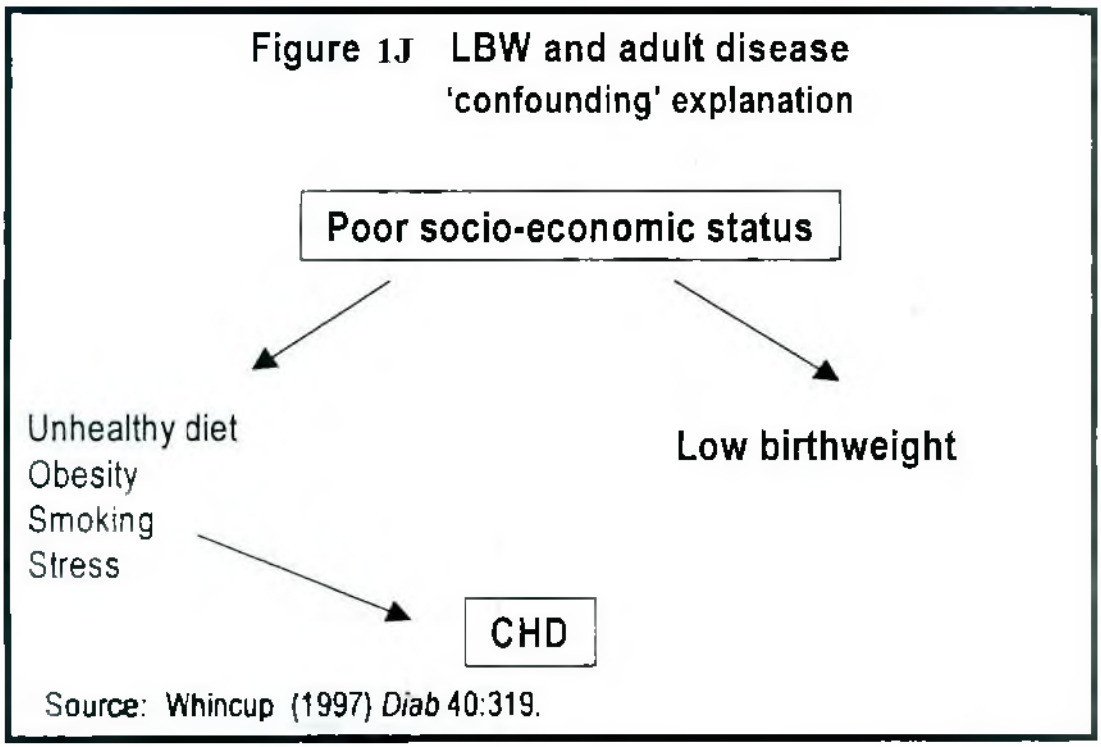
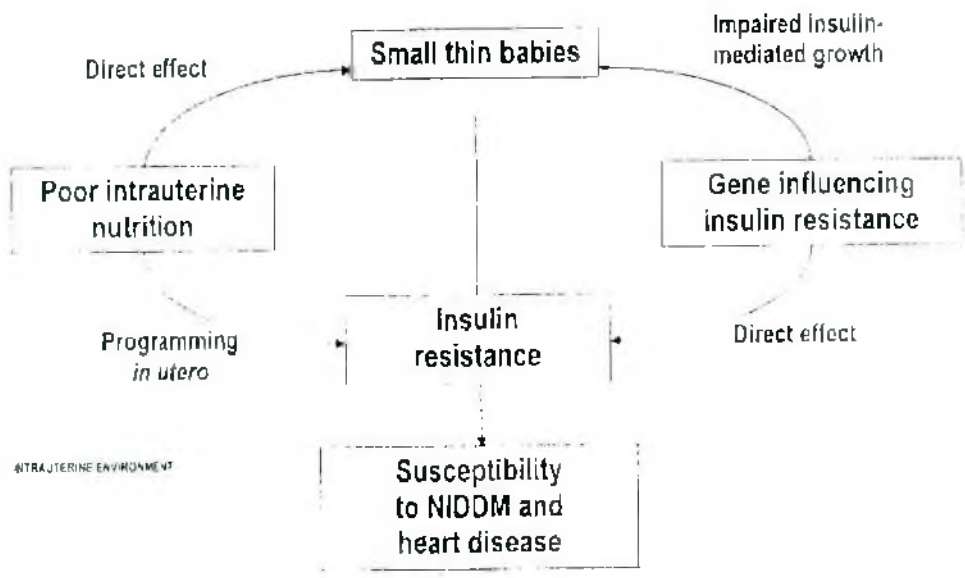


Figure 1J LBW and adult disease 'confounding' explanation

Source: Whincup (1997) *Diab* 40:319.

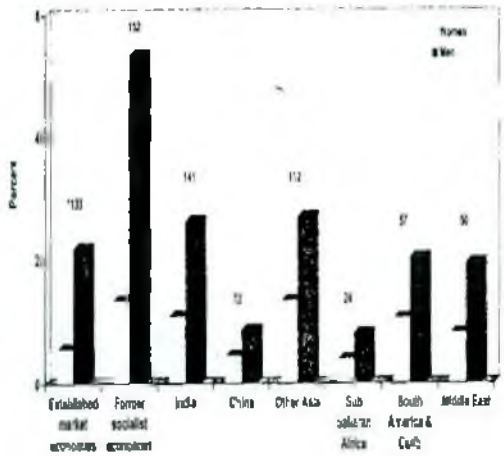
Figure 1K LBW and adult disease 'genetic' explanation



Source: Hattersley (1999) *Lancet* 353:1789.

Lack of information on possible confounding lifestyle and environmental factors, limitation of the initial Barker studies to two populations in the UK, the retrospective nature of the observations, and differences in study methodologies all underscore the need to establish a core research protocol to investigate a longitudinal relationship between LBW due to poor foetal growth and disease in later life.

Figure 1L oronary heart disease probability of death ages 15-60 years



Source: Murray & Lopez (1994) *Bull WHO* 72:447. * estimated numbers of deaths in thousands (1990 - sexes combined)

The fetal origins theory appears to be of greatest relevance to developing countries where mean birth weights remain low and rates of LBW are high. Many of these countries are experiencing a nutrition transition which includes changes in dietary intake, physical activity and body composition. The nutrition transition refers to a shift to diets high total fat, sugar and refined grains; it includes a more sedentary lifestyle; and increased use of tobacco products. Simultaneously an epidemiological transition is occurring in these countries. This is evident by a shift away from the high prevalence of infections disease and under nutrition as cause of mortality to a high prevalence of chronic and degenerative disease conditions made worse by the nutrition transition. This raises urgent concerns regarding prevention of

the already burdensome and growing epidemic of CHD in these countries (Figure 1L) because LBW especially in association with increased body fat, either as an adult or as a child leads to insulin resistance, and an increased risk of CHD. Regardless of the controversy over the fetal origins theory the fact remains that the stages of gestation are poorly understood. The fetal origins theory leaves the scientific community with unanswered questions although waiting for these and other answers should not delay the programme implementation of those interventions that have already been shown to be or are likely to be efficacious against low birth weight. The role of adequate pregnancy weight has been established as a determinant of LBW in developing countries. So improvement in nutrition of young girls and women is very probably one important step toward the prevention of LBW and is accompanying disease burden.

Thus the literature suggest that a study to supplement zinc in Low Birth Weight infant in Bangladesh is useful, timely and feasible in term of technology an expert manpower. So we under took this prospective double blind control trail to find out the rate of weight gain and related parameter for survival of LBW neonate.

1.10: HYPOTHESIS

Oral zinc supplementation during neonatal period enhances quick weight gain in low birth weight neonates.

CHAPTER- 2

OBJECTIVES

2. OBJECTIVE

General Objective

To measure the effectiveness of zinc supplementation on weight gain of low birth weight neonates.

Specific Objective

1. To list low birth weight (LBW) babies admitted in neonatal ward of Pediatrics Department of Sher-E-Bangla Medical College Hospital, Barisal during one clander year.

2. To supplement Zinc in a group low birth weight neonate and to compare with another group of low birth weight neonate will receive placebo for a period of 28 days along with necessary treatment for both groups.

3. To compare the study group with control to find out where and when zinc have contributed to weight gain, side effect of supplementation and acceptance of supplementation by the neonates.

CHAPTER- 3

REVIEW OF LITERATURE

3. REVIEW OF LITERATURE

3.1 Review of the past Research involving zinc & LBW

Growth is the major factor used to determine zinc requirements of preterm infants. Calculations of zinc requirements for preterm infants between 24 and 28 weeks of gestational age indicate a requirement of 600 μg/day for the formation of new tissues (except zinc for storage), necessary to provide growth similar to the one achieved by a 40 weeks. The release of hepatic zinc by a newborn weighing 1,000 g is on average 150 μg/day. Extremely preterm around 32-36 weeks infants have fewer reserves and depletion occurs earlier. The calculation of dietary zinc in order for optimal growth to occur is equivalent to 500 μg/day, with approximately 1,000 g of birth weight and 27 weeks of gestational age; 400 μg/kg/day for newborn infanta between 1,500 and 2,000 g (30-32 weeks) and 200-300 μg/kg/day for those weighing between 2,500 and 3,500 g (35-40 weeks).[83]

Studies involving isotope-labeled compounds show that preterm infants are able to take up exogenous zinc, increasing its absorption and reducing its exogenous zinc, increasing of this behavior in extremely preterm infants are still unknown. Preterm infants can take up 25% to 40% of dietary zinc[83]. In addition to lower enteral uptake and lower hepatic reserve, compared to other microelements, formula components, such as iron, can affect zinc bioavailability in the presence of a high Fe: Zn ratio. Interference of iron with zinc is observed in adults and is arguable in preterm infants. However Klein[83] states that a 2:1 Fe: Zn ratio should be used in the formulas with a maximun of 3.0mg of zinc for 1.5 mg of iron per 100 kal.

Zinc bioavailability in breast milk is greater than in cow's milk; therefore, zinc concentration should be high in the supplied formulas. The difference in bioavailability is due to the strong binding of zinc to casein[80]. It has been shown that 60% of zinc found in the milk for preterm infants is absorbed compared to 36% of zinc found in fortified breast milk and 14% found in preterm formulas. Zinc concentration in breast milk quickly decreases after the colosterum , when levels are their highest[84].

Given the low absorption of zinc from formulas an expert panel in 20025 recommended that the minimum and maximun concentrations in preterm formulas be 1.1mg/100 lcal and 1.5mg/100 kcal. In the initial period, authors recommended 500-800 µg/kg/day increasing to 1mg/kg/day when growth is established[84]. In stable preterm infants 400 µg/kg/day given parenterally is recommended, while for the transition preiod (up to 2 weeks), the recommendation is of 50 µg/kg/day[84].

Low zinc concentration in the cord blood of LBW newborns have been noted in a number of settings, and birth weight has been shown to be highly correlated with cord zinc concentration in India[82-88].

Three studies reported lower zinc concentration in SGA births[89-98].

There are reports of symptomatic zinc deficiency in breastfed infants in the literature[99-103]. SGA infants are born with impaired immune function, leading to increased respiratory [104] and diarrhoea[105] morbidity and mortality in infancy [106, 107- 108].

Zinc is the second most important deficiency in infants after iron and has been described in preterm infants predominatly fed with breast mild[109-110].

A beneficial effect of zinc administered to LBW Neonates was also observed in India. Preliminary results of a resent RCT indicate that mortality was significantly reduced by 67% in LBW. 1-8 months old who were supplemented daily for the first year of life with zinc only [111]. The article by Sur et al[112] in this issue further emphasizes the value of both breastfeeding and an adequate zinc intake for neonates and infants. The notable contribution of zinc deficiency in neonates, infancy and early childhood to stunting[113] and infections disease morbidity[114] and mortality[115]. Especially from dirrhoea and pneumonia is now well-documented in developing countries like Bangladesh. Zinc supplementation of LBW from 1 – 10 months postnatal age was associated with a two-thirds reduction in mortality[116]. Neonatal reserves of zinc in LBW are lower than those of appropriate for gestational age infants, even on a body weight basis[117]. Zinc deficiency after 6 months when milk zinc concentrations are very low relative to requirements[118-119].

Meta analysis of trials that evaluated the effect of zinc supplements on growth[120]. Full-term infants born small for gestational age showed significantly greater gains in length and weight when supplemented with 3mg Zn/d for 6 months[121].

Zinc supplementation is likely to be advantageous for LBW neonates in Northeast Brazil[122]. Poor growth in LBW neonates as has been documented

already could be related in part to low body stares of zinc and inadequate zinc intake early in life[123].

Zinc is required for production of enzymes involved in nucleic acid metabolism and protein synthesis which are essential processes for growth[124]. Shrivastava et al on malnourished children aged 8 to 24 months showed that children supplemented with zinc for 3 months had a significant weight gain ($p<.001$) compared with the placebo group[125].

Another study showing that supplement with 30mg elemental zn/d during the last 2 trimesters of pregnancy reduced morbidity from diarrhoeal diseases among LBW infants[126-127]. Zinc supplementation on the rate of weight gain in children recovering from severe protein energy malnutrition. The effect of zinc supplementation on linear growth has been proposed to be a reliable functional index of zinc status in children .

The impact of zinc supplementation in the form of reduced diarrheal episodes in children with zinc deficiency, because zinc supplementation leads to accelerated regeneration of mucosa, increased levels of brush booder enzymes, enhanced cellular immunity and higher levels of secretary antibodies[128].

In a study conducted Freil et al[129] on very LBW infants, the supplemented group showed improved linear growth velocity.

Zinc increasing appetite and decreasing infections disease morbidity.

Zinc supplementation plays an important role in reducing childhood diarrheal incidence by up to 25% according to a systematic review of 10 randomizeds controlled trials performed in developing countries[130].

The development of effective and feasible interventions to improve the zinc status of developing country population is essential[131].

Zinc supplements are proven value in evaluation of the benefits of correcting zinc deficiency. They are also of benefit in treating established diseases.

Zinc deficiency has been associated with reduced growth, impaired immunity, and increased prevalence and incidence of infectious diseases among infants and children in developing countries[132-133].

The size of the total body zinc store is extremely limited, so that there is a day to day requirement for dietary zinc[134] have shown that maternal zinc depletion is strongly associated with intra-uterine growth retardation[145].

The mother of small for gestational age babies had significantly lower levels of zinc in polymorphonuclear and mononuclear cells than mothers of appropriate for gestational age babies. Zinc deficiency has been reported to causes anorexia in animals[136]. Zinc supplementation appears to promote the synthesis of lean tissue rather than of adipose tissue[136].

3.2 Risk Factor of Zinc deficiency : Pregnant & Lactating mother, Neonates, Infants & Young children, Vegetarian, Children experience high rates of diarrhoea.

3.3 Zinc deficiency in mother

Zinc deficiency in mother associated with poor fetal outcome, stillbirth, abortion, low birth weight, and increased prevalence of congenital abnormality[137].

Maternal zinc deficiency may be relatively common worldwide. Eighty two to one hundred percent of pregnant women in the world likely have inadequate usual intakes of zinc. Maternal zinc deficiency as it relates to fetal growth and development, complications of pregnancy, labor and delivery, and maternal and infant health. Zinc deficiency has also been related to complications of labour and delivery including prolonged or inefficient first-stage labour and protracted second stage labour, premature rupture of membranes, and the need for assisted or operative delivery. These complications in turn impair maternal and perinatal health as they lead to increased risk of maternal lacerations, high blood loss, maternal infections, fetal distress, stillbirth, neonatal asphyxia, respiratory distress and neonatal sepsis[138].

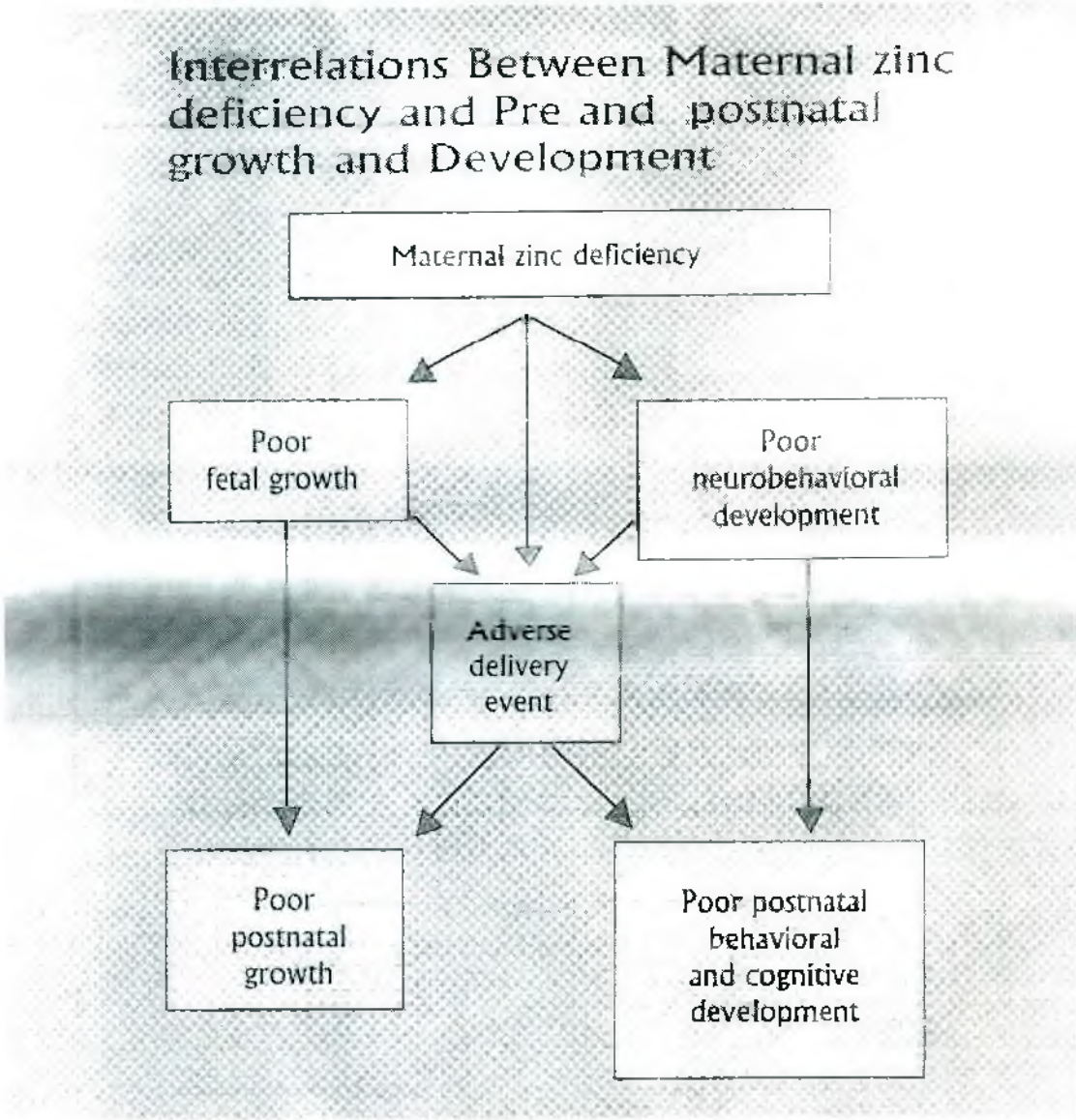


Fig. 1M. Interrelations between maternal zinc deficiency and pre and postnatal growth and development.

3.4 Zinc deficiency in low birth weight

During normal pregnancy, low birth weight has been associated with decreased circulating zinc levels[139].

Low zinc concentrations in the cord blood of LBW newborns have been noted in a number of settings and birth weight has been shown to be highly correlated with cord zinc concentration in India.

Another study reported lower zinc concentrations in LWB[140].

Zinc deficiency among exclusively breastfed LBW infants has been suggested based on the findings that after the first few months of lactation a large proportion of women may have breast milk zinc concentrations lower than that needed to provide the recommended daily allowance of zinc to infants[141]. There are reports of symptomatic zinc deficiency in breastfed infants in the literature [142, 143, 144].

The pathology of severe zinc deficiency was described by some authors including growth retardation, delay in sexual & skeletal maturation, alopacea, dermatitis, hyperkeratosis, loss of appetite, atrophy of germinal, immune tissue and behavioral changes[145-148].

Studies evaluating the relationship between maternal zinc nutritutre, assessed by tissue zinc levels or dietary zinc intake, and various measures of pregnancy outcome, including birth weight, gestational age at delivery, growth retardation[149,150].

3.5 . History of zinc

Zinc is important for metabolism, cell growth, immunity. Todd et al[151] first showed that zinc is an essential trace metal in 1934. Zinc is an essential trace mineral in the nutrition of microorganisms[152] in plants[153] and animals. Zinc was discovered in 1940 to be an essential part of carbonic anhydrous which was the first metallo-enzyme to be recognised[154]. It serves as a catalytic component of over 300 enzymes and structural component of various proteins, hormones and nucleotides[155,156].

3.6 Biochemical function of zinc

Most biochemical roles of zinc reflect its involvement in a large number of enzymes or as a stabilizer of the molecular structure of sub-cellular constituents and membranes. Zinc participates in the synthesis and degradation of carbohydrates, lipids, proteins and nucleic acids. It has recently been shown to play an essential role in polynucleotide transcription and translation and thus in the processes of genetic expression. Its involvement in such fundamental activities probably accounts for the essentiality of zinc for all forms of life.

3.7 Physiological functions of zinc

Zinc is an essential constituent of many enzymes, such as carbonic anhydrous, alkaline phosphatase, pancreatic carboxy-peptidases, and crytosolic superoxide dismutase. The retina contains a zinc metalloenzyme, retinene reductase which is required for the formation of retinene. It

maintains normal concentration of vitamin A in plasma. It is required for the mobilization of vitamin A from the liver. It is required for the preparation of insulin and increases the duration of insulin action when given by injection. Zinc is used in the β-cells of the pancreas to store and release insulin as required. It is concerned with the healing of wounds. Zinc is important for digestion of proteins in the gastrointestinal tract. It is essential for the normal growth and reproduction of animals. Zinc is the mineral coenzyme for collagenase, a key enzyme in collagen production. It is a important antioxident, protects the liver and helping with detoxification of the body. Zinc supplement has been shown to reduce infection. It maintain proper vision, taste and smell. It is also used for the treatment & prevention of acne. Zinc is used in Wilson's disease to reduce serum copper. It is important in the metabolization of vitamin E and therefore assists with anti-oxidation. It is also used for treatment of rheumatoid arthritis. It is involved in the synthesis and stabilization of proteins. DNA and RNA plays a structural role of ribosome and membranes. Zinc is involved in a large number of biological process[157,158,159] for helping physiological & psychological development of neonate, infant & children.

3.8 Metabolic function of zinc[160]

Zinc is a cofactor of the protein splitting enzyme, carboxypeptidase which removes the carboxyl group (COOH) from peptides to produce amino acids, zinc, therefore, has a key role in protein digestion.

Zinc is a part of lactic dehydrogenase. This enzyme is essential for the interconversion of pyruvic acid and lactic acid in the glycolytic pathway for glucose oxidation. Thus, zinc also plays a part in carbohydrate digestion.

Zinc has an integral part of carbonic anhydrous, which acts as a carbon dioxide carrier, especially in the red cells. It takes up carbon dioxide from cells. It combines with water to from carbonic acid (H_2CO_3), and then releases carbon dioxide from the capillaries into the alveoli of the lung. This enzyme also functions in the renal tubule cells in the maintenance of acid-base balance, in the mucosal cells, and in glands of the body. Zinc combines readily with insulin in the pancrease: zinc insulin serves perhaps as the storage form of this hormone. The diabetic pancreas contains about half the normal amount of zinc. The leukocytes of patients with leukemia contain about 10% less zinc than normal.

Zinc is an important part of the enzymes that help to manufacture of HCL in the stomach, the enzyme that breaks down alcohol in the body, the enzyme involved in vitamin A utilization and an enzyme that is involved in the metabolism of the nuclic acids. Zinc assists enzymes in all cells[161].

Zinc is needed for the body to make protein. Every cells genetic material is derived from protein. So body needs zinc for every cell from the hair to the soles of feet. Zinc preventing cancer.

3.9 Role of zinc immunocompetence

Adequate supplies of zinc are essential for the development and maintenance of a healthy immune system. Zinc therapy led to complete recovery and rapid remission but its absence caused death from severe infection.

Zinc supplement corrects the less developed immune system of the newborns. Zinc is necessary for production of T (thymus) cells, a form of white blood cells, involved in production of antibodies.

Acrodermatitis enteropathica found in A-46 mutant cattle showing similar increased susceptibility to infection on zinc.

Depressed antibody dependent cytotoxicity of killer lymphocytes has also been demonstred in zinc deficient rates[162].

3.10 Epidemiology of zinc deficiency

Mild zinc deficiency and growth limiting have been observed in some studies on otherwise healthy male American and Canadian infants and preschool children[163].

Zinc responsive growth failure has also been found in adolescents in rural areas of Egypt and the Islamic Republic of Iran[164,165].

Zinc supplementation led to growth rate in preterm babies and full term healthy babies compared unsupplemented ones.

The deficiency of zinc is very widespread throughout the world affecting nearly one billion people[171]. Zinc deficiency impairs many cellular and humoral (involving hormones and similar compounds) immune functions including lymphocyte number and function. Zinc deficiency in man results in dwarfism and hypogonadism (retarded genital development). There is loss of taste acuity. There is also poor growth, loss of appetite and hypoglossia in young malnourished children with subnormal hair zinc levels. The deficiency of zinc causes hepatosplenomegaly, delayed closure of the epiphyses of the long bones and anemia. Zinc deficiency disturbs thyroid function and metabolic rate. Deficiency causes growth failure associate infectious disease is well documented. Further recent evidence suggests that of the fetal organs effected by zinc deficiency, failure to thrive and night blindness.

3.11 Cell mediated immunity in zinc deficiency

Depressed cell mediation immunity has been reported in patients of nutrition lacking zinc supplements[167]. There were abdominal migration of T lymphocytes, increased proportion of immature T cells (null cells) and diminished mitogenic response to in vitro PHA and conacavalin A[168].

There was delayed cutaneous hypersensitivity response to candia antigen in zinc deficient children, which improved with local application of zinc.

3.12 Daily requirement of zinc

0 – 5 month	**3 mg,**	**5 months – 1 year**	**5mg.**
Children	**10 mg.**	**Adolescents**	**13 mg.**
Adult	**15 mg**	**Pregnancy**	**30 mg.**
Lactation	**25 mg.**		

3.13 Dietary sources of zinc

The zinc content of the total diet is influenced, not only by the range of food items selected, but also by the degree of refinement of any constituent cereals. Fats, from while zinc is virtually absent, tend to dilute zinc from the total diet. The average zinc content of some major food proteins and energy sources is given in Table 1A, as the primary goal of nutrition in developing countries is to provide sufficient energy, the most appropriate basis for the comparison of foods is the relationship of their zinc content to their energy content. As is evident from Table 1A, lean, red meat is an outstanding zinc source. Furthermore, its zinc is present in a highly available form. Many staple foods provide amounts of zinc similar to those of foods derived from animal tissues. However, energy sources such as fats, oils, sugar and alcohol have a very low zinc content. Green leafy vegetables and fruits are only modest sources of zinc (as of energy) because of their high water content.

Table 1A. Zinc contents of food groups on a weight basis and in relation to their protein and energy contents[169].

Food	mg/kg raw wet weight	mg/g protein	mg/mj
Whole grains, whole meal bread, unpolished rice	30-50	0.2-0.4	2-4
Pulses, legumes	25-35	0.1-0.2	2-3
Rice (polished) corn	10-12	0.2-03	1-2
Wheat, low extraction rate	8-10	<0.1	<1
Roots, tubers	3 – 5	0.1 – 0.2	<1
Coconut	5	0.1 – 0.2	<0.5
Milk	3 – 5	0.1	1 – 2
Cheese	30 – 40	0.2 – 03	2 – 10
Red meat (lean)	40 – 50	0.-2	2 – 4
Red meat (fat)	10 – 15	0.1	<0.5
Pork (lean)	20 – 30	0.1	3 – 5
Pork (fat)	4 – 5	<0.1	<0.5
Chicken	7 – 20	<0.1	1 – 3
Fish	3 – 5	<0.1	1

3.14 Absorption of zinc

Zinc is well absorbed from the duodenum. Absorption decreased by fibres, phytate, calcium, copper, and increased by glucose, amino acid, peptides and

other chelating agent. 90% of zinc is lost in the feces. Five percent zinc excreated in the urine and 5% retained in the body.

3.15 Losses of zinc

The tentative estimates of zinc losses summarized in Table 2 suggest that the average physiological requirement for absorbed zinc to ensure the maintenance of a metabolically available body-zinc pool in the fully adapted adult is approximately 1 mg/day for men and 0.7 mg/day for women (see Table 1B).

Table 1B : Tentative estimates of endogenous losses of zinc from adults adapted or unadapted to low intakes of zinc[169].

A. Before adaptation

Data used for estimates	Losses (mg/day)	
of normative requirement	Male	Female
Faceal loss	0.8	0.5
Urinary loss	0.3	0.3
Skin loss	0.3	0.2
Total	1.4	1.0

B. After adaptation

Data used for estimates of basal requirement	Male	Female
Faecal loss	0.5	0.3

Urinary loss	0.2	0.2
Skin loss	0.3	0.2
Total	1.0	0.7

3.16 Dosage range for treating deficiency

In general, 30 – 50 mg daily, usually required in the form of zinc sulphate.

3.17 Adverse effect of zinc

Chronic zinc poisoning in man has not been identified with certainly, although prolonged use may lead to copper deficiency and anemia which has responded to withdrawal of zinc and symptomatic therapy. Zinc Sulphate, the form of zinc, often used for oral administration causes adverse gastro-intestinal effects. It can be converted to the corrosive zinc chloride, and it is this corrosive action that accounts for the acute toxicity of the soluble zinc salts.

3.18 Toxicity of zinc

Zinc supplements in excess of 10 times the recommended daily allowance cause a conditioned deficiency of copper including anemia.

The symptomatic toxicity are gastric ulcers, pancreatitis, lethargy, anemia, fever, nausea, vomiting, pulmonary fibrosis salivation, headache, cough, leucocytosis and central nervous system disturbances & Respiratory distress.

3.19 Management of overdosing

Gastric lavage and emesis should be avoided, Demulcents such as mild should be given chelating agent such as sodium edetate may be useful.

3.20 Precaution

Concurrent administration of zinc salt with penicillamine might diminish the effect of penicillamine. The absorption of zinc although poor, may be decreased by various compounds including some foods, Chelation may occur with tetracyclines. Large amount of calcium decreases the absorption of zinc.

3.21 Drug interaction:

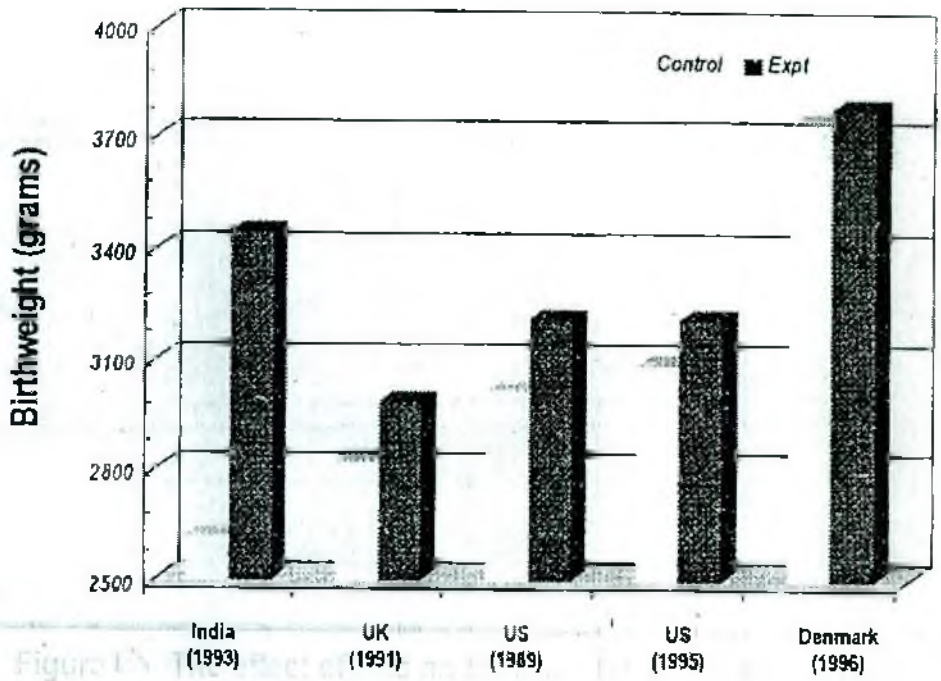
Penicillamine, Tetracycline, Iron ciprofloxacin, Norflocacin, Phosphorus, Estrogens, progestins, NSAIDS, Sodium Valproate, Ethambutal.

3.22 Contra-indications: Hypersensitivity to zinc.

3.23 Zinc Supplementation during pregnancy:

The physiological role of zinc during periods of rapid growth and development emphasizes the importance of zinc during foetal life and gestation[170]. Results of cross sectional studis have associated low dietary zinc intake or low maternal plasma zinc with increase risks of LBW and preterm delivery[171,172,173].

Figure 1N The effect of zinc on birthweight: Experimental trials



Source: Garg et al. (1993) *Ind J Phy Pharm* 37(4) 276; Simmer et al. (1991) *Eur J Cl Nutr* 45:139; Cherry et al. (1989) *Am J Cl Nutr* 50:945; Goldenberg et al. (1995) *JAMA* 274(6):463; Jonsson et al. (1996) *Acta Ob Gyn Scand* 75(8).725.

In 1993 study in India demonstrated significant increase in birth weight and gestational age, a reduced incidence of pre-maturity and of IUGR, and a higher Apgar score in the group supplemented with 45 mg of elemental zinc as compared to the untreated group[174]. However, caution is warranted in interpreting these results because of methodological limitations. Zinc supplementation has also been associated with reductions in the incidence of

IUGR and in delivery complications for pregnant women who were at high risk of delivering SGA infants. The inclusion criteria for this 1991 study were low pre-pregnant weight, birth of a previous SGA infant and smoking. Results showed a three to four-fold reduction in the prevalence of IUGR (27% controls; 7% treatment). Although the mean birth weight was 170 g greater in the zinc supplemented group, these differences were not statistically significant, probably due to the small sample size[175]. Evidence of an interaction between maternal weight and response to zinc supplements was demonstrated in a trial among low income pregnant adolescents in the USA. The pre-maturity rates were reduced in the group of normal-weight women who received zinc supplements, and underweight mothers given zinc supplements had longer gestational lengths than the control group[176].

Study show that an increase in birth weight after zinc supplementation in women with low plasma zinc concentrations[177].

All above studies mentioned that there was no risk of zinc supplementation in pregnancy & its outcome was also good & all the baby was healthy & no adverse effect was reported. So zinc supplementation in neonates is harmless.

3.24 Zinc supplementation in infant & Children :

A beneficial effect of zinc administered to SGA infants was also observed in India. Preliminary results of a recent RCT indicate that mortality was significantly reduced by 67% in SGA infants 1 – 8 months old who were supplemented daily for the first year of life with zinc only.

A community based randomized controlled trial of zinc supplementation in Indonesia infants. Daily supplementation with 10mg zinc from 6 months to 12 months in 680 infants. The zinc group had higher serum zinc 11.58 compared with 9.06μ mol/L; $p<0.05$) than did the placebo group[183]. There is no side effect of zinc occurs.

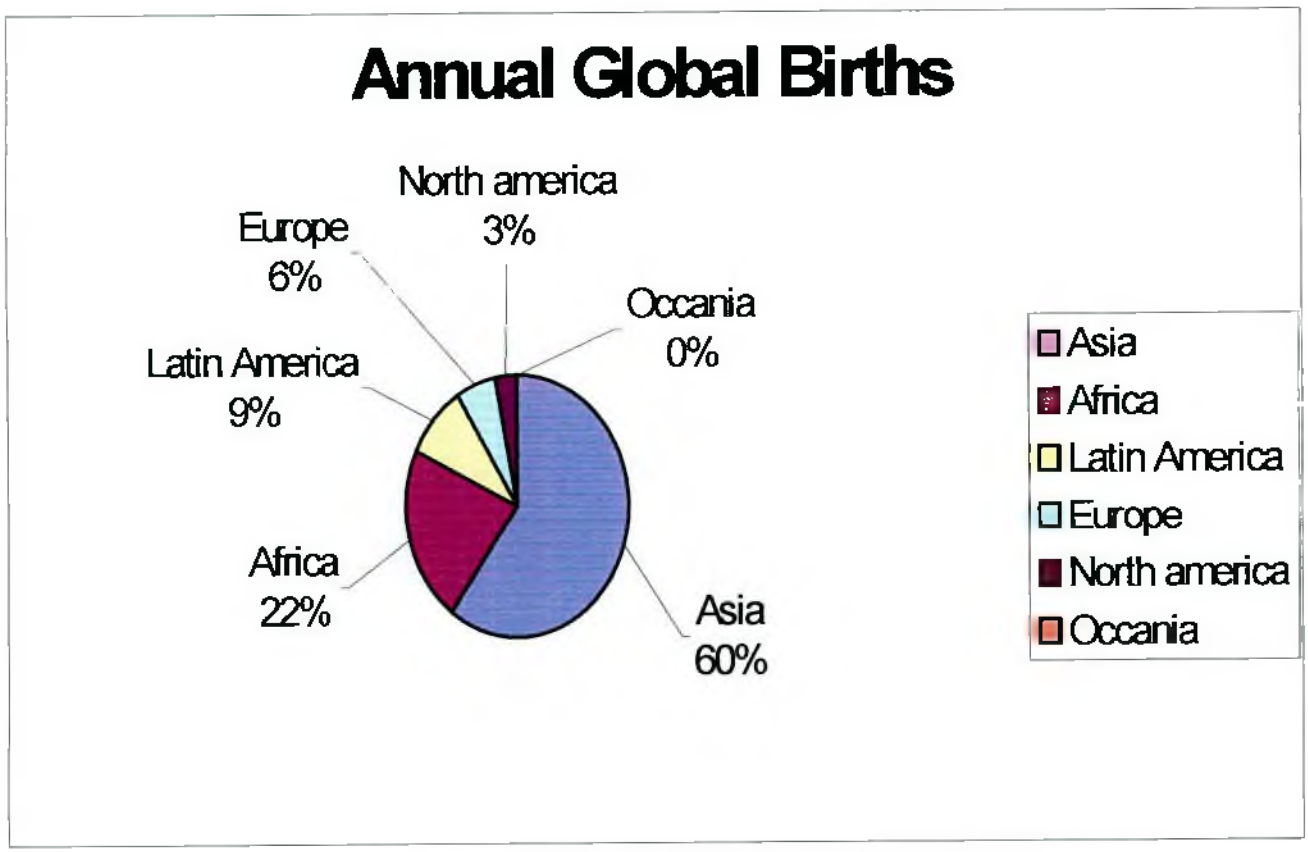
Zinc supplementation decreased the risk of infant mortality in low birth weight.

Above studies show that zinc supplementation in infant & children was beneficial, as well as it reduced mortality rate. So supplementation during neonatal period will be beneficial too.

3.25 THE NEONATE

The first 28 days of life of a live born is neonate

Fig 1O. shows annual global births, highest in Asia (60%)



Source : State of World Children (WHO)

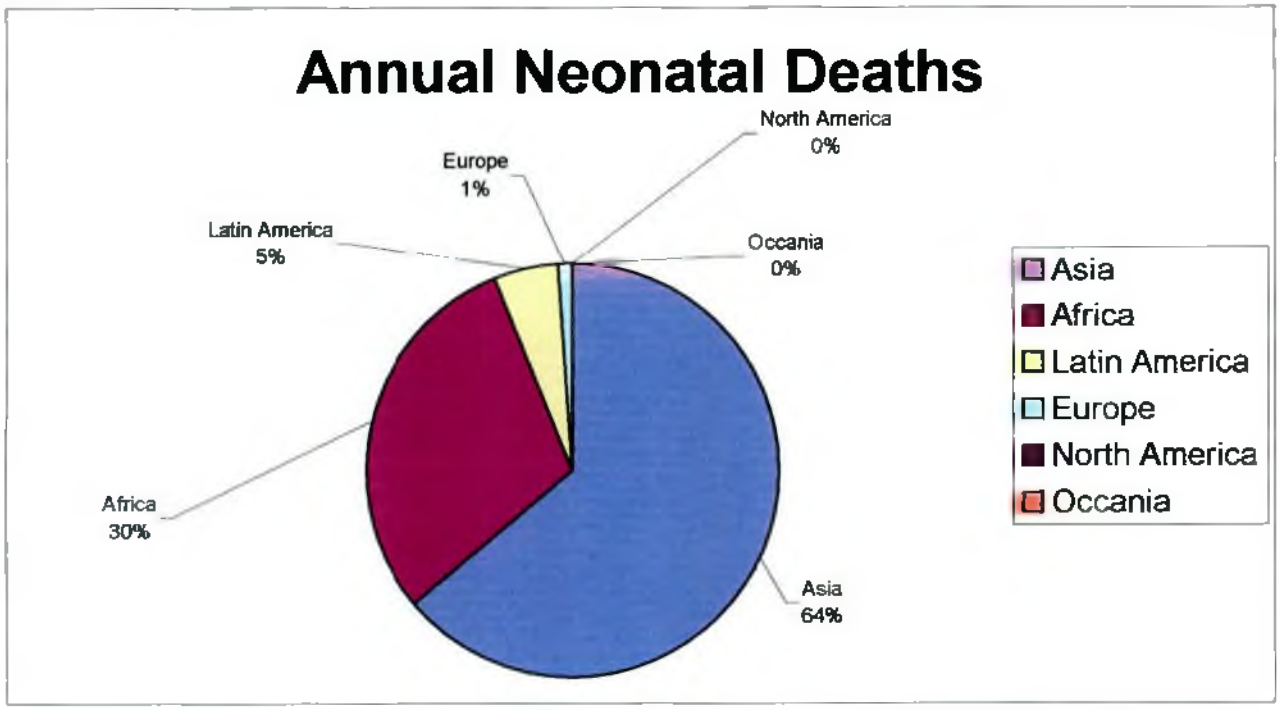


Fig 1P. Shows Annual neonatal deaths, highest in Asia (64%)

Source : State of World Children (WHO)

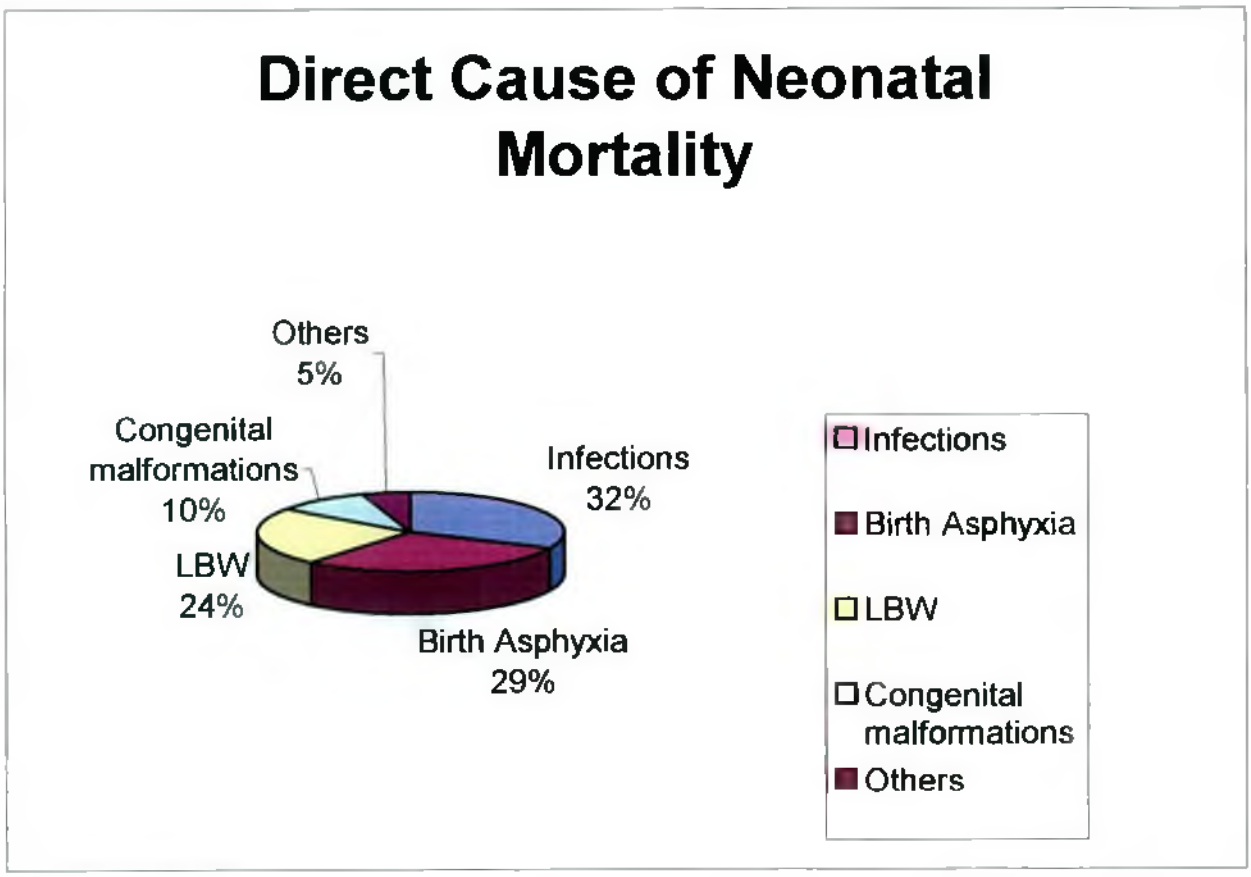


Fig 1Q. Shows causes of neonatal mortality, 24% due to pre-term.

Source : State of World Children (WHO)

3.26 Neonatal Care in Bangladesh

Existing facilities

The existing facilities which are available in Bangladesh for care of newborn, are not adequate. This is available mainly in tertiary care hospitals and some of the district hospitals. As such the facilities available are giving service to the urban and periurban areas. As the vast majority (90%) of population are living in rural areas and most of the deliveries (90%) occurring in rural areas by untrained persons. The real break through in neonatal care and reduction in neonatal mortality rate will occur only when neonatal care is provided in rural areas.

Grade III (Level III) and Grade II (Level II) facilities are available only in city hospitals. Grade III facility provides care to very sick newborns that is ELBW, extreme preterm baby, severe perinatal asphyxia and severe respiratory depression due to other causes. The facilities include ventilators, central oxygen supply, closed and open incubators, blood gas analyzer, syringe pump, phototherapy unit and arrangement to control room temperature. These facilities are available in Bangabandhu Sheikh Mujib Medical University (BSMMU), some Medical College Hospitals (13 Govt. and 7 Private), some District Hospitals, Institute of child and Mother Health (ICMH), and some private hospitals and clinics in major cities. Besides the

expansion of neonatal care facilities in government hospitals, some private hospitals and clinics are also developing neonatal health care facilities now a day, which includes both Level-III and Level-II care.

Govt. of Bangladesh is going to introduce HPNSP (Health Population and Nutrition Sector Program) and under this program the facilities are being extended in the rural areas.

The Essential Service Package (ESP) under the HPNSP for neonatal care likely to include-

I) Training of manpower-Doctors, nurses, paramedics, FWV etc.

II) Services in the community at thana, union and village level. Each communities clinic situated in the village will serve 6000 populations in the area.

Table-1:C Neonatal and child health statistics.

Total Area	:	147,570 sq km.
Population	:	140369 thousands
Children below 15 years	:	47%
Population below 5 years	:	16.7%
Infant mortality rate (IMR)	:	51/1000
Neonatal mortality rate	:	42/1000
Perinatal mortality rate	:	75/1000
Under 5 mortality rate	:	77/1000
Incidence of LBW	:	50%

IUGR-LBW rate	:	39.4%
Total Neonatal death	:	152,000/yr
Maternal mortality rate (MMR)	:	4.2/1000

NB: 1000=per 1000 live birth.

Source : UNICEF 2003 state of the world's children.

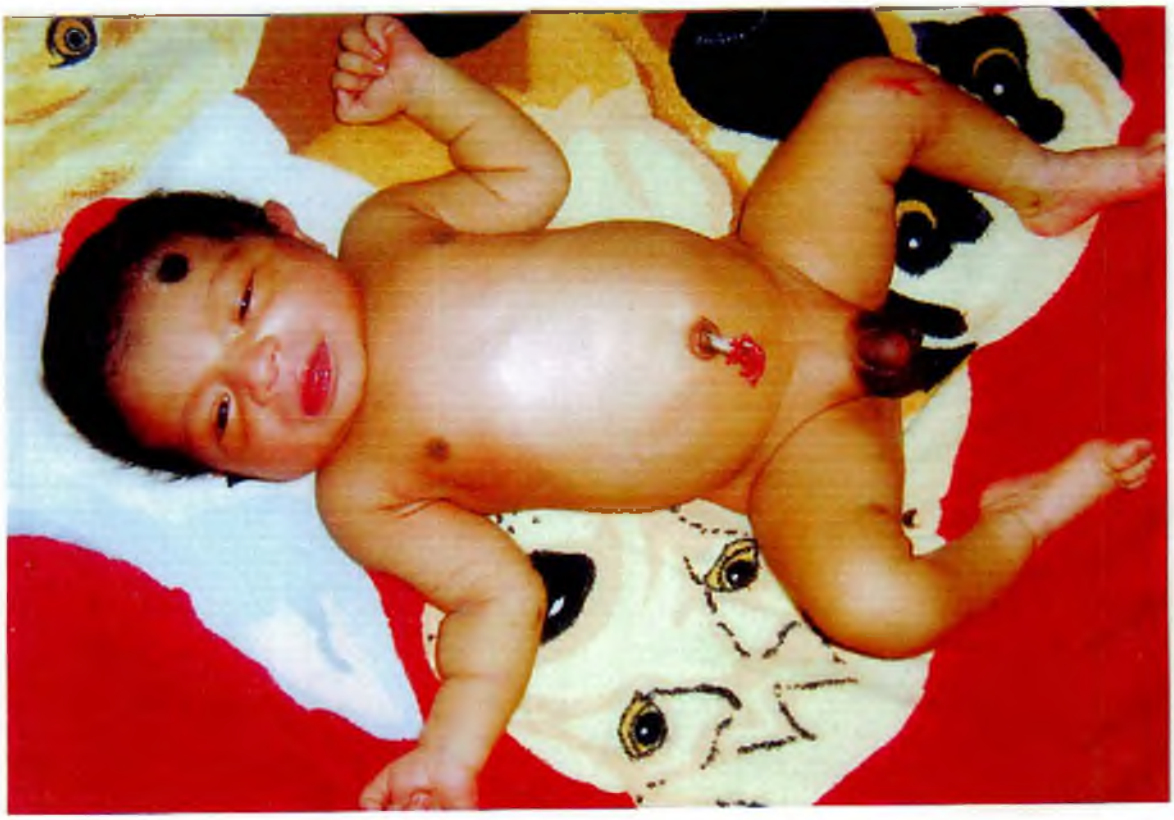


Figure 1R: Normal Newborn

3.27 CRITERIA OF THE NORMAL NEWBORN.

A normal newborn, Fig. 16 has all of the following features:

Gestation: 37 to 42 completed weeks.
Birth weight: between 2500g and 4000g
Breathing: spontaneous, regular and rate between 30-60 per minute.
Coloru: pink but slight peripheral cyanosis soon after birth is normal.
Heart rate: 100-160 beats per minute.
Axillary temperature: 97:5-99°F
Occipitofrontal circumference (OFC) 33-35 cm. increases 1 cm/ month for 1st year then by about 1cm/year.
Normal baby should be able to such soon after birth.
Most babies pass urine within 24 hours of birth but some babies may not pass urine up to 48 hours of birth.
Most babies will pass meconium within 24 hours of birth.
A newborn baby sleeps around 18 hours a day
No apparent congenital malformation.

3.28 Physical examination of a neonate

It is important to carry out routine examination of a newborn baby at some time during the first few days of life (preferably within 72 hours) If the baby is born in a medical facility this is best done before discharge.

Before examining a neonate, a health care provider should be aware of the following history:

mode of delivery
time of first cry
problems during delivery
problems after delivery
whether the baby is breastfeeding
whether he/she has passed urine and stool

whether the parents have any particular worry

Before examining any baby, you must first wash and your hands. Then fully undress the baby in a warm environment with a good light so that the baby does not get cold and can be clearly seen.

The routine newborn examination can be comfortably carried out with the baby in the mother's lap or on a clean lat surface. Be sure to examine the baby throughly from head to toe.

1. **Overall impression**: Observe the face, trunk, limbs and activity to gain a general impression.
2. **Measurement:** Record birth weight, head circumference and length if possible.
3. **Colour:** Check that the baby is pink and assess the degree of any jaundice.
4. **Skin examination:** Pallor, jaundice, erythema toxicum should be looked for
5. **Head:** Feel the fontanelles, sutures and check for any trama e.g. cephalhaematoma, superficial injuries.
6. **Eyes:** Look for discharge, inflammation or cataract (red reflex)
7. **Face:** Any dismorphic features like epicanthic folds in eyes, widely spaced eyes, low set ears, facial asymmetry.
8. **Ears:** any deformity and low set ears.
9. **Neck:** Neck musele should be palpated to exclude sternomastoid tumor. Branchial and thyroglossal cysts may be present. Webbing of neck is present in Turner syndrome.
10. **Mouth:** Look for cleft lip or palate.
11. **Upper limbs**: Check for evidence of brachial palsy and extra digits.

12. **Chest:** Check breathing pattern, Accessory nipple, widely apart nipple, breast hypertrophy should be looked for.
13. **Heart:** Listen to the heart for murmurs.
14. **Abdomen:** Is it distended? Feel for the liver, kindeys and spleen. Are there any other masses?
15. **Umbilicus:** Is is clean? Are there any signs of infection (redness, discharge bad smell)?
16. **Genitalia:** Normal male or female. If male, are the testes descended? Is the urethral orifice correctly positioned? In the female, you may see a small amount of mucus discharge perhaps with a few sport of blood this is normal
17. **Anus:** Is it patent and in the correct position?
18. **Femoral pulses:** Can you feel them?
19. **Spine:** Dose if look and feel normal? Back of the baby should be examined to detect the midline detects e.g. spina bifida, meningomyelocele
20. **Lower limbs:** Are they normal? Is there talipes? Count the toes.
21. **Primiteive reflexes:** Is the baby behaving normally? Check Moro and sucking reflexes.

3.29 Care of the normal neonate[185]

Principles of neonate care

Listen to the parents concerns and deal with any questions they may have.
Explain about normal baby care and the need for breastfeeding and immunization.
Check that the baby is well.
Search for congenital malformation.

Box 2. Components of Essential Newborn Care (ENC)

clean delivery and clean cord care to prevent newborn infection
establishment of breathing
keeping the baby warm
encouraging early and exclusive breastfeeding
give eye care
starting immunization schedule
correct management of neonate illness
extra care of low birth weight (LBW) babies

Care at birth

A clean and safe delivery in a clean environment, ideally in the presence of a skilled birth attendant and using a safe delivery kit (plastic sheet, soap, boiled blade and boiled thread).
Cut the cord about 2 cm from the abdominal skin with a clean instrument and double tie with clean thread.
Dry the baby throughly at delivery and cover with clean dry warm cloth.
Check the baby's breathing and colour.
Help establish early breastfeeding. Keep mother and baby together. Do not offer any other feeds.

It is not necessary to bathe the baby immediately after birth nor is it necessary to use oil to clean or to remove vernix from the babies body.

It is not necessary to shave the head.

Care following birth

Exclusive breastfeeding on demand.

Keep the baby warm. In winter, close doors and windows switch off electric fans and use room heater if possible.

Do not bathe the baby until the $2^{nd}/3^{rd}$ day of life.

It is not necessary to use oil regularly.

The cord needs to be kept clean, dry and bare. Do not wash with spirit or other medication.

Check for urine and stool output. Some meconium (black stool) should be passed in the first 24 hours. Urine may not be passed in the first 48 hours but once breastfeeding established you should expect urine at least 6 times in 24 hours.

Immunization- Give baby BCG and Oral Polio vaccination in the first week of life and if possible, Hepatitis B vaccination.

Vitamin K (Inj. Konakion MM) should be given to all neonate babies: 1 mg IM as a single does or two 2 mg doses orally 4-7 days apart.

3.30 Gestational age assessment[179].

Gestational age calculation is very important in categorizing and identifying the high risk babies. Using the birth weight/gestational age relationship, the weight of newborn infants can be categorized as appropriate for gestational age (AGA), small for gestational age (SGA) or large for gestational age (LGA) Similarly from the gestational age alone, infants can be identified as

preterm term or post term. Thus nine separate categories of newborn growth can be identified at birth.

The Dubowitz score, Ballard score. Parkin's score are used for gestational age calculation.

Table 1D: **Parkin's method** (cannot be done on babies<34 weeks of gestation)

	0	1	2	3	4
Skin texture	Very thin, gelatinous	Thin & smooth	Smooth & medium thickness	Slight thick, stiff super-ficial creck	Thick parehment like with cracking
Skin color	Dark red	Uniformly pink	Pale pink	Uniformly paly pink	
Breast size	No breast tissue	<0.5cm	0.5-1cm	>1cm	
Ear firmness	Soft easily folded no spring back	Spring back slowly	Cartilage felt, spring back readily	Firm with definite cartilage	

Scores	4	5	6	7	8	9	10	11-12
GA(wks)	34.5	36	37	38.5	39.5	40	41	>41

Physical Maturity[180]

Physical Maturity Sign	Score							Record Score Here
	-1	0	1	2	3	4	5	
Skin	Sticky friable transparent	Gelatinous red transfucent	Somooth pink visible veins	Superficial peeling &/or rash few veins	Cracking pale areas rare veins	Parchment deep cracking no vessels	leathory cracked wrinkled	
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald		
Plantar surface	Heel toe 40-50mm -1 <140mm-2	>50mm no carease	Faint red marks	Anterior	Creases anterior2/3	Creases over entire sole		
Breast	Impeceptible	Barely perceptible	Flat areola no bud	Stippled areola 1-to 2-mm bud	Raised areola 3-to 2mm bud	Full areola 5-to 10mm bud		
Eye/Ear	Lids fused loosely-1 tightly-2	Lids open pinna flat stays folded	Slightly curved pinna soft slow recoil	Well curved firm instatant recoil	Formed & firm instant recoil	Thick cartlage ear stiff		
Genitals (male)	Scrotum flat, smooth	Scrotum empty faint rugase	Testes in upper canal rear rugae	Testes descending few rugae	Testes down good rugae	Testes pindulous deep rugae		
Genitals (female)	Clitoris prominent & labia flat	Prominent clitoris & small labia minora	Prominent clitoris & enlarging minora	Majora & minora equaly prominent	Majora large minora small	Majora cover clitoris & minora		
Total Physical Maturity Score								
Maturity Score –1 –5 0 5 10 15 20 25 30 35 40 45 50								
Rating Weeks 20 22 24 26 28 30 32 25 36 38 40 42 44								

3.31 Assessment of gestational age at birth

A. Assessment of gestational age at birth by Expanded New Ballard Scoring (NBS) System[181]

1. Gestational age in weeks is calculated by Maturity rating (Fig-1H)
2. Maturity rating is calculated by adding the physical and neurologic score from the physical criteria for maturity an neuromuscular criteria for maturity respective (Fig-1H)
3. Accuracy of the NBS= ± 2 weeks

B. Assessment of gestational age at birth by clinical criteria

Since dates of last menstruation are frequently not forthcoming from the illiterate mothers, assessment of gestational age may be made on the basis of the following criteria:

Physical Characteristics:

1. Length From crown to sole (cm) x 0.8= gestational age weeks.

Thus 50 cm shall mean 40 weeks, 40cm meaning 32 weeks.

2. Sole creases-

Only anterior transverse <36 weeks

Occasional creases, mostly interiorly, 36 to 38 weeks

Covered with multiple creases: 40 weeks.

3. Ear lobe-

No cartilage < 36 weeks, Some cartilage: 36 to 38 weeks.

Stiff cartilage: 40 weeks.

4. Breast nodule- Not palpable at all or <2mm: <36 weeks. 2 to 4 mm: 36 to 38 weeks, 7 mm: 40 weeks.

5. Testes and scrotum Testes in inguinal canal or in scrotum but few rugae: <23 weeks. Numbers of rugae more: 36 to 38 weeks. Extensive rugae, pendulous tested with full scrotum: 40 weeks.

Reflexes and Tone:

1. Posture recoil-

Complete hypotonic in <32 weeks. Some flexion of lower limbs <36 weeks. Good flexion of lower limbs <36 weeks. Good flexion of lower limbs with some flexion of upper limbs: 36 to 38 weeks.

Good movements of both upper and lower limbs: 40 weeks.

2. Toe or heel to ear maneuver-

Easy <34 weeks. Difficult <36 weeks. Very difficult: 36 to 38 weeks. Not possible: 40 weeks.

3. Scarf sign- with the baby lying flat on back, his arm is moved across the body and the examiner makes a note of the extent to which the elbow reaches. Beyond the opposite side of the body <32 weeks. The same but with difficult <36 weeks. Only up to midline: 36 to 38 weeks. Stops short of midline: 40 weeks.

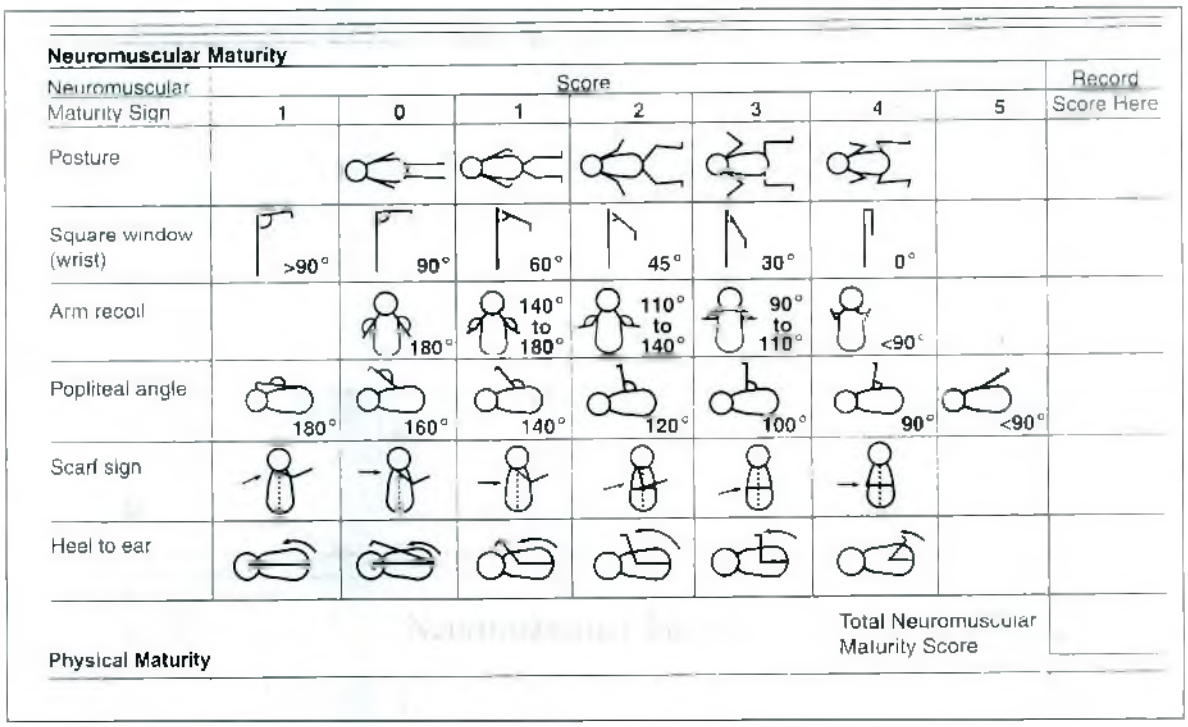
4. Window sign-Based on flexion of the hand on forearm, or dorsiflexion of foot at ankle joint. Up to 90°<36 weeks, Up to 45°<36 weeks. Very little: 40 weeks.

5. Sucking and swallowing reflexes- Weak and poorly synchronized <32 weeks. Strong and synchronized <32 weeks.

6. Rooting Reflex- When corner of mouth or lower lip of the baby is touched. Mouth turns towards the stimulated side. Slow <32 weeks.

7. Moro Reflex- When the examiner allows to drop the child's head momentarily (see Fig-1) there is extension of arms followed by flexion and adduction. The baby seems to be attempting to embrace. Weak <32 weeks. Strong >32 weeks.

Neuromuscutar Maturity Score [180]



Maturity Score	–1	–5	0	5	10	15	20	25	30	35	40	45	50
Rating Weeks	20	22	24	26	28	30	32	25	36	38	40	42	44

Maturity rating as calculated by physical and Neurologic score, thus calculating the Gestational age.

Figure 1s : Expanded New Ballard Scorting (NBS) System for assessment of Gestational age at birrth

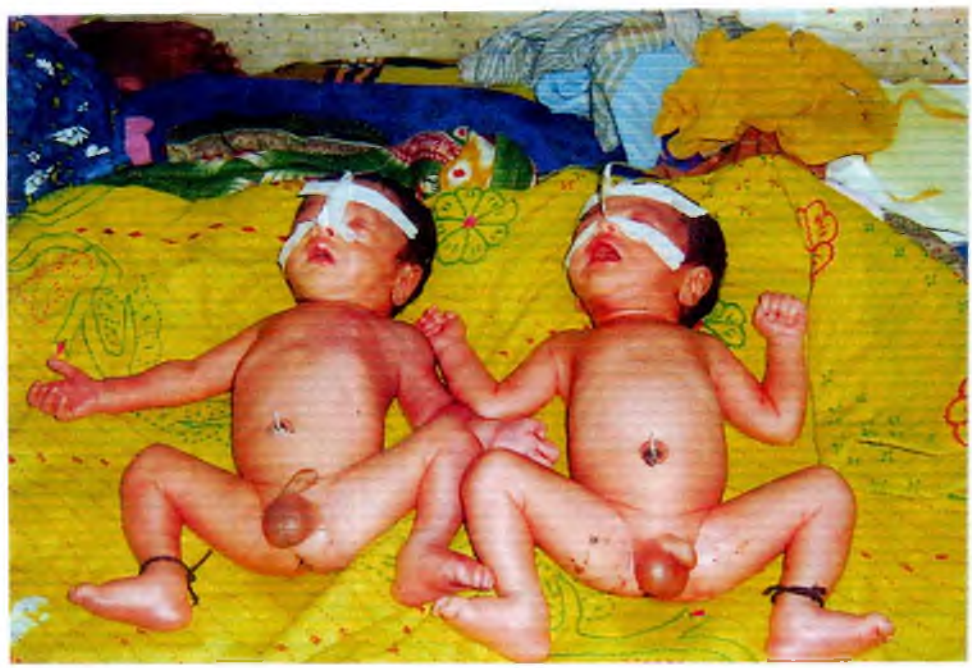


Figure 1T. Low Birth Weight

3.32 LOW BIRTH WEIGHT NEONATES[182].

The newborn baby may be LBW because of prematurely or intrauterine growth retardation (IUGR). Approximately one-third of LBW neonates in our country are preterm. The second situation that leads to LBW is IUGR; the gestation may be full term or preterm, but the baby is malnourished and, therefore, LBW; such a baby is also called a small-for-date (SFD) baby. Two-thirds of our LBW neonates fall in this category. At times, an LBW neonate may be both preterm as well as SFD.

3.33 Causes of Preterm Birth

Fetal :

Fetal distress

Multiple gestation

Erythroblastosis

Placental :

Placental dysfunction

Placenta previa

Abruptio placenta

Uterine :

Bicornute uterus

Incompetent cevix (premature dilatation)

Maternal:

Teenage mother

Preeclampsia

Chronic medical illness (e.g. cyanotic heart disease, renal disease)

Infections (e.g. Listeria monocytogenes, group B streptococcus, urinary tract infection, chorioamnionitis)

Others :

Premature rupture of memberanes

Polyhydramnios

Iatrogenic (DM, Rh incompatibility)

Unknown.

3.34 Causes of Intrauterine Growth Retardation

Fetal :

Chromosomal disorders (e.g. trisomies)

Chronic fetal infections (e.g. cytomegalic inclusion disease, congenital rubella, syphilis)

Radiation

Multiple gestations

Insulin deficiency

Placental:

Decreased placental weight or cellulariaty or both

Villous placentitis (bacterial, viral, parasitic)

Tumor (chorioangioma, hydatidiform mole)

placental separation, infarction

Twin-twin transfusion syndrome

Maternal :

Toxemia

Hyprtension or renal disease or both

Hypoxemia (high altitude, cyanotic cardiac or pulmonary disease)

Malnutrition or illness or anemia

Drugs (narcotics, alcohol, cigarettes)

3.35 Classification of LBW[189]

Using the birth weight, gestational age relationship the weight of newborn infants can be categorized as appropriate for gestational age (AGA); small for gestational age (SGA) or large for gestational age (LGA) A baby is said to be AGA if the weight for gestational age falls within 10th to 90th centile. SGA if below 10th centile and LGA if above 90th centile. Similarly from the gestational age alone infants can be identified as preterm (less than 37 weeks gestational) full term (38-42 weeks gestational) or post term (greater than 42 weeks gestation).

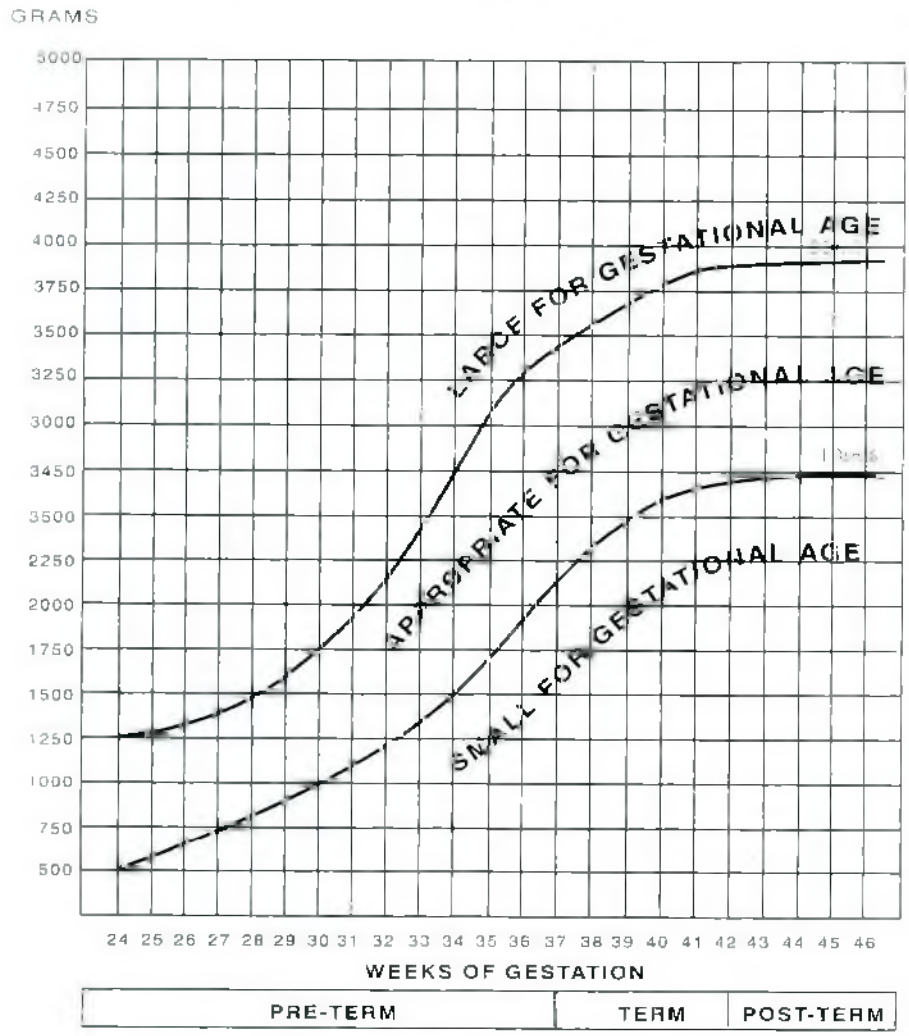


Fig. 1S : Intrauterine growth curve.

3.36 Recognition of LBW neonates

It is desirable to make clinical distinction between the two types of LBW babies. A preterm baby is diagnosed on the basis of the period of gestation calculated from the last menstrual cycle of the mother or from NBS score. If it is less than 37 completed weeks the baby is designated as preterm. Preterm babies also have distinct physical and neurological features which help in their recognition. The deep sikn creases over the soles are present only over the anterior one-third. The external ear or the pinna is soft and devoid of cartilage, and it does not recoil back promptly on being folded. In males, the scrotum does not have rugae and testes may not be descended into the scrotum. In female infants, the labia are widely separated and do not cover the labia minora, resulting in the prominent appearance of the clitores. The back of the preterm babies has abundant growth of fine hair called lanugo. Small-for-dates neonates have an emaciated look and loose folds of skin because of lack of subcutaneous tissue; these are particularly prominent over the buttocks and the thighs. They are undernourished, undersized and underweight. They look alert and often plethoric. In SFD babies the head circumference exceeds the chest circumference by more than 3 cm. The SFD babies are often full term or borderline term in gestation. When their birth weight is plotted on the intrauterine growth chart, in falls below the tenth percentile.

3.37 Difference between preterm and small-for-dates babies

Table 1E : Physical features

Preterm (but normal weight-for-dates)	Small-for-dates (but born at term)
1. Weight for age corresponds to gestational age.	1. Weight for age less than gestational age (< 10th percentile)
2. Small but plump	2. Wasted
3. Pink	3. White or pale pink
4. Length < 50cm	4. Length > 50cm
5. Head circumference < c.35cm	5. Head circumference >c.35cm
6. Lanugo hair	6. Thick, dark hair
7. Skin: shiny transparent, thin, edematous	7. Skin: dry, loose, thick
8. Ears, breast tissue, genitalia-all immature	8. Ears, breast tissue, genitalia-all mature
9. Hypotonic (floppy)	9. Good muscle tone.

Table 1G : Problems and outcome

Problems	Preterm	Term small-for-dates
1. Intrauterine Hypoxia	+	+ +
2. Respiratory Difficulties		
a) Birth Asphyxia	+	+ +
b) Meconium Aspiration	0	+
c) Hyaline Membrane Disease	+ +	0
d) Apneic Attack	+ +	0
3. Feeding Difficulties		
a) Inability To Suck And Swallow	+ +	0
b) Aspiration of Feeds	+ +	0
4. Symptomatic Hypoglycemia	+	+ +
5. Hypothemia	+ +	+

6. Hyperbilirubinemia	+ +	+
7. Liabilities of Infection (NEC)	+ +	+
8. Congenital Malformations	+	+ +
9. Hemorrhage		
a) Intraventricular	+	0
b) Pulmonary	+	+ +
10. Prognosis		
a) immediate	High mortality	Better prognosis
b) Future physical & mental development	Good if no perinatal complication occur	Poor in hypoplastic babies

In preterm small for dates babies, combined hazards of immaturity and intrauterine growth retardation would be manifested.

3.38 Problems and Complications

Preterm LBW Neonates:

A. Immediate Problems

1. Respiratory

Respiratory distress syndrome-RDS (Hyaline membrane disease-HMD)*

Pneumothorax

Congenital pneumonia

Apnea

2. Cardiovascular

Patent ductus arteriosus- PDA*

3. Hematologic

Anemia (early or late onset)

Hyperbillirubinemia-indirect*, Kernicterus

Subcutaneous, organ (liver, adrenal) Hemorrhage*

Diseminated intravacular coagulopathy

Vitamin K deficiency.

4. Gastrointestinal

Poor gastrointestinal function-poor motility*

Necortizing enterocolitis

5. Metabolic-Endocrine

Hypothermia*, hypocalcaemia*, hypoglycemia*.

6. Central Nervous System

Intraventricular Hemorrhage*

Periventricular leukomalacta

Hypoxic-ischemic encephalopathy

Sizures

Retinopathy of rpematurity (ROP)

Hypotonia*

7. Renal Hyponatremia*, hypernateremia*, hyperkalemia*

Edema

8. Orther

Infections* (congenital, perinatal, nosocomial, bacterial, viral, fungal) common

B. Late Complications

1. Neurodevelopmental disorders-mental retardation, cerebral palsy

2. Seizure

3. Behavioral problem

SGA (IUGR) Neonates:

Table 1F. Problems and outcome of LBW

A. Immediate problems

Problems	Pathogenesis
1. Intrauterine fetal demise	Hypoxia, acidosis, Infection, lethal anomaly. Uteroplacental perfusion during labor chronic fetal hypoxia-acidosis meconium aspiration syndrome.
2. Hypoglycemia	Tissue glycoge stores gluconeogenesis, hyperinsulnism glucose needs of hypoxia hypothermia large brain.
3. Polycythemia hyperviscosity	Fetal hypoxia with? erythropoietin production
4. Reduced oxygen consumption	Hypoxia, hypoglycemia stavation affect hypothermia poor subcutaneous fat stores.
5. Dysmorphology	Syndrome anomalads chromosomal genetic disorders, oligohydramnios induced deformations TORCH infections.
6. Pulmonary	Hemorrhage.
7. Infections	

B. Late compilations

1. Neurodevelopmental disorders mental retardation, cerebral palsy
2. Seizure
3. Behavioral problem
4. Malnutrition
5. Diabetes mellitus, hypertension, coronary heart disease.

3.39 Treatment of low birth weight neonates

1. Delivery of LBW Babies

Ideally the delivery of an anticipated LBW baby should be conducted in a hospital. The in utero transfer of a low weight fetus is far more desirable, convenient and safe than the transport of a LBW baby after birth. Delivery should be conducted by trained health professionals at lest one of them should be well-versed with the art of neonatal resuscitation. Resuscitation equipment like suction catheters, bag and mask, oxygen cylinder laryngoscope etc should be kept ready beforehand. Baby must be provided warmth from a heat source like a heater, or a lamp with 200 W bulb to prevent hypothermia.

An LBW newborn with a birth weight of 1800g or above, or a gestation of 34 weeks or more can be managed at home by the mother and the family under the supervision of a health worker.

The following infants should be hospitalized for care:

i. Birth weight of less than 1800 g.

ii. Gestation of less than 34 weeks.

iii. Neonate who is not able to take feeds from the breast or by cup spoon (irrespective of birth weight and gestation)

iv. A sick neonate (irrespective of birth weight and gestation)

2. Keeping the LBW Babies Warm

Provision of warmth to prevent hypothermia is one of the cardinal principles of newborn care. A baby under cold stress wastes energy and oxygen in trying to maintain temperature. Hypothermia can lead to hypoglycemia, bleeding diathesis, pulmonary hemorrhage, acidosis, apnea, respiratory

failure shock and even death, All this is entirely preventable through the following simple measures:

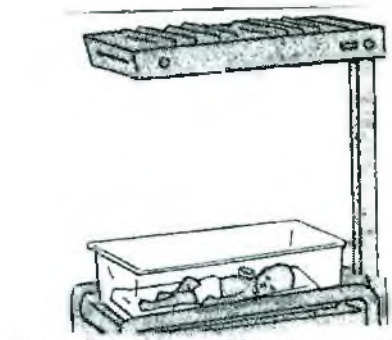
a. First and foremost the mother herself is a source of warmth for the baby. It is of immense help to nurse the baby next to the mother day and night by kangaroo-Mother care (1. baby's condition should be stable, 2. baby is held upright & prone between her breasts 3. baby's head on its side under the mother's chin)

b. The room where an LBW baby is nursed should be kept warm (temperature between 28°C to 30°C in all weathers).

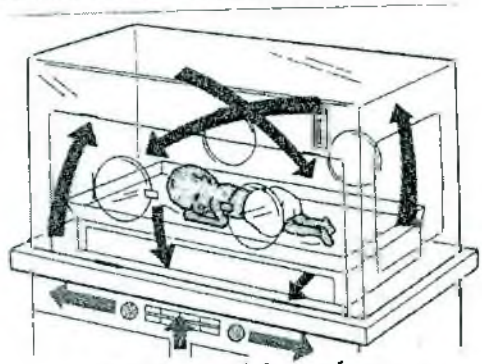
c. While in summer months no extra effort is required to maintain this temperature in winter a room heater or any other warming device may have to be used. The baby should be cloths well. Two or three layers of clothes are generally required. If the room is not warm enough, woolen sweater should also be put on. Feet should be covered with socks, hands, mittens and head with a cap. Besides, a blanket should be used to cover the baby. In a rural set-up- it may be a necessary to use hot water bottle (filled with lukewarm water at 39°C wrapped in double layered clothes) to keep the baby warm. The temperature regulation of the baby is satisfactory when trunk feels warm to touch, while the soles and the palms are pink and warm.

d. In the hospital apart from the above measures, overhead radiant warmer or incubator may be used to keep the baby warm.

Regular monitoring of auxiliary or skin temperature with a thermometer should be carried out.



Overhead radiant warmer

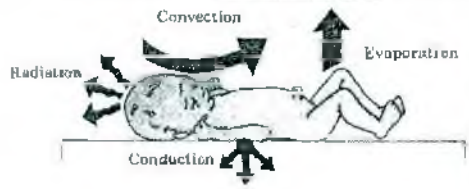


Air-heated incubator

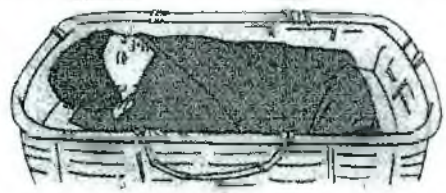
Skin -to - skin contact

Birth weight (kg)	Room temperature
1.0 - 1.5	34 - 35 °C
1.5 - 2.0	32 - 34 °C
2.0 - 2.5	30 - 32 °C
greater than 2.5	28 - 30 °C

Warm room, fire or heater



Prevent heat losses



Baby warmly wrapped

Keeping preterm, low birth weight and sick babies warm **at home**

Figure 1 : Keeping warm of LBW.

3. Nutrition and Fluids

Birth weight, gestation, presence or absence of sickness and individual feeding effort of the baby determine the decision as to how an LBW neonate be provided with fluid and nutrition. Ultimate goal is to meet both these needs from exclusive breastfeeding.

Guidelines for the modes to provide fluids and nutrients to LBW babies:

Age	Categories of neonates		
Birth weight(g)	<1200	1200-1800	>1800
Gestation	<30wk	30-40wk	>34wk
Initial	intravenous fluids. Try gavage feeds if not sick	Gavage	Breastfeeding. If unsatisfactory give cup spoon feeds
After 1-3 days		Gavage	Cup Spoon Breast
Later (2-4wk)	Cup spoon	Breast	Breast
After some more time (4-6wk)	Breast	Breast	Breast

Note :

1. For gavage and cup spoon feeds use expressed breast milk only. Start with small volume, and gradually build up.
2. When the baby is on gavage or cup spoon feeds it is important that he is put on the breast before every feed. Although the baby may not obtain much milk. it will help promote lactation and enable the baby to learn how to suck.

3. When shifting a baby from one mode of feeding go another be careful. Introduce the new mode for only some of the feeds to begin with and then build up gradually.
4. The feeding of every baby should be individualized. The above recommendations should only serve as broad guidelines.

Neonates weighing less than 1200 g or gestation of less than 30 weeks, or those having sickness should receive IV fluids initially. Enteral feeds should be introduced gradually by gavage as the baby's acute problems begin to settle. In due course, the baby is shifted to cup spoon then to direct breastfeeds.

Infants weighing 1200 to 1800 g (or 30-34 weeks gestation) and not having any significant illness should be put on gavage feeds initially. In a couple of days, it should be possible to shift them to cup spoon feeds, and then gradually to breastfeeds. In order to promote lactation and enable the baby to learn sucking all babies on gavages or cup spoon feeds should be put on the breast before each feed for 5 to 10 minutes, Breast milk is the best milk for a LBW baby.

Most LBW babies weighing more than 1800 g or over 34 weeks of gestation are able to feed directly from the breast. However some of them may not be able to do so satisfactorily during the first few days of life. During this period, the feeds may be provided with a cup spoon.

If lactation is inadequate in spite of best efforts, the baby should be carefully evaluated for supplementary feeding and resorted to for the minimum necessary period until breast milk feeding can be ensured. Any formula (Premature formula i.e.Pre-lactogen) providing (per dl) about 2g protein (why-dominant), 4.0g fat (containing polyunsaturated fatty acids and medium chain triglycerides), and 10 to 12g of carbohydrate (as lactose and

maltodextrins) and 70 to 80 kilocalories is quite suitable. If it is not possible to afford formula milk, any milk obtained for household use may be fed to the baby without dilution.

For infants on gavages or cup-spoon feeds, total daily requirements can be estimated from the table on the fluid requirements. In a stable LBW baby daily intake of feeds should be gradually built up to 180 to 200 ml/kg. LBW babies should be fed every 2 hours starting at ½ - 2 hours of age. Two hourly feeds are also applicable to LBW receiving direct breastfeeding.

Technique of feeding :

Gavage feeds: for gavage feeding, 5 or 6 FG size polythene feeding catheter is used for nasogastrict or orogastric placement. For nasogastric introduction, the catheter is measured from the external nares to the tragus of the ear, and from there to the ansiform cartilage, and marked. This length of the tube should be introduced through the nose. For the orogastric catheter the distance between angle of the mouth to tragus and then to the ansiform cartilage is used for introduction. During nasogastric or orogastric insertion, the head is slightly raised and a wet (not lubricated) catheter is gently passed through the nose (nasogastric) or mouth (orogastric) down through the esophagus to the stomach. Its position is verified by aspirating the gastric contents, and by injecting air and auscultating over the epigastric region. At the time of feeding, the outer end of the tube is attached to a 10 or 20 ml syringe (without plunger) and milk is allowed to trickle down by gravity. At the end, about 2 ml of sterile water should be injected to rinse the tube. The baby should be placed in the right lateral position for 15 to 20 minutes to avoid regurgitation.

There is no need to burp a gavage-fed baby. The polythene nasogastric or orogastric tube may be inserted before every feed or left in situ for 2 to 3 days. While pulling out a feeding tube, it must be kept pinched and pulled out gently while applying constant negative pressure with a syringe to avoid trucking of gastric contents into the trachea. Gavage feeding may be risky in very small babies. They have a small capacity of stomach and the gut may not be ready to tolerate feeds. Stasis may also result from paralytic ileus due to autonomic immaturity. This, gavage-fed preterm babies are candidates for regurgitation, aspiration and necrotizing enterocolitis (NEC). Before every feed, the abdominal girth (just above the umbilical stump) should be measured. If the abdominal girth increases by more than 2cm from the baseline, the baby should be evaluated carefully for any illness. The enteral feeds may have to suspended till the abdominal distention improves.

Fluid requirements of neonates (ml per kg body weight)

Daily life	Birth weight		
	>1500g	1000 to 1500g	<1000g
1	60	80	100
2	75	95	115
3	90	110	130
4	105	125	145
5	120	140	160
6	135	155	175
7 onwards	150	170	200

Note:

1. On the first day fluid requirements range from 60 to 100ml/kg (the difference between the three categories 20ml/lg each day)
2. The daily increment in all groups is around 15ml per kg till day 7.
3. For those receiving phototherapy add extra 10 to 15ml/kg fluid.
4. These are general guidelines; fluid therapy of every baby should be individualized.

Cup-spoon feeding:

Feeding with cup-spoon has been found safe in LBW babies. This mode of feeding is a bridge between gavages feeding and direct breast feeding. Neonates with gestation of 30 to 32 weeks or more are in position to swallow the feeds satisfactory even though they may not have coordinated sucking efforts. The required amount of expressed breast milk is taken in a spoon. The baby is placed in semi upright posture with a napkin around the neck to mop up the spillage. The spoon is filled with milk, a little short of the brim. place at the lips of the baby in the corner of the mouth. The baby will actively swallow the milk. Similarly, feeding can be given from a cup.

Breastfeeding:

LBW babies may be slow in sucking and take longer time to feed.

Assessment of Adequacy of Nutrition :

A LBW baby loses up to 1 to 2 percent weight during the first week of life. Birth weight is regained between 10^{th} and 14^{th} day. All babies start gaining weight by second week of life at a rate of about 15 to 20g per day. Hospitalized LBW babies should be weighed everyday.

Excessive weight loss & delay in regaining birth weight are suggestive of inadequate feeding, cold stress or systemic illness (like anemia, sepsis etc).

4. Nutritional supplements[182]

All LBW babies should receive vitamin K1 at birth (1mg IM or IV, 2mg PO). Vitamin A and D are required in doses of 1000 IU and 400 IU everyday, respectively from 2 weeks of age. At 8 weeks of age, iron supplements should be started in a dose of 2mg/kg/day. Very low birth babies (<1500 g, <32 wk gestation) need vitamin E (1 mg/kg/d, 6-12 IU/kg/d), calcium and phosphorus supplementation till 37 weeks.

5. Protection against infection & early detection of sickness

Hand washing before and after handling each baby, handling should be minimum, visitors should be controlled. Keep way infected persons. Early diagnosis of severe infection & treatment.

Prognosis

Mortality of LBW babies is inversely related to the gestation & birth weight directly to complications. More than 90% of LBW have no neurodevelopment handicaps.

The outlook for uncomplicated premature babies is as good as that for babies born after full maturity. In fact several renowned and famous people who were premature grew up to become leaders and intellectuals. Sir Isaac Newton, the greatest mathematician genius weighed merely 3 lbs at birth. Sir Winston Churchill the legendary Prime Minister of Britain was born after 7 months of pregnancy when his mother was participating in royal dance. The world renowned artist Pablo Picasso came into this world a bit too early. The parents of premature, children therefore should not feel despondent. With timely health expert valued weight gain survival may be restored after zinc supplementation for full life despite LBW.

CHAPTER 4

MATERIAL AND METHODS

MATERIALS AND METHODS

4.1 Type and period of study

This was a prospective randomized, double blind study. The duration of study was 2 years from May 2005 to May 2007. The research proposal was approved by Faculty of Postgraduate Medical Science and Research, Dhaka University and Ethical clearance was obtained from Bangladesh Medical Research Council.(Appendix 10.1)

4.2 Study Population and Selection of the subjects.

This study was carried out at the Neonatal ward of Sher-E-Bangla Medical College Hospital, Barisal, Bangladesh. The duration of study was from May 2005 to February 2007. One hundred pairs of Low birth weight neonates were included in this study.

The selection criteria of neonates in the study:

1. Birth weight less than 2.5kg (between 1200 gm to 2300 gm) with gestation period between 28 and 42 weeks.
2. Neonates who where admitted in the first day of life and the mother of whom consented to reside in the hospital for continues 28 days.
3. Neonates of mother who did not have history of zinc supplementation during pregnancy.

The exclusion criteria :

1. Neonates admitted with respiratory distress syndrome (RDS). Birth Asphyxia, Hypothermia etc.

2. The parents did not consent to participate in the study.

4.3 Development of Questionnaire

In order to obtain quality data, a standard Questionnaire was developed for this study, which included newborn health information; measurement of weights of neonates, gestational age, and any LBW related problems. The questionnaire was pre-tested and finalized before date collection. (Appendix 10.4)

4.4 Study procedure.

After admission a detailed history and thorough clinical examination was done in all cases and controls. Gestational age was assessed according to new Ballared scoring system. Then parents were informed (Appendix 10.2) and consent was taken from them after explaining the purpose of the study (Appendix 10.3). Close monitoring was done for study neonates.

The case selection method :

1. Each of the enrolled neonates consecutively by following inclusion and exclusion criteria and was randomized either of the 2 groups.

2. The case and control were matched by weight, sex, type of LBW and type of feeding.

One hundred pairs, representing 200 neonates were included in the study. After randomization and pair matched neonates were grouped into two groups, 100 neonates were included group A, and 100 neonates in group B.

4.5 Zinc Supplement and placebo

The syrups administered for the neonates of both groups were prepared by Orion Laboratories Ltd., 153-154 Tejgaon I/A, Dhaka-1208, a drug manufacturing company. Syrup for the case neonates was prepared by elemental zinc, sucrose, flavor and preservatives as 100ml in a sealed bottle with beautiful carton of which 2.5 ml contained 5 mg of zinc. The placebo syrup with same color and taste contained sucrose, flavor and preservatives but no zinc. The syrups were labeled as D_1 & D2 and these codes were kept confidential with the pharmacist. Neither the investigator nor the subjects knew the intervention agent. The two syrups were indistinguishable in presentation. At the end of the study the code of D_1 & D2 syrup was decoded and found D_1 contained zinc and D_2 was placebo. In the first 28 days of life, the neonates of group A received labeled di syrup at a dose of 2.5ml and group B received 2.5ml of syrup labeled as D2 per day. The mother or care-giver of each child was shown individually how to administer the syrup by using disposable syringe and advised to give child the daily dose. The parents or care givers were instructed to feed 2.5ml of the D_1 or D2 syrup by disposable syringe (without needle) in every morning at 10AM to their neonatest as up to 28 days.

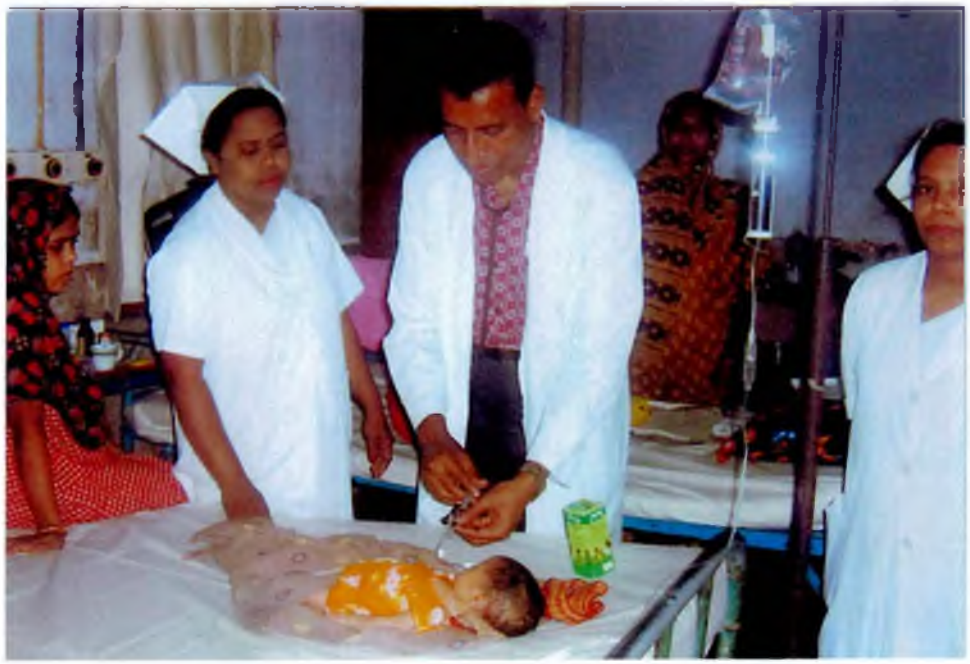


Fig.1 ৺ The syrup administered to the study neonate by researcher.

Neonate who were unable to take feeds either from breast or dropper or spoon, nasogastric tube (size no. 6) was used. Sixty ml expressed breast milk or infant formula (lactogen) was given in 24 hours and gradually increased to 20ml after every 24 hours up by 200ml per kg body weight per day. The feeding of the study and control neonates remained same. The overall supervision was maintained by the researcher.

4.6 Anthropometric data collection

Measurement of weight of case and control neonates without cloth before feeding at 9 a.m. with the use of a portable weight measure scale (models RGZ-20. Baby Table weighing machine with a capacity of 15 kg x 50gm) after 72 hours, 7 days, 14 days, 21 days and 28 days of birth and recorded in the questionnaire.

Fig. 1৲: Measurement of weight of the study neonate by researcher.

4.7 Data processing

Record form (Questionnaires) were precoded and checked daily. Before entering data into the computer, individual record form was scrutinized thoroughly for accuracy and consistency.

4.8 Data Entry

A data entry package were developed, dBASE II plus were used to develop the data entry package. After computer entry of the entire data was checked and edited by the researcher.

Data entry was verified by using loss checks and logical checks. Gains in weight were analyzed using two-way ANOVA with sex and supplement group as factors.

4.09 Data analysis plan.

A tabulation plan was prepared and necessary programs were developed using statistical software package SPSS/PC+ and EPI Info by a data analyst under the guidance of researcher. During analysis frequency distribution for all the variables were worked out and produced in tabular form. In the second stage of the analysis a number of cross tables consistent to the research objectives were produced. Some important findings were presented in graphical form.

4.10 Anthropometric data analysis.

The anthropometric data were calculated and analyzed as standard deviation scores (Z-scores) of NCHS (The US National Center for Health Statistics) reference weight-for-age as percentage of reference median of the indicator. The anthropometric software package was used in this regard. The following cut-off level was used to categories severe, moderate and normal forms of malnutrition or under nutrition.

Weight-for-age Z score (WAZ)

WAZ = Less than or equal to – 3 SD	: Severely underweight
WAZ = - 2SD to – 2.99 SD	: Moderately underweight
WAZ = Greater than – 2 SD	: Not underweight

4.11 Uni variate data analysis.

Socio-demographic and child data were analyzed by sing SPSS software package. Outputs of two-way classification were transferred into EPI Info software package to calculate Chi-squre value, Odds ratio and Relative risk.

1.12 Bivariate and multivariate analysis.

Chi-Square test was done to find out the association between dependent and independent variables. Odds ratio (OR) were done to find out the association of exposure with risk factors. Relative risk (RR) was done to find out the risk of exposure than non-exposure to form abnormal. Correlation coefficient was done to find out the degree of relationship among the variables. Analysis of variance (ANOVA) was done to find out the subjects effected on zinc supplementation. Multiple comparisons and mean test were done to compare between groups. Logistic regression analysis was done to find out the effect of independent variable on weight gain.

CHAPTER – 5

RESULTS

RESULTS :

A total 0f 200 hundred neonate infants (100 in the zinc supplemented and 100 in the control group) were randomly selected to complete the study until 28 days of age. Five follow up weight including birth weight were noted. After decoding, analysis was done and data presented by graphs.

Table 1: Baseline characteristics of the selected infants

Variables	Cases (n=100)	Control (n=100)
Children	Neonate	Neonate
Sex		
Male	54.0%	54.0%
Female	46.0%	46.0%
Average birth weight (gm)	1789.0±228.89	1789.0±228.89
Types of low birth weight		
IUGR	22%	22%
Preterm	78%	78%
Average gestational age	33.8±4.6	33.8±4.6
Problems / complication		
No problem	72.0%	44.0%
Jaundice	15.0%	24.0%
Infection	7.0%	26.0%
Convulsion	2.0%	3.0%
Apnoea	4.0%	3.0%

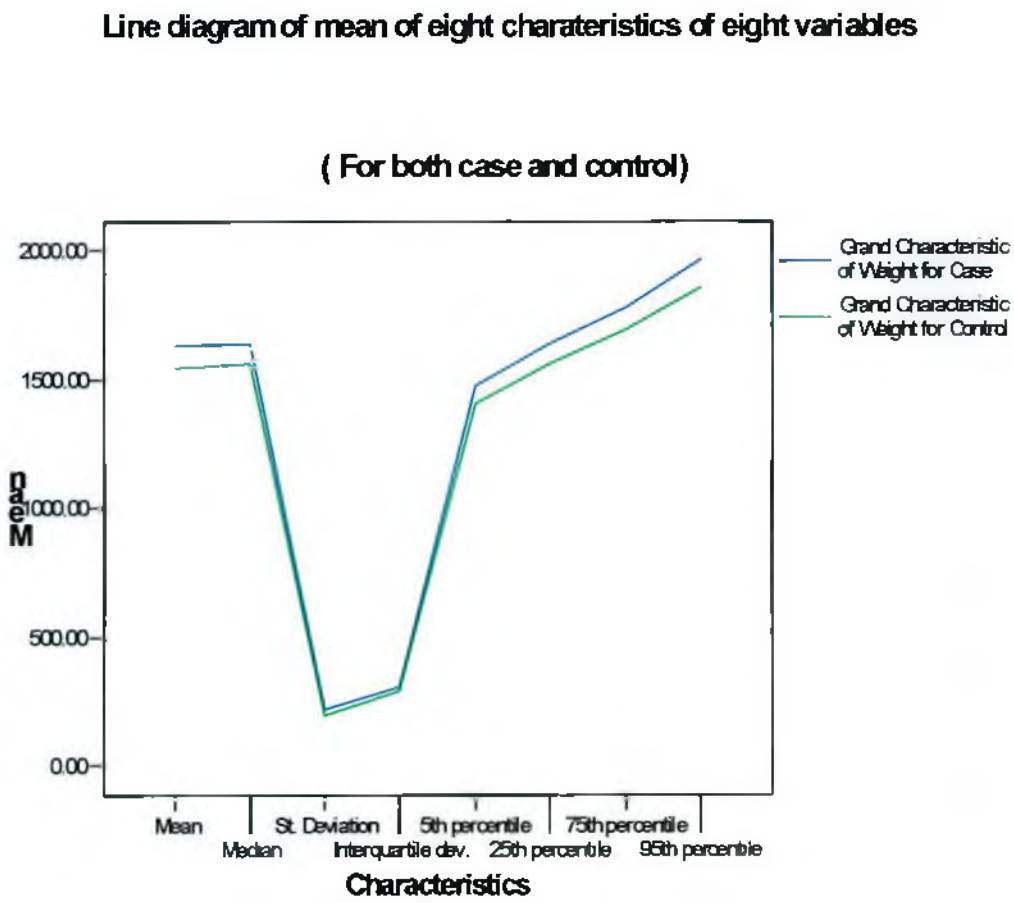
Table 1 showed the baseline characteristics including male (54%), female (46%), average birth weight (1789.0±228.89 gm.), IUGR (22%), preterm (78%) and average gestational age (33.8±4.6) were similar in two groups. Seventy two percent of cases had no problems / complication during the study period. The rest 28 percent had various types of problems / complication such as jaundice, infection, convulsion and apnoea. On the other hand only 44 percent of control had no problems/complication. The rest 56 percent had various types of problems / complication.

Table 2. Descriptive Measurements for Weight at Different Periods, Weight Gain, and Gestational Period (For Case and Control)

Variables		Central Tendencies		Dispersions		Percentiles				Shape	
		Mean	Median	St. Deviation	Inter Quartile Range	5	25	75	95	Skewness	Kurtosis
Birth Weight	Case	1788.50	1800.00	229.718	350.00	1450.00	1600.0	1950.0	2100.00	-.402	-.1
	Control	1789.50	1800.00	228.885	350.00	1450.00	1600.0	1950.0	2100.00	-.4	.1
Weight After 72 hours	Case	1610.50	1625.00	216.759	300.00	1252.50	1450.0	1750.0	1950.00	-.0	.1
	Control	1614.00	1600.00	216.384	350.00	1300.00	1450.0	1800.0	1947.50	-.531	.5
Weight After 7 days	Case	1810.00	1850.00	230.940	350.00	1405.00	1650.0	2000.0	2147.50	-.394	.1
	Control	1802.50	1850.00	229.775	300.00	1402.50	1650.0	1950.0	2150.00	-.425	.3
Weight After 14 days	Case	1966.00	1975.00	240.463	338.00	1600.00	1800.0	2137.5	2350.00	-.353	.1
	Control	1957.00	1950.00	232.464	350.00	1600.00	1800.0	2150.0	2347.50	-.289	-.
Weight After 21 days	Case	2273.00	2300.00	285.988	400.00	1802.50	2050.0	2450.0	2700.00	-.302	-.0
	Control	2168.50	2200.00	247.579	337.50	1750.00	2012.5	2350.0	2550.00	-.252	-.1
Weight After 28 days	Case	2665.50	2650.00	331.182	450.00	2102.50	2450.0	2900.0	3197.50	-.250	-.2
	Control	2407.00	2400.00	267.991	400.00	1950.00	2200.0	2600.0	2847.50	033	-.264
Total wt gain at the end	Case	883.00	900.00	194.913	250.00	550.00	750.00	1000.0	1197.50	-.100	-.2
	Control	616.00	650.00	160.472	200.00	400.000	500.00	700.00	900.000	.310	-.188
Average weight gain	Case	31.404	32.00	6.9267	9.0	19.600	26.700	35.700	42.740	-.100	-.215
	Control	21.63	22.200	5.675	7.20	13.050	17.800	25.000	32.000	.176	-.479
Gestational Age	Case	34.09	34.50	4.526	6.00	28.00	30.00	36.00	42.00	.210	-.958
	Control	34.09	34.00	4.59	6.00	28.00	30.00	36.00	42.00	.200	-.997

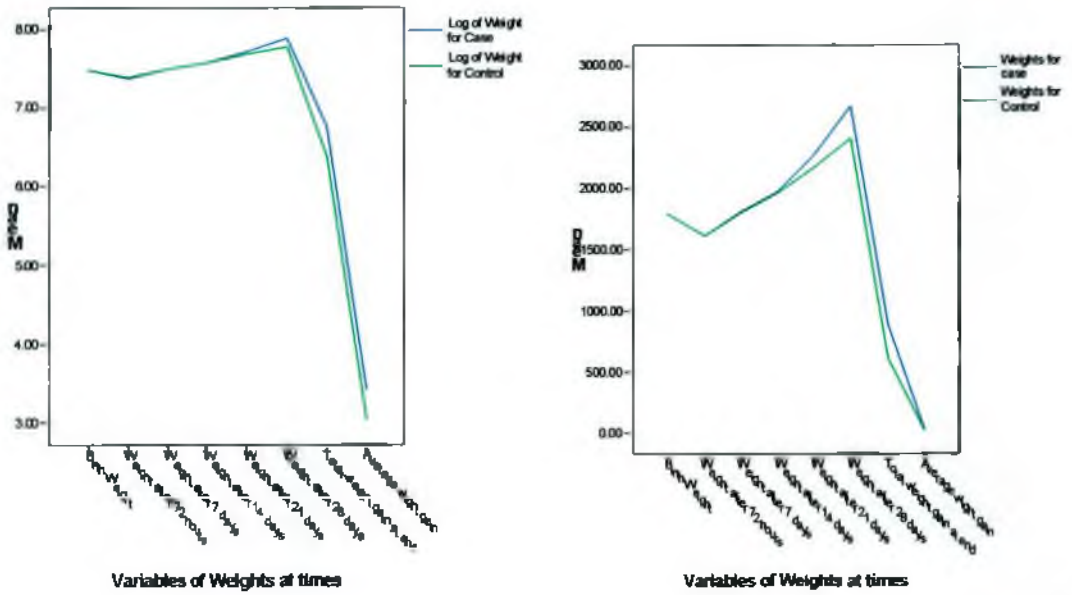
Table 2 Contains important descriptive measures of continuous variables of the data set for both case and control. To grasp traits of the table we draw in Fig. 1 line diagrams of a) mean, median (measures of central tendency); b) standard deviation, quartile deviation (measures of dispersion) and c) four important percentiles of eight weight variables for both case and control. In the figures it is clear that both almost all measures of central tendency and percentiles of case are higher than those of control. The weight gain stated to increase by 7 days of intervention and maintained till the end of the study. This increment was more marked in cases. The weight was 883.0 and 616.0g respectively in cases and control. The average weight observed in 31.4g and 21.63g for case and control respectively.

Figure. 1 represents means of eight characteristics of eight weight variables.



The Figure 1 only represents means of eight characteristics of eight weight variables. The diagram depicts that measures of case in each of the three categories, specially the first and the last ones are higher than those of control.

Figure. 2. Lines through the weights at different times for both the Case and Control



In the last six weight variables we observed case are higher weight gain than control. All these findings suggest that treatment has positive effect on weight.

Table 3: Paired Samples Test

		Paired Differences					T-test	DF	P-value
		Mean Difference	Std	Std Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Weight after 72 hours for case - Weight after 72 hours for control	-3.50000	53.30255	5.33025	-14.07638	7.07638	-.657	99	.513
Pair 2	Weight after 7 days for case - Weight after 7 day for control	7.50000	57.89881	5.78988	-3.98838	18.98838	1.295	99	.198
Pair 3	Weight after 14 days for case - Weight after 14 days for control	9.00000	83.29696	8.32970	-7.52792	25.52792	1.080	99	.283
Pair 4	Weight after 21 days for case - Weight after 21 days for control	104.50000	184.23950	18.42395	67.94289	141.05711	5.672	99	.000
Pair 5	Weight after 28 days for case - Weight after 28 days for control	258.50000	248.33333	24.83333	209.22528	307.77472	10.409	99	.000
Pair 6	Aver weight gain for case - Aver weight gain for control	9.76500	8.75421	.87542	8.02797	11.50203	11.155	99	.000
Pair 7	Gestational Age for Case - Gestational Age for control	.00000	1.05409	.10541	-.20915	.20915	.000	99	1.000

This table 3 showed that weight gain was significantly higher in cases than control from 21 days to 28 days. Average weight gain in cases was also significantly higher in cases than the control (P=.001).

Table 4: Independent samples test between the outcomes of zinc supplemented and without zinc supplemented group

Source of variation	Zinc supplementation (cases)		Without Zinc supplementation (control)		z-test for Equality of Means	Sig. (2-tailed
	Mean	Std. Deviation	Mean	Std. Deviation		
Birth weight	1789.50	228.89	1789.50	228.89	0.000	1.00
Weight after 3rd day	1610.50	216.76	1613.00	215.04	- 0.082	0.93
Weight after 7th day	1810.00	230.94	1803.50	231.08	0.199	0.84
Weight after 14th day	1964.00	241.84	1958.00	232.54	0.179	0.85
Weight after 21st day	2261.5*	292.14	2165.5*	243.47	2.52	0.01
Weight after 28th day	2665.0*	331.32	2374.0*	410.07	5.52	0.00

* The mean difference is significant at the .05 level.

Table 4 showed that mean birth weigh of cases and control was similar. Mean weight after 3rd, 7th and 14th days of cases were not significantly different (P>0.05) when compared with control group respectively. Mean weight after 21st and 28th days of cases was significantly higher (P<0.05) than that of control group respectively.

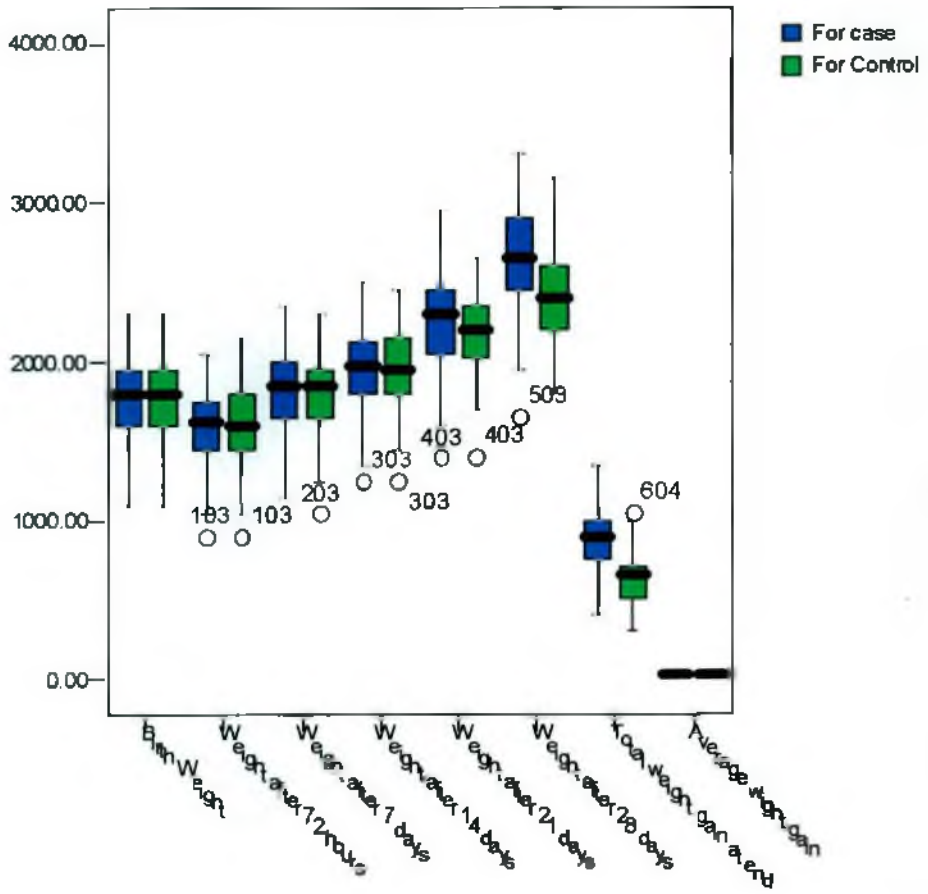
Table 5: Mean, standard deviation, skewness of weight and its rate of change by follow up

Variable	Groups	Source of variation	N	Mean	skeswness	Rate of change (per unit) of weight
Weight (gm.)	Case	Birth weight	100	1789.50±228.89	– 0.41	From baseline
		Weight after 3rd day	100	1610.50±255.38	– 0.41	.10(–)
		Weight after 7th day	100	1810.00±230.94	– 0.54	.01(+)
		Weight after 14th day	100	1964.00±241.84	– 0.55	.09(+)
		Weight after 21st day	100	2261.50±296.14	– 0.39	.26(+)
		Weight after 28th day	100	2665.00±331.52	– 0.40	.48+)
	Control	Birth weight	100	1789.50±228.89	– 0.35	From baseline
		Weight after 3rd day	100	1613.00±215.04	– 0.28	.09(–)
		Weight after 7th day	100	1803.50±256.86	– 0.65	.007(+)
		Weight after 14th day	100	1958.00±232.54	– 0.30	.09(+)
		Weight after 21st day	100	2165.50±243.47	– 0.24	.17(+)
		Weight after 28th day	100	2374.00±410.07	– 2.82	.32(+)

+ increase – decrease

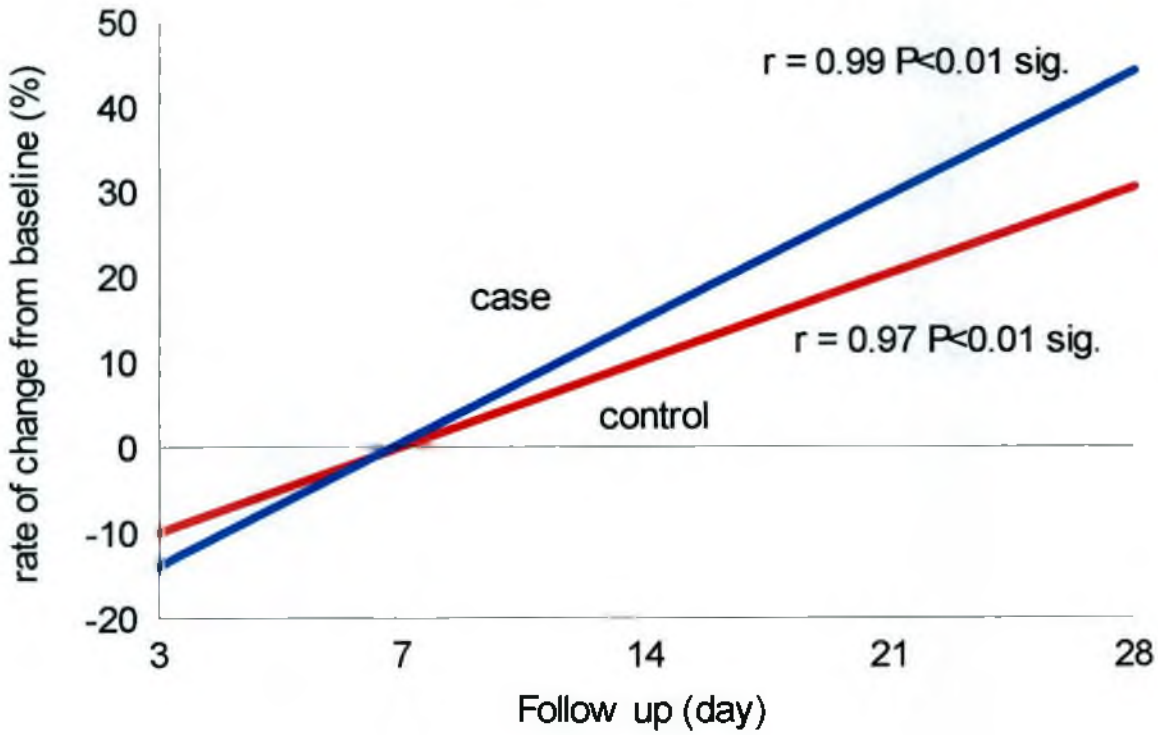
Table 5 showed the mean values with standard deviation, skewness of weights and its rate of change of different indicators of the infants surveyed. After 7th day follow up, average weight of case and control were found to increased gradually across the follow up. Small values of skewness of different indicators indicate that the sample were normally distributed and were representative of the population. After 3rd, 7th, 14th, 21st and 28th days follow up, rate of change (per unit) of weight from baseline of cases were – 0.10, 0.01, 0.09, 0.26 and 0.48 respectively. Whereas the rate of change of control group were - 0.09, 0.007, 0.09, 0.17 and 0.32 respectively. Rate of change of weight among cases were found to be higher than control group.

Figure 3. Box Plot of Several Weights for Case and Control



shows that both median and dispersion of the weight at later periods and weight gains are higher for case than control.

Figure 4 Linear trend of rate of change (%) of weight from baseline by follow up



Positively significant correlation (r = 0.99, P<0.01) between rate of change of weight and follow up days of cases was found. Positive correlation implies that rate of change tends to increase as follow up days increase. Rate of change of weight of control group was also significantly correlated (r = 0.97, P<0.01) with the follow up days. Strength of correlation in cases was higher than that of control group.

Figure 5 Comparison between initial weight and final weight

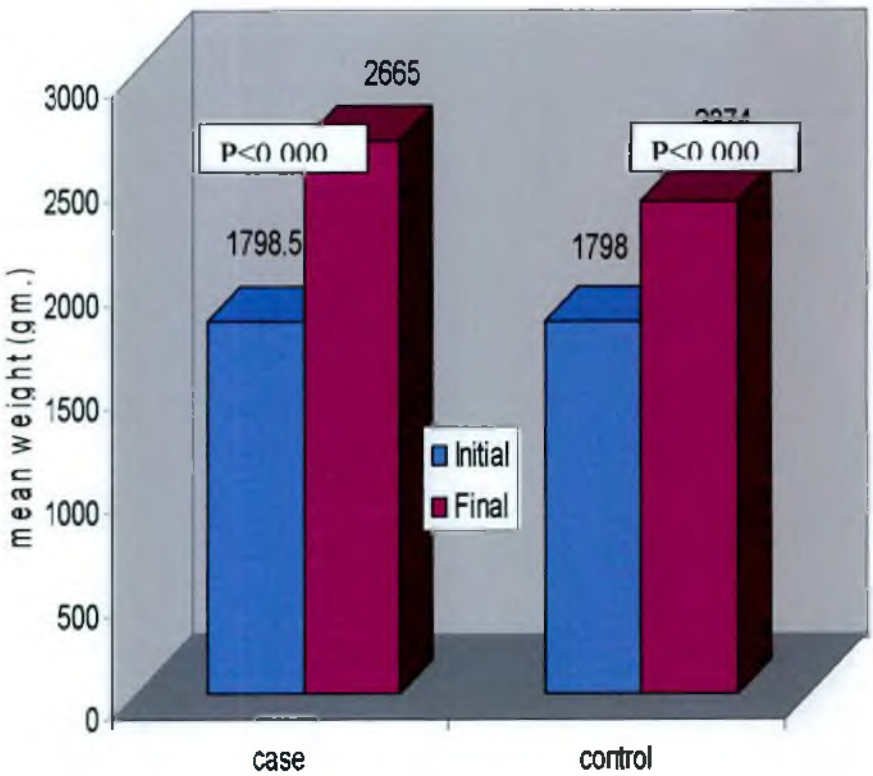


Figure 5 showed that mean weight of final follow up of cases and control group were significantly higher (P<0.000) when compared with mean birth weight. Improvement of weight in cases and control were 48.92 percent and 32.66 percent respectively.

Table 6: Tests of between subjects effects of zinc supplementation and without zinc supplementation

Groups zinc supplementation	Source of variation	N	Mean	Std. Deviation	Analysis of variance (ANOVA)	
					F	Sig.
Zinc supplementation (Cases)	Birth weight	100	1789.50	228.89	219.24	0.000
	Weight after 3rd day	100	1610.50	216.76		
	Weight after 7th day	100	1810.00	230.94		
	Weight after 14th day	100	1964.00	241.84		
	Weight after 21st day	100	2261.50	292.14		
	Weight after 28th day	100	2665.00	331.32		
	Total	600	2016.75	437.13		
Without zinc supplementation (Control)	Birth weight	100	1789.50	228.89	107.13	0.000
	Weight after 3rd day	100	1613.00	215.04		
	Weight after 7th day	100	1803.50	231.08		
	Weight after 14th day	100	1958.00	232.54		
	Weight after 21st day	100	2165.50	243.47		
	Weight after 28th day	100	2374.00	410.07		
	Total	600	1950.58	369.15		
Overall cases	Combined	600	2016.75	437.13	8.02	0.005
Overall control	Combined	600	1950.58	369.15		

Table 6 showed that the subjects effects in cases (F=219.24, P<0.000) and control (F=107.13, P<0.000) were significantly different. Effect between zinc supplementation in case and without zinc supplementation in control group was significantly different (F=8.02, P<0.005). Strength of effectiveness in case was higher than the strength of effectiveness in control group.

Table 7: Multiple comparisons among the outcome of zinc supplemented and without zinc supplemented groups

(I)	(J)	zinc supplementation (cases)		without zinc supplementation (control)	
		Mean Difference (I-J)	Sig.	Mean Difference (I-J)	Sig.
Birth weight	Weight after 3rd day	179.00*	.000	176.50*	.001
	Weight after 7th day	-20.50	.997	-14.00	1.00
	Weight after 14th day	-174.50*	.000	-168.50*	.002
	Weight after 21st day	-472.00*	.000	-376.00v	.000
	Weight after 28th day	-875.50*	.000	-584.50*	.000
After 3rd day	Birth weight	-179.00*	.000	-176.50*	.001
	Weight after 7th day	-199.50*	.000	-190.50*	.000
	Weight after 14th day	-353.50*	.000	-345.00*	.000
	Weight after 21st day	-651.00*	.000	-552.50*	.000
	Weight after 28th day	-1054.50*	.000	-761.00*	.000
After 7th day	Birth weight	20.50	.997	14.00	1.00
	After 3rd day	199.50*	.000	190.50*	.000
	Weight after 14th day	-154.00*	.004	-154.50*	.006
	Weight after 21st day	-451.50*	.000	-362.00*	.000
	Weight after 28th day	-855.00*	.000	-570.50*	.000
After 14th day	Birth weight	174.50*	.000	168.50*	.002
	Weight after 3rd day	353.50*	.000	345.00*	.000
	Weight after 7th day	154.00*	.004	154.50*	.006
	Weight after 21st day	-297.50*	.000	-207.50*	.000
	Weight after 28th day	-701.00*	.000	-416.00*	.000
After 21st day	Birth weight	472.00*	.000	376.00*	.000
	Weight after 3rd day	651.00*	.000	552.50*	.000
	Weight after 7th day	451.50*	.000	362.00*	.000
	Weight after 21st day	297.50*	.000	207.50*	.000
	Weight after 28th day	-403.50*	.000	-208.50*	.000
After 28th day	Birth weight	875.50*	.000	584.50*	.000
	Weight after 3rd day	1054.50*	.000	761.00*	.000
	Weight after 7th day	855.00*	.000	570.50*	.000
	Weight after 14th day	701.00*	.000	416.00*	.000
	Weight after 21st day	403.50*	.000	208.50*	.000

* The mean difference is significant at the .05 level.

Multiple comparisons by Post Hoc test of weight by follow up showed that average birth weight after 3rd day of cases was significantly flat ($P<0.05$) when compared with average birth weight. Average weight after 3rd, 7th, 14th, 21st and 28th days were significantly different ($P<0.05$) when compared to each other. Similar significant results were found in control group (Table 7).

Figure 6 Comparison of weight gain (gm./day) between cases and control

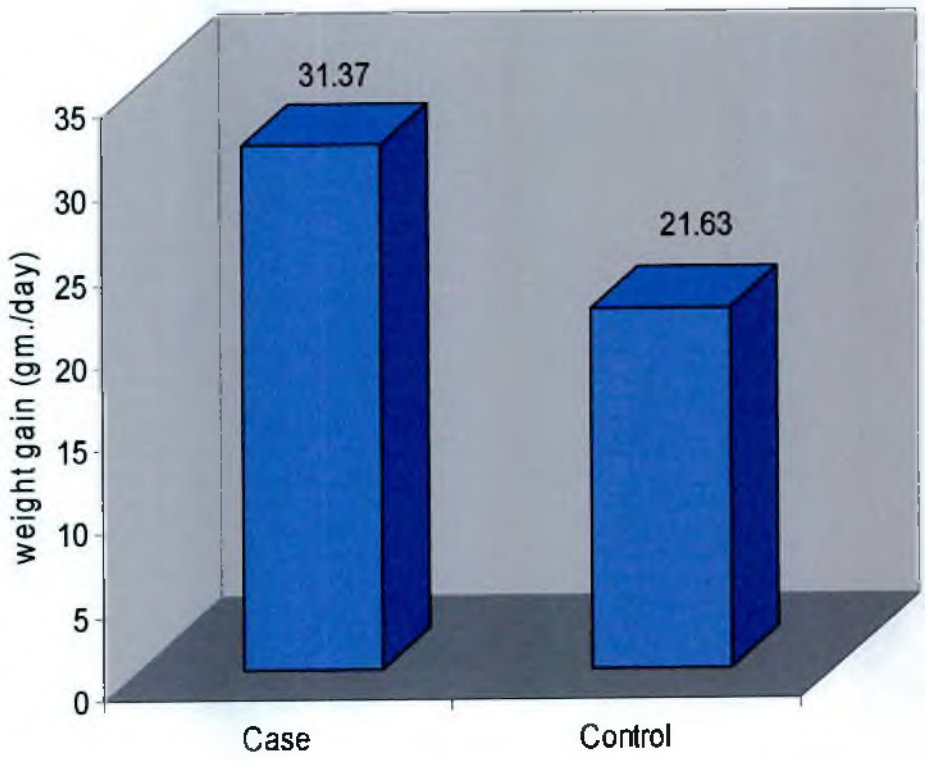


Figure 6 showed that mean weight gain (31.37 ± 6.91 gm./day) of cases was significantly higher (P<0.000) than the mean weight gain ((21.63 ± 5.67 gm./day) of control group.

Table 8: Weight for age z-score (WAZ) by follow up

Variable	Groups	Source of variation	N	Mean	Std. Deviation
Weight (gm)	Case	Birth weight	100	-3.6618	0.35
		Weight after 3rd day	100	-3.9679	0.38
		Weight after 7th day	100	-3.6300	0.35
		Weight after 14th day	100	-3.3882	0.37
		Weight after 21st day	100	-2.9222	0.45
		Weight after 28th day	100	-2.2896	0.52
	Control	Birth weight	100	-3.6618	0.35
		Weight after 3rd day	100	-3.9374	0.33
		Weight after 7th day	100	-3.6239	0.40
		Weight after 14th day	100	-3.3975	0.36
		Weight after 21st day	100	-3.0710	0.37
		Weight after 28th day	100	-2.7431	0.64

Table 8 showed that mean weight for age z-score after 3rd day of cases was lower than baseline (birth weight). After 7th day, mean weight for age z-score were gradually increased across the follow up. Similar trend was observed in control group.

Table 9: Nutritional status (%) of the children by weight for age z-score (WAZ) classification

Source of variation	Cases (n=100)			Control (n=100)		
	WAZ ≤ – 3 SD (Severely underweight)	WAZ – 2.99 to – 2 SD (Moderately under weight)	WAZ > – 2 SD (Not under weight)	WAZ ≤ – 3 SD (Severely underweight)	WAZ – 2.99 to – 2 SD (Moderately underweight)	WAZ > – 2 SD (Not under weight)
Birth weight	98.0	2.0	0.0	98.0	2.0	0.0
Weight after 3rd day	100.0	0.0	0.0	100.0	0	0.0
Weight after 7th day	96.0	4.0	0.0	97.0	3.0	0.0
Weight after 14th day	85.0	15.0	0.0	85.0	15.0	0.0
Weight after 21st day	38.0	62.0	0.0	54.0	46.0	0.0
Weight after 28th day	8.0	62.0	30.0	22.0	72.0	6.0

Nutritional status of the children by weight for age z-score classification of cases during baseline showed that severely underweight, moderately underweight and normal were 98 percent, 2 percent and 0 percent respectively. Similar results were found in control group. After final follow up, severely underweight of cases and control group were reduced from 98 percent to 8 percent and 22 percent respectively. On the other hand normal nutrition status of cases and control group increased to 30 percent and 6 percent. According to severely underweight, improvement were 90 percent of cases and 76 percent of control group (Table 9).

Table 10: Association of zinc supplementation with weight for age z-score classification after final follow up

Zinc supplementation	WAZ ≤ - 2 SD (underweight)	WAZ > - 2 SD (Normal)	Total
No (control group)	94	6	100
Yes (cases)	70	30	100
Total	164	36	200

Chi-square = 17.92 P < 0.000 Odds ratio (OR) = 6.71 Relative risk (RR) = 1.34

Table 16 showed that zinc supplementation was significantly associated (Chi-square = 17.92 P < 0.000) with nutritional status. Odds ratio (OR=6.71) showed that control group (without zinc supplementation) was positively associated with underweight. Relative risk (RR=1.34) showed that control group had 1.34 times higher risk to form underweight than cases.

Table 11: Effectiveness (%) of zinc supplementation on severely underweight

Zinc supplementation	Follow up	WAZ ≤ – 3 SD (Severely underweight) %	Effectiveness (%)
Yes	Birth weight	98.0	From baseline
	Weight after 7th day	96.0	2.04
	Weight after 14th day	85.0	13.27
	Weight after 21st day	38.0	61.22
	Weight after 28th day	8.0	91.84
No	Birth weight	98.0	From baseline
	Weight after 7th day	97.0	1.02
	Weight after 14th day	85.0	13.26
	Weight after 21st day	54.0	44.89
	Weight after 28th day	22.0	77.55

Effectiveness = [(baseline – final follow up) ÷ baseline] × 100

After 7th, 14th, 21st and 28th days follow up effectiveness of the program on severely underweight of cases were 2.04, 13, 27, 61.22 and 91.84 percent respectively. Whereas the effectiveness of control group were 1.02, 13.26, 44.89 and 77.55 percent respectively. Effectiveness of cases was higher than the effectiveness of control group (Table 11).

Figure 7: Effectiveness of the program on weight for age z-score (WAZ)

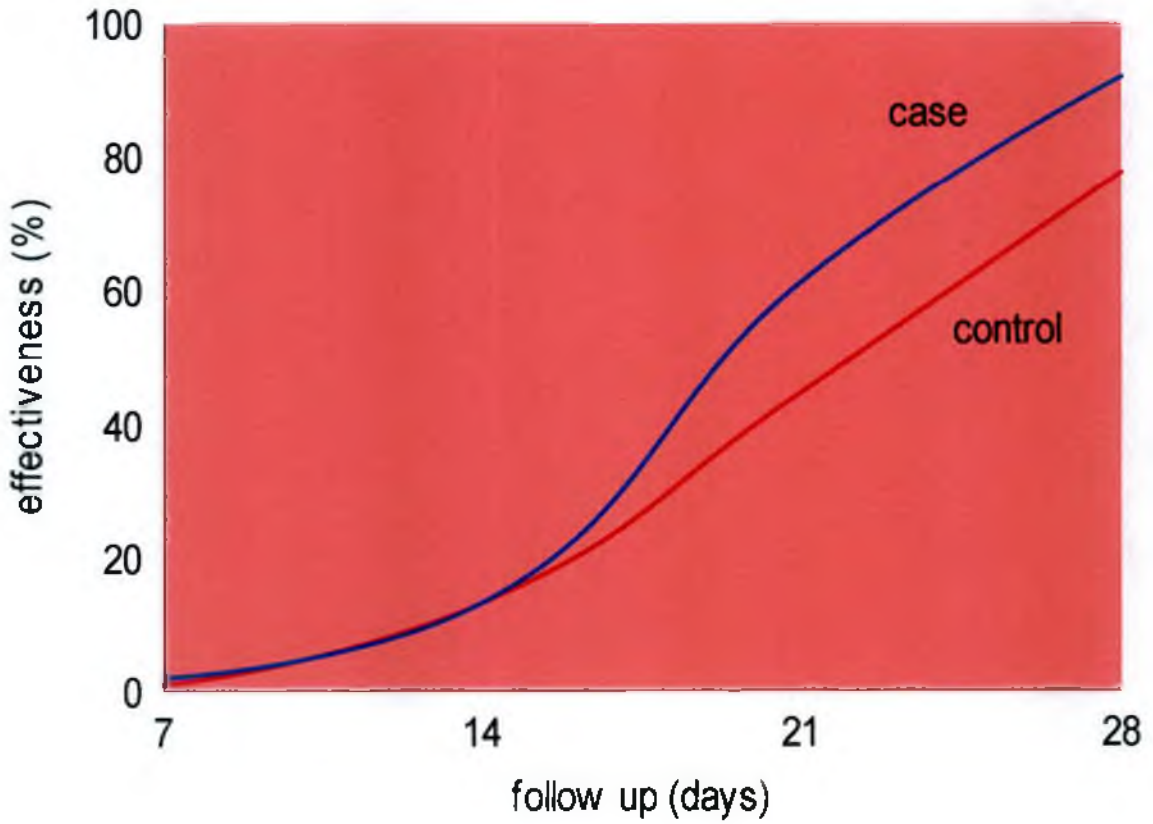


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Figure 7 showed the linear curve of effectiveness of the program on weight for age z-score by follow up days. It was found that effectiveness of cases and control group gradually increased across the follow up and effectiveness in case was higher than that of control group.

Table 12: Association of zinc supplementation with nutritional status by weight for age z-score

Zinc supplementation	Underweight (waz ≤ − 2 SD) Normal (waz > − 2 SD)	Chi-square	Sig.	Odds ratio (OR)	Relative risk RR)
No (control) Yes (cases)	Birth weight	0.26	1.00	1.00	1.00
	Weight after 7th day	0	1.00	1.35	1.01
	Weight after 14th day	0.04	0.84	1.00	1.0
	Weight after 21st day	4.43	0.03	1.92	1.42
	Weight after 28th day	6.0	0.01	3.24	2.75

Table 12 showed the association between zinc supplementation and nutritional status. Up to 14th day follow up it was found that zinc supplementation was not significantly associated (P>0.05) with nutritional status. This implies that prevalence of underweight was equally common in all groups. After 21st and 28th day follow up, Chi-square test showed that zinc supplementation was significantly associated (P<0.05) with nutritional status. Odds ratio 1.0 showed that control group (without zinc supplementation) was not positively associated with underweight. After 21st and 28th day follow up, odds ration 1.92 and 3.24 showed that control group was positively associated with underweight. Up to 14th day follow up, relative risk 1.0, 1.01 and 1.0 showed that risk of case and control group had equal common to form underweight. After 21st and 28th day follow up, relative risk showed that control group had 1.42 times and 2.75 times higher risk to form underweight than cases.

Figure 8: Linear curve of Odds ratio between zinc supplimentation (no, yes) and nutritional status (underweight, normal)

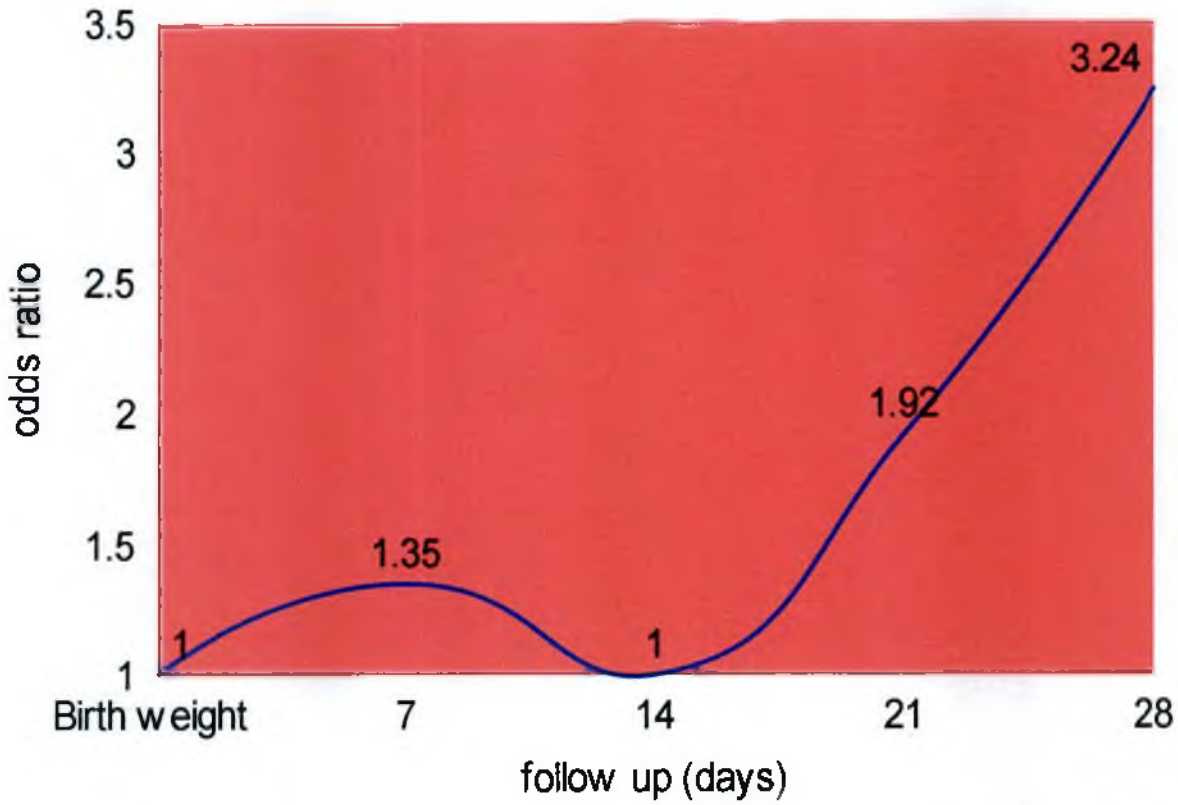


Figure 8 showed the linear curve of odds ration between zinc supplementation and nutritional status by follow up. After 14th day follow up, strength of positive association of control group to form underweight gradually increased across the follow up.

Figure 9 :Linear curve of relative risk between zinc supplimentation (no, yes) and nutritional status (underweight, normal)

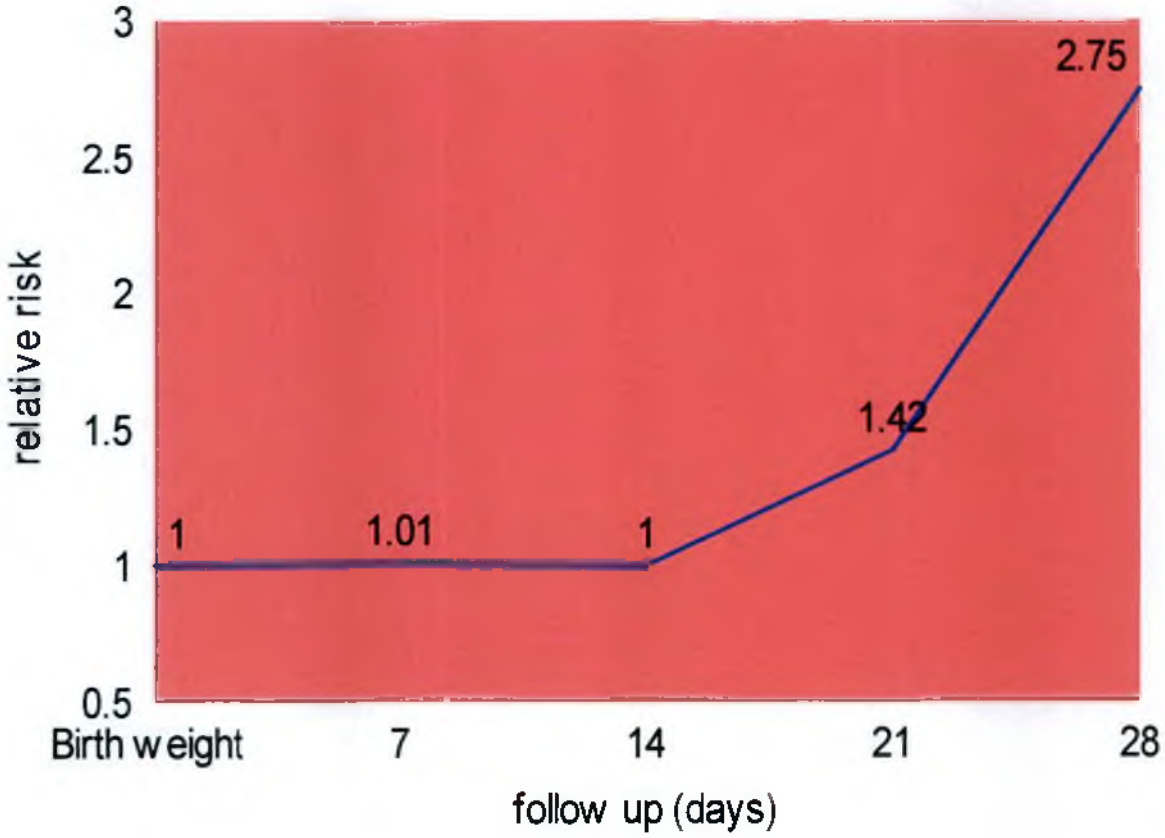


Figure 9 showed the risk of control group to form under weight. Up to 14th days follow up risk of case and control group had equally common to form underweight. After 14th day follow up risk of control to form underweight gradually increased.

Table 13: Sex wise average weight by follow up

Follow up	Sex	Case (n=100)	Control (n=100)
Birth weight	Male	1779.63	1779.63
	Female	1801.09	1801.09
	Total	1789.50	1789.50
Weight after 72 hours	Male	1569.44	1596.30
	Female	1619.57	1632.61
	Total	1592.50	1613.00
Weight after 7 days	Male	1804.63	1787.96
	Female	1816.30	1821.74
	Total	1810.00	1803.50
Weight after 14 days	Male	1959.26	1940.74
	Female	1969.57	1978.26
	Total	1964.00	1958.00
Weight after 21 days	Male	2260.87	2139.81
	Female	2262.04	2195.65
	Total	2261.50	2165.50
Weight after 28 days	Male	2662.04	2337.96
	Female	2668.48	2416.30
	Total	2665.00	2374.00
Total weight gain at the end of study	Male	891.67	601.85
	Female	864.13	618.48
	Total	879.00	609.50
average weight gain (gms./day)	Male	31.581	21.381
	Female	31.139	21.941
	Total	31.378	21.639

Table 13 showed that mean weight of male and female of cases were gradually increased across the follow up. It was found that mean weight of female was higher than the mean weight of male respectively. Similar trend was found in control group.

Figure 10 Sex wise linear curve of average weight of cases by follow up

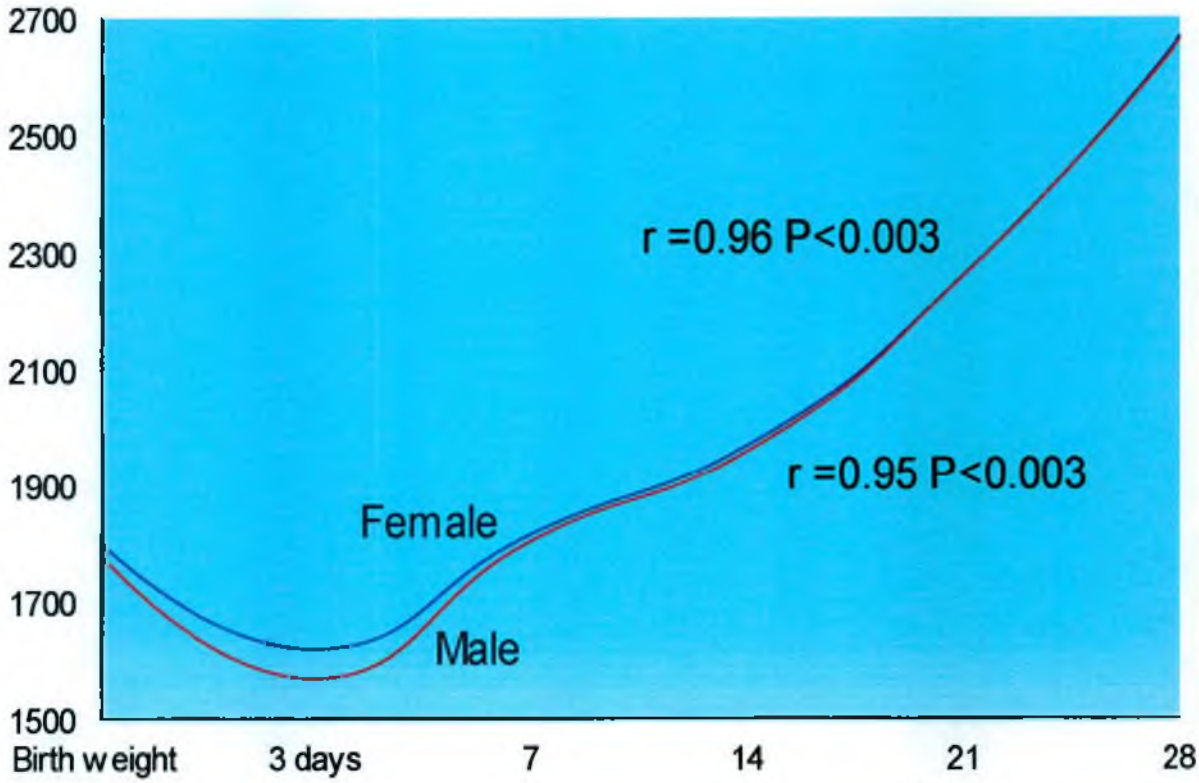
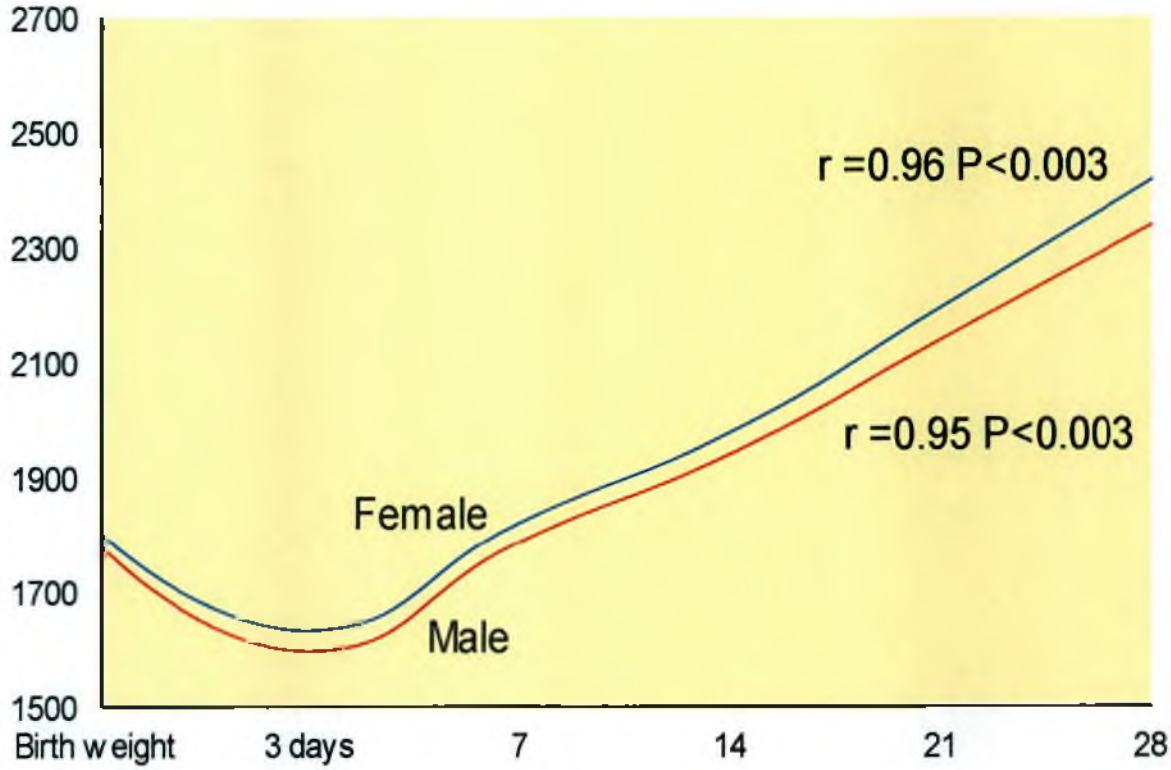


Figure 10 showed the sex wise linear relationship between mean weight and follow up days of cases. It was found that mean weight of female was significantly correlated (r=0.96, P<0.003) with follow up days. Mean weight of male was also significantly correlated (r=0.95, P<0.003) with follow up days. Linear trend of female was higher than that of male.

Figure 11Sex wise linear curve of average weight of control group by follow up



Sex wise linear curve of control group showed that mean weight of female and male were significantly correlated (r=0.96 P<0.003, r=0.95 P<0.003) with the follow up days respectively. Strength of relationship among female group was higher than that of male group.

Figure 12. Box Plot of Several Weights w.r.t. Sex (Case)

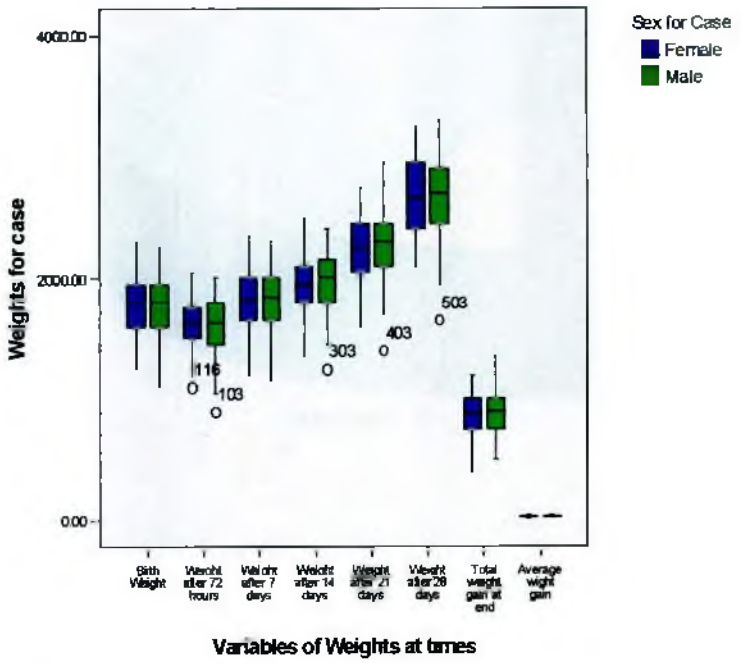


Figure 12 indicate that sex has no clear-cut influence on the weight.

Figure 13 Group wise more weight gain

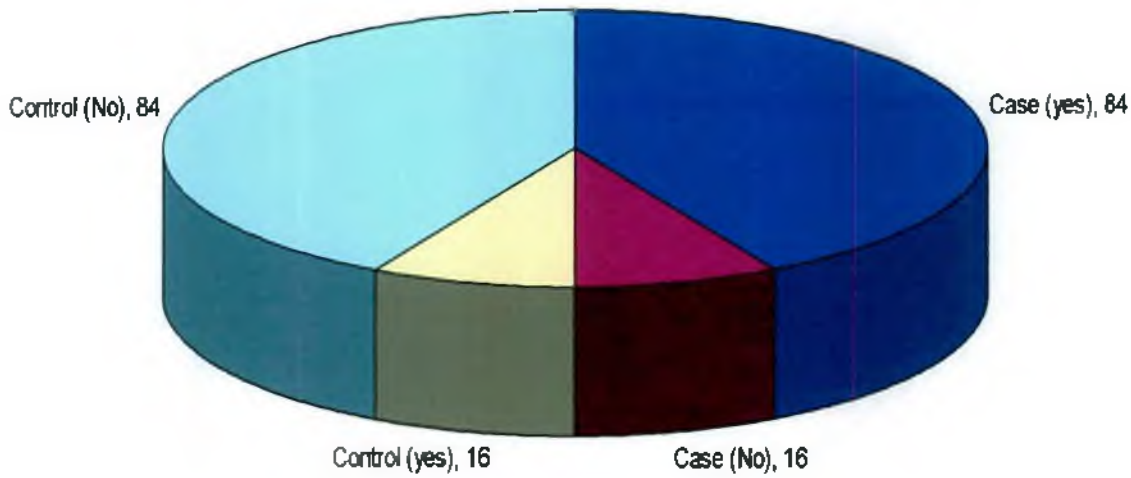


Figure 13 showed that 84 percent of cases had weight gained more than control group. The rest 16 percent did not weight gain more than control group. Inverse results were in control group.

Table 14: Association of zinc supplementation with more weight gain

Zinc supplementation	More weight gain		Total
	No	Yes	
Control	16	84	100
Cases	84	16	100
Total	100	100	200

Chi-square = 89.79 P < 0.000 Odds ratio (OR) = 27.56 Relative risk (RR) = 5.25

Based on Chi-square test it was found that zinc supplementation was significantly associated (Chi-square = 89.78, P<0.000) with weight gain. Odds ratio (OR = 27.56) showed that control group was positively associated with not weight gain more than cases. Relative risk (RR = 5.25) showed that control group had 5.25 times higher risk than cases for not weight gain more than cases (Table 14).

Table 15: Mean weight of cases and control group by gestational age (weeks)

Groups	Gestational age (weeks)	N	Mean	Std. Deviation	Analysis of variance (ANOVA)	
					F	Sig.
Zinc supplementation (Cases)	≤30	36	1591.67	183.81	39.29	0.000
	31-35	24	1787.50	149.82		
	36-40	28	1926.79	128.73		
	>or=41	12	2066.67	128.51		
	Total	100	1789.50	228.89		
Without zinc supplementation (Control)	≤30	30	1566.67	179.24	45.44	0.000
	31-35	30	1783.33	147.00		
	36-40	23	1878.26	138.03		
	>or=41	17	2073.53	101.73		
	Total	100	1789.50	228.89		

Table 15 showed that the subjects effects in cases (F=39.29, P<0.000) and control (F=45.44, P<0.000) were significantly different. Mean weight of cases and control group were gradually increased across the gestational age respectively.

Figure **14** Curvilinear relationship between mean weight and gastational age (weeks)

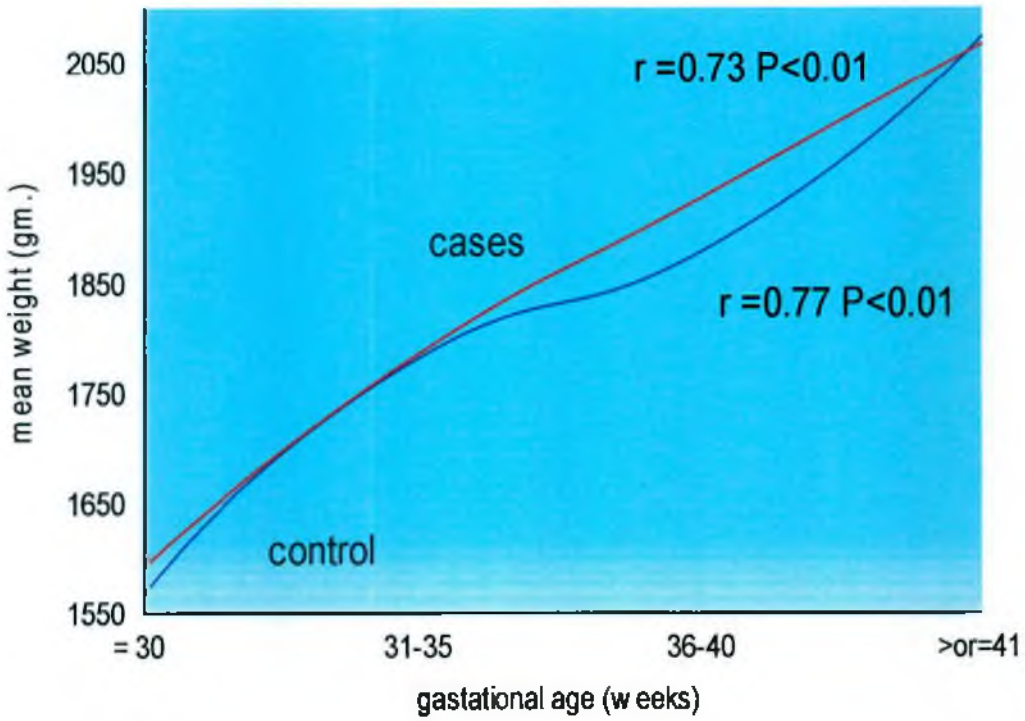


Figure 14 showed the curvilinear relationship between mean weight and gestational age of cases and control group. It was found that mean weight of cases was positively correlated (r=0.73, P<0.01) with gestational age. Similarly trend (r=0.77, P<0.01) was found in control group. Positive relationship implies that mean weight tends to increase as gestational age increase.

Table 16: Types of feeding by cases and control

Types of feeding	Case		Control	
	Frequency	Percent	Frequency	Percent
10% dextrose + Express breast milk by NG tube + breast feeding	35	35.0	35	35.0
Formula feeding + Express breast milk + Breast feeding	43	43.0	43	43.0
Exclusive Breast feeding by suckling	22	22.0	22	22.0
Total	100	100.0	100	100.0

Table 16 showed that 10% dextrose + Express breast milk by NG tube + breast feeding, Formula feeding + Express breast milk + Breast feeding, Exclusive Breast feeding by suckling of cases were 35 percent, 43 percent and 22 percent respectively. Types of feeding were similar in control group.

Figure 15 Box Plot of Several Weights w.r.t. Type of Feeding (Control)

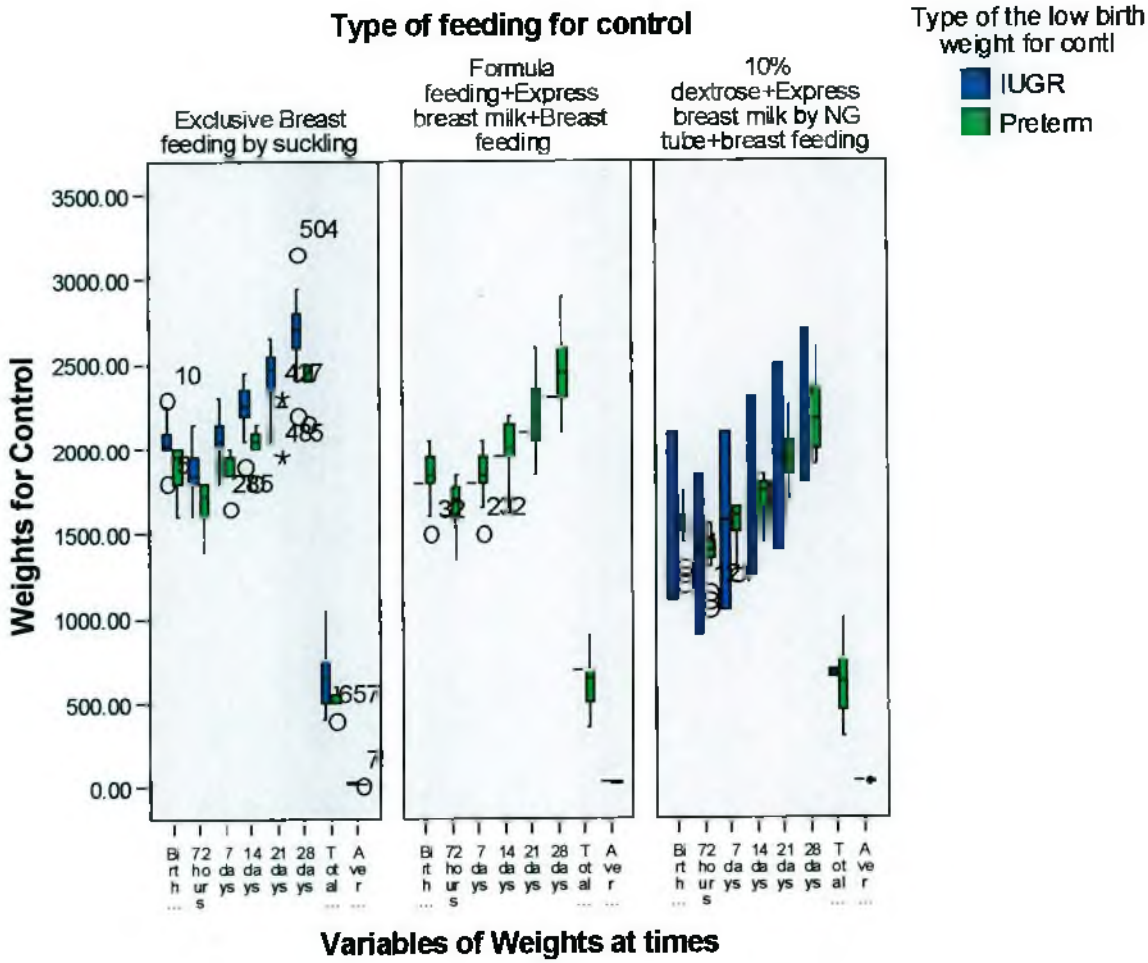


Figure 15 demonstrate that for both case and control low birth type IUGR has more positive effect on weight in every type of feeding.

Table 17 Types of low birth weight by follow up weight

Follow up	Types of low birth weight	N	Case	Control
			Average weight	Average weight
Birth weight	Preterm	78	1728.21	1728.21
	IUGR	22	2006.82	2006.82
	Total	100	1789.50	1789.50
Weight after 72 hours	Preterm	78	1558.33	1561.54
	IUGR	22	1713.64	1795.45
	Total	100	1592.50	1613.00
Weight after 7 days	Preterm	78	1748.72	1742.95
	IUGR	22	2027.27	2018.18
	Total	100	1810.00	1803.50
Weight after 14 days	Preterm	78	1898.72	1896.15
	IUGR	22	2195.45	2177.27
	Total	100	1964.00	1958.00
Weight after 21 days	Preterm	78	2190.38	2109.62
	IUGR	22	2513.64	2363.64
	Total	100	2261.50	2165.50
Weight after 28 days	Preterm	78	2587.18	2310.26
	IUGR	22	2940.91	2600.00
	Total	100	2665.00	2374.00
Average weight gain (gms/day)	Preterm	78	30.863	21.532
	IUGR	22	33.205	22.018
	Total	100	31.378	21.639

Table 17 showed that mean weight of IUGR group of cases was higher than the mean weight of preterm group across the follow up days. Similarly trend was found in control group.

Figure 16 Linear curve between follow up days and types of low birth weight

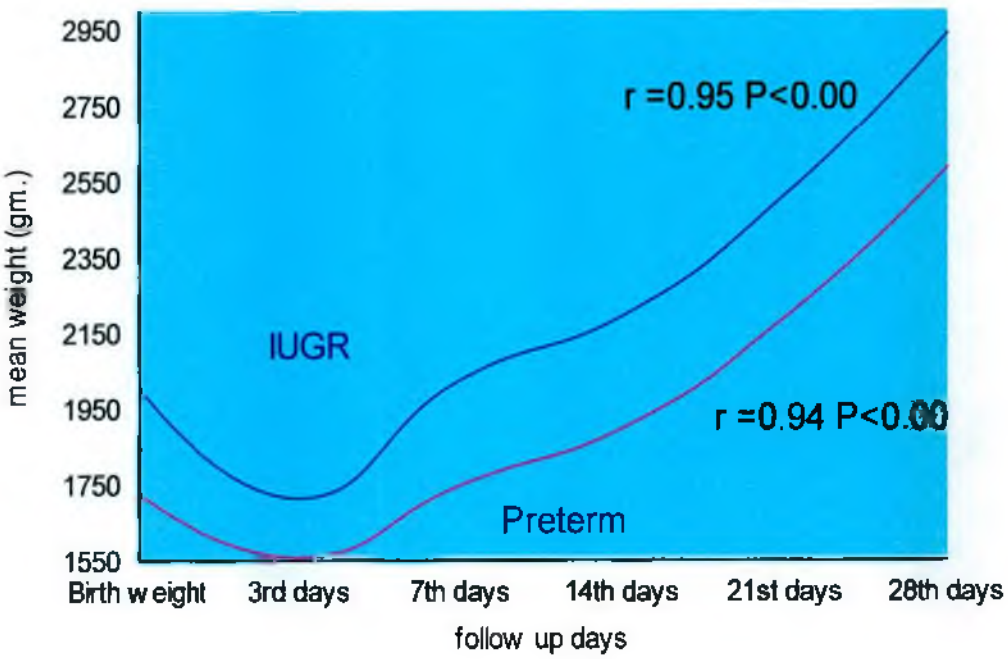


Figure 16 showed the linear relationship between follow up days and types of low birth weight. It was found that mean weight of IUGR group of cases was positively correlated (r=0.95, P<0.00) with follow up days. Similarly trend (r=0.94, P<0.0-0) was found in preterm group. Higher trend among IUGR than Preterm group was found..

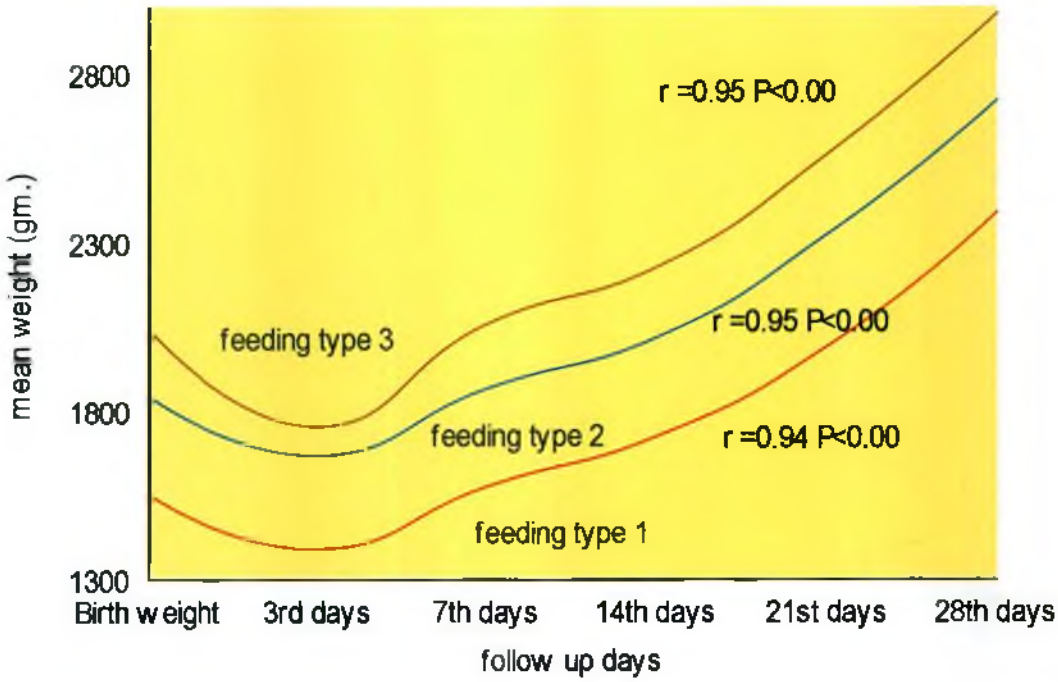
Table 18: Types of feeding by follow up weight

Follow up	Types of feeding	N	Case	Control
			Average weight	Average weight
Birth weight	10% dextrose + Express breast milk by NG tube + breast feeding	35	1555.71	1555.71
	Formula feeding + Express breast milk + Breast feeding	43	1847.67	1847.67
	Exclusive Breast feeding by suckling	22	2047.73	2047.73
	Total	100	1789.50	1789.50
Weight after 72 hours	10% dextrose + Express breast milk by NG tube + breast feeding	35	1392.86	1394.29
	Formula feeding + Express breast milk + Breast feeding	43	1670.93	1675.58
	Exclusive Breast feeding by suckling	22	1756.82	1838.64
	Total	100	1592.50	1613.00
Weight after 7 days	10% dextrose + Express breast milk by NG tube + breast feeding	35	1578.57	1567.14
	Formula feeding + Express breast milk + Breast feeding	43	1869.77	1863.95
	Exclusive Breast feeding by suckling	22	2061.36	2061.36
	Total	100	1810.00	1803.50
Weight after 14 days	10% dextrose + Express breast milk by NG tube + breast feeding	35	1727.14	1725.71
	Formula feeding + Express breast milk + Breast feeding	43	2020.93	2017.44
	Exclusive Breast feeding by suckling	22	2229.55	2211.36
	Total	100	1964.00	1958.00
Weight after 21 days	10% dextrose + Express breast milk by NG tube + breast feeding	35	1992.86	1955.71
	Formula feeding + Express breast milk + Breast feeding	43	2325.58	2216.28
	Exclusive Breast feeding by suckling	22	2563.64	2400.00
	Total	100	2261.50	2165.50
Weight after 28 days	10% dextrose + Express breast milk by NG tube + breast feeding	35	2392.86	2185.71
	Formula feeding + Express breast milk + Breast feeding	43	2724.42	2397.67
	Exclusive Breast feeding by suckling	22	2981.82	2627.27
	Total	100	2665.00	2374.00

Table 18 showed that mean wt of Exclusive Breast feeding by suckling of cases were higher than the mean weight of 10% dextrose + Express breast milk by NG tube + breast

feeding and Formula feeding + Express breast milk + Breast feeding across the follow up days respectively. Similarly trend was found in control group.

Figure 17 Linear curve between follow up weight and types of feeding



type 1: 10% dextrose + Express breast milk by NG tube + breast feeding

type 2: Formula feeding + Express breast milk + Breast feeding

type 3: Exclusive Breast feeding by suckling

Figure 38 showed the linear relationship between follow up weight and types of feeding. It was found that mean weight of type 3 feeding group of case was positively correlated (r=0.95, P<0.00) with follow up weight. Similarly trend (r=0.95 P<0.0-0, and r=0.94 P<0.0-0) were found in type 2 and type 1 group respectively. Higher trend among type 3 group was found..

Table 19: Weight gain more by average gestational age of cases and control

Weight gain more than control	N	Mean ± SD	Weight gain more than control	N	Mean ± SD
Yes	84	34.05±4.7	Yes	16	33.19±4.2
No	16	32.88±4.4	No	84	33.98±4.73
Total	100	33.86±4.65	Total	100	33.85±4.64

Table 19 showed that mean gestational age (34.05 weeks) of case was higher who had weight gained more than control group. On the other had mean gestational age (33.19 weeks) of control group was lower who had weight gained more than cases.

Table 20: Weight gain more by types of low birth weight

Groups	More weight gain	Number %	Types of low birth weight		Total
			Preterm	IUGR	
Cases	Yes	Number	65	19	84
		% of column	83.3%	86.4%	84.0%
		% of Total	65.0%	19.0%	84.0%
	No	Number	13	3	16
		% of column	16.7%	13.6%	16.0%
		% of Total	13.0%	3.0%	16.0%
	Total	Number	78	22	100
		% of column	100.0%	100.0%	100.0%
		% of Total	78.0%	22.0%	100.0%
Control	Yes	Number	13	3	16
		% of column	16.7%	13.6%	16.0%
		% of Total	13.0%	3.0%	16.0%
	No	Number	65	19	84
		% of column	83.3%	86.4%	84.0%
		% of Total	65.0%	19.0%	84.0%
	Total	Number	78	22	100
		% of column	100.0%	100.0%	100.0%
		% of Total	78.0%	22.0%	100.0%

Table 20 showed that 86.4 percent of IUGR group of case had weight gained more than control group. The rest 13.6 percent did not weight gained than control group. The inverse results were found in control group.

Table 21: Association of weight gain more of cases by types of low birth weight

Types of low birth	weight gain more than control group		Total
	No	Yes	
Preterm	13	65	78
IUGR	3	19	22
Total	16	84	100

Chi-square = 0.0 P < 1.0 Odds ratio (OR) = 1.27 Relative risk (RR) = 1.22

Based on Chi-square test it was found that types of low birth was not significantly associated (Chi-square = 0.0, P>0.05) with weight gain more than control group. Odds ratio (OR = 1.27) showed that preterm group was positively associated with not weight gain more than control. Relative risk (RR = 1.22) showed that preterm group had 1.22 times higher risk than IUGR (Table 21).

Table 22: Association of weight gain more of control by types of low birth weight

Types of low birth	More weight gain		Total
	No	Yes	
Preterm	65	13	78
IUGR	19	3	22
Total	84	16	100

Chi-square = 0.98 P < 1.0 Odds ratio (OR) = 0.79 Relative risk (RR) = 0.96

Based on Chi-square test and Odds ratio (Chi-square = 0.0 P>0.05, OR=0.79) it was found that types of low birth of control group was not associated with weight gain more than cases.

Table 23: Weight gain more by types of feeding

Groups	Weight gain more	Number %	Types of feeding			Total
			10% dextrose + Express breast milk by NG tube + breast feeding	Formula feeding + Express breast milk + Breast feeding	Exclusive Breast feeding by suckling	
Cases	Yes	Number	27	37	20	84
		% of row	32.1%	44.0%	23.8%	100.0%
		% of column	77.1%	86.0%	90.9%	84.0%
		% of Total	27.0%	37.0%	20.0%	84.0%
	No	Number	8	6	2	16
		% of row	50.0%	37.5%	12.5%	100.0%
		% of column	22.9%	14.0%	9.1%	16.0%
		% of Total	8.0%	6.0%	2.0%	16.0%
	Total	Number	35	43	22	100
		% of row	35.0%	43.0%	22.0%	100.0%
		% of column	100.0%	100.0%	100.0%	100.0%
		% of Total	35.0%	43.0%	22.0%	100.0%
Control	Yes	Number	27	37	20	84
		% of row	32.1%	44.0%	23.8%	100.0%
		% of column	77.1%	86.0%	90.9%	84.0%
		% of Total	27.0%	37.0%	20.0%	84.0%
	No	Number	8	6	2	16
		% of row	50.0%	37.5%	12.5%	100.0%
		% of column	22.9%	14.0%	9.1%	16.0%
		% of Total	8.0%	6.0%	2.0%	16.0%
	Total	Number	35	43	22	100
		% of row	35.0%	43.0%	22.0%	100.0%
		% of column	100.0%	100.0%	100.0%	100.0%
		% of Total	35.0%	43.0%	22.0%	100.0%

Table 23 showed that Exclusive Breast feeding by suckling group of case had weight gained more than others feeding group. Similar results were found in control group.

Table 24: Logistic regression analysis showing the effect of independent variable on weight gain (1 = yes, 2 = no)

Independent variables	B	S.E.	Sig.	Exp(B)
Sex	0.611	0.401	0.127	1.842
Gastational age	0.031	0.021	0.136	1.032
Type of low birth weight	- 0.017	0.055	0.720	0.983
Types of feeding	0.058	0.315	0.853	1.06
Zinc supplementation	3.435	0.406	0.000**	31.032
Constant	-7.046	1.210	0.000**	0.001

** highly significant

Table 24 showed the effect of independent variable on weight gain by using logistic regression analysis. It was found that zinc supplementation had significant influence (b=1.21, P<0.000) on weight gain.

CHAPTER – 6

DISCUSSION

DISCUSSION

In Bangladesh the newborn's health problem start long before birth. The intergenerational cycle of malnutrition starts with the mother of the child. She herself was born with LBW and soon after menarche she was married and became pregnant, the child who is born to her also is LBW, may be premature and subsequently poised to repeat the same cycle.

LBW Neonates have their own metabolic characteristics and a large number of diseases and complications in the postnatal period, making their nutrition a real challenge. Nowadays, the postnatal nutrition of these newborn infants has risen in importance, since fetal malnutrition, and possibly, postnatal malnutrition have been considered in epidemiological studies to play a crucial role in the determination of adult diseases such as diabetes. hypertension and heart diseases. Therefore, neonatologists have a greater responsibility to provide these newborn infants with a nutrition that ensures appropriate physical growth and neuropsychomotor development. Given this scenario, the nutrition of extremely preterm infants using mineral supplementation has become important, due to the fact that minerals have different functions in the body, although little is known about them, especially with regard to the nutrition of extremely preterm infants. As the role of some minerals has been under investigated, it should be underscored that calcium and zinc are also important to the nutrition of LBW.

Zinc deficiency is common in Low birth weight neonates in the developing world like Bangladesh. Zinc deficiency most often occurs when zinc intake

is inadequate or poorly absorbed, when there are increased losses of zinc from the body, or when the body's requirement of zinc increases. The physiological role of zinc during periods of rapid growth and development emphasizes the importance of zinc during fetal life and gestation[184].

Serum zinc is not ideal indication of zinc status because it is affected by several factors other than zinc intake and zinc status . It is generally agreed, however, that serum zinc is of some value as an indicator when used for large groups is similar settings and when care is taken to standardize conditions for blood sampling. Results of cross sectional studies have associated low dietary zinc intake or low maternal plasma zinc with increase risks of LBW and preterm delivery. The development of effective and feasible interventions to improve the zinc status of developing country populations is essential[131].

LBW Neonates have higher postnatal requirements of zinc and unless replenished, the neonates will remain at increased risk of developing zinc deficiency. Zinc requirements of LBW neonates are high because of their immature gastrointestinal tracts which leads to both high endogenous losses and decreased absorption, an extended period of rapid growth, and low body stores of zinc.

The impact of zinc supplementation on growth parameters has also been studied in countries of Asia, Latin America, and Africa. Trials in different populations of young children from these countries have provided conflicting results on the effects of zinc supplementation on growth. While

some have found no effect, others have provided evidence for zinc supplementation increasing growth velocity[185-191]. In a meta analysis of 25 studies, there were small but highly significant effect sizes for changes in height and weight of +0.22 SD and 0.26 SD respectively with zinc supplementation[185].

Studies on zinc supplementation to LBW neonates from birth have been rarely conducted. However, studies on shorter duration on very LBW neonates and also on children in older age groups have shown varying results.

Evidence for an effect of zinc supplementation on the growth of children came from a recent meta-analysis that concluded that zinc supplementation during childhood is responsible for a small but statistically significant effect on growth, particularly among growth retarded children[120].

Beneficial effects of zinc on growth and morbidity were observed after zinc supplementation among LBW and small for gestational age infants in Brazil[188] and chile[121] respectively.

Earlier zinc interventions might be more effective in preventing growth faltering and reducing morbidity patterns among children at risk [153].

We hypothesized that 5mg zn/day during neonatal period would enhance weight gain in LBW. The decision to supplement for 4 week was based on the supposition that if, in the future, zinc supplements for LBW neonates were to be offered through existing health service channels.

LBW neonates exhibit prolonged growth deficit as compared with their normal birth weight counterparts, they probably suffer from sub-optimal zinc intake, and, as such supplementation may improved growth.

In our study, zinc supplemented group (84%) more weight gain than control. zinc supplementation accelerated weight gain. Most zinc supplementation trials performed in the United States and Canada on short but well-nourished children did not report a stimulatory effect on weight gain [114,115,116]. Our findings, however, agree with those trials performed in malnourished populations in developing countries where zinc supplementation increased gains in weight and height[5,30,31,32,33,119]. The weight response of our subjects to zinc supplementation may be explained by their low initial WAZ score. Our study shows a growth response to zinc supplementation in neonates of both sexes, which agrees with the findings of other zinc supplementation studies of malnourished children in developing countries, where zinc deficiency is likely to be severe. However, in children with mild zinc deficiency, increases in growth have usually been greater in boys than in girls, perhaps because of their greater requirement for zinc[114,115,116,118,120]. This is supported by the fact that the zinc concentration in the liquar amnii of female Neonates was higher is compared to male neonates.

Although our observations show that zinc supplementation stimulated growth, the mechanism for this effect is unknown. The effect of zinc may result from increased appetite[4,5,6,7] and improved utilization of energy and protein. Zinc may promote growth through changes in protein synthesis and

cell replication, contributing to accumulation of lean tissue[113, 119]. Zinc might modulate the biological activity of other micronutrients, such as vitamin A. Zinc availability controls hepatic release of retinal binding protein (RBP) and consequently may modulate the mobilization of hepatic vitamin A stores[193]. Vitamin A deficiency, a major health problem in Vietnam[194]. is also associated with growth retardation and immunodeficiency.

Our results, agree with those of Rosado et al[147] and Ruel et al[195], go further by showing decreased morbidity in zinc-treated children. Our results, however, suggest that decreased occurrence of infectious diseases is not the sole factor responsible for the growth-promoting effect of zinc. The stimulatory effect of zinc on growth velocity was still significant after the incidence of infections was controlled for. Further more, schlesinger et al[196] reported a growth-stimulating effect of zinc without significant changes in the incidence of infections.

Because IGF-I is the mediator of the growth-promoting action of growth hormone, low circulating IGF-I observed in protein-enerby malnutrition is believed to be responsible for the growth retardation observed in this condition. Experimental zinc deficiency is also associated with low IGF-I in humans and animals[197,198,199], and there is evidence that zinc per se may regulate circulating IGF-I concentrations. These observations suggest that zinc deficiency may impair growth by altering circulating IGF-I. Although a positive effect of zinc supplementation on circulating IGF-I was reported previously[10,12].

The effect of zinc supplementation on linear growth has been proposed to be a reliable function index of zinc status in children[120].

In this study mean weight gain (31.37±6.91) ($p<0.00$) in zinc group than the mean weight gain (21.63±5.67 gm/day) of control group. It is highly likely that zinc supplements need to be given every day along with appropriate balance diet because there may be no adequate stores of zinc and other nutrients and zinc turnover is also rapid.

The accelerated weight gain in LBW neonates, showed 900 grams in cases and 600gms in controls. Average daily weight gains in cases 32 gms and in controls 21 gms. A Placebo controlled study conducted by Sharivastava et al on malnurished children aged 8 to 24 months showed that children supplemented with zinc for 3 months had a significant weight gain ($p<001$) compared with the placebo group. Findings of this study agree with those of trials performed in malnourished populations in developing countries where zinc supplementation increased gains in weight.

Although our observations show that zinc supplementation stimulated growth. The effect of zinc may result from increase appetite and improved ingestion of energy and protein. Zinc may promote growth through changes in protein synthesis and cell replication, contributing to accumulation of lean tissue.

Jaundice is a common problem in low birth weight Neonates. In this study, 15% of cases and 24% of controls of low birth weight neonates developed Jaundice.

Neonatal infection was more (26%) in controls but less in cases (7%).

In this study convulsion was 2% in cases and 3% in controls, and Apnea was 4% in cases and 3% in controls.

Sample size was not big large due to pair matched with birth weight, sex, types of LBW and types of feeding. We could not perform the estimation of serum zinc level due to lack of facility and fund. In our country all the parents do not co-operate with us in completing such studies. Many parents of neonate are disinterested to stay in hospital for a longer period.

It is evident from this study that zinc supplementation improved weight gain in LBW neonates. The findings could have important implications for child health and survival programs in developing countries with high incidence of LBW, and operational feasibility studies of large scale implementation of prolonged zinc supplementation especially in this group of neonates, need to be conducted in the future.

Neonatal mortality in Bangladesh is very high. The most common causes of death during neonatal period are due to low birth weight. The results of the study provide evidence that zinc supplementation in low birth weight enhanced more weight gain and experienced less problems during neonatal period. There was no adverse effect in zinc supplementation groups. Therefore, we may conclude, zinc supplementation to LBW neonates is significant beneficial.

CHAPTER – 7

CONCLUSION

CONCLUSION

Neonatal mortality in Bangladesh is very high. The most common causes of death during neonatal period are due to low birth weight. Average birth weight, IUGR and average gestational age were similar in two groups (case & control). Percentage of various complications among control group was higher than cases. Almost all measures of central tendency and percentile of cases were higher than that of control beginning from the 2nd week of life. After final follow up, rate of change, median and dispersion of the weight at later period, strength of correlation between rate of change of weight and follow up day, strength of effectiveness of the program among cases were higher than that of control group. Improvement of weight-for-age z-score classification and effectiveness of the program on severely underweight of cases were higher than that of control group. Up to 14th day follow up, Zinc supplementation was not significantly associated with nutritional status. After 21st and 28th day follow up, Zinc supplementation was significantly associated with improvement in nutritional status. Chi-square test, Odds ratio and Relative risk showed that Zinc supplementation was significantly associated with underweight. Sex has no clear cut influence on the weight. For both cases and control low birth type IUGR has more positive effect on weight in every type of feeding. Mean weight of IUGR group was higher than the mean weight of preterm group. Mean weight of exclusive breast feeding by suckling of case was higher than others types of feeding groups.

More weight gain was found among higher gestational age group of cases. IUGR group of cases has weight gained more than control group. Based on Chi-square test, Odds ration and Relative risk it was found that types of low birth of control group was not associated with weight gain more than cases. Logistic regression analysis showed that sex, gestational age, type of low birth weight and type of feeding had no significantly influence on weight gain. All these finding suggested that treatment has positive effect on weight. There was some limitation of the study. The sample size was not large due to pair matched birth weight, sex, types of LBW and types of feeding. Blood sample was not possible to draw due to underweight of the neonate and not perform the estimation of serum Zinc level due to lack of facility and fund. Parents of neonate were disinterested to stay in hospital for a long period. The results of the study provide evidence that zinc supplementation in low birth weight enhanced more weight gain and experienced less problems during neonatal period. There was no adverse effect in zinc supplementation groups. Therefore, we may conclude, zinc supplementation to LBW neonates is significant beneficial.

Limitations :

1. Sample size was not large due to pair matched with birth weight. sex. types of LBW and types of feeding.
2. We could not perform the estimation of serum zinc level due to lack of facility and fund.
3. In our country all the parents do not co-operate with us in completing such study.
4. Many parents of neonate are disinterested to stay in hospital for a longer period.

CHAPTER – 8

SUMMARY

SUMMARY

Background : Evidence for an effect of zinc supplementation on growth in every young infants in developing countries is scarce and inconsistent.

In Bangladesh, the highest incidence of Low Birth Weight (LBW) is the main cause of neonatal mortality and morbidity. It is hypothesized that LBW neonates is zinc deficient and that might adversely affect postnatal growth. The present study was carried out to measure the effect of zinc supplementation on LBW neonates during the first month of life and to observe the growth pattern of supplemented (zn) with non supplemented group.

Aim and Objective: It is supported by literates that zinc has an effective positive role in the growth and development in children. But evaluation of the effect of zinc on weight gain in LBW not done so our primary objectives are. (1) The study was done to measure the effectiveness of zinc supplementation on weight gain in low birth weight neonates. (2) To list low birth weight (LBW) babies admitted in neonatal ward of Pediatrics Department of Sher-E-Bangla Medical College Hospital, Barisal during one clander year. (3) To supplement Zinc in a group low birth weight neonate and to compare with another group of low birth weight neonate will receive placebo for a period of 28 days along with necessary treatment for both groups. (4) To compare the study group with control to find out where and when zinc have contributed to weight gain, side effect of supplementation and acceptance of supplementation by the neonates.

Materials and methods : In a randomized, double-blind, placebo-controlled trial study of the effect of zinc on weight gain in low birth weight neonates. The study was carried out in the neonatal ward of pediatrics department of Sher-E-Bangla Medical College, Barisal, Bangladesh. The duration of the study was from May '05 to May '07. The research proposal was approved by Faculty of Post-graduate Medical Science and Research, Dhaka University. Ethical clearance was obtained from Bangladesh Medical Research Council (BMRC). One hundred low birth weight neonates were included in this study and the same number of controls matched for birth weight sex, types to LBW, feeding pattern was studied.

After randomization and pair matched neonates were grouped into two groups, 100 neonates were included in group A and 100 neonates in group B.

In the first 28 days of life, the A group received Syrup D_1 2.5ml /day in and B group received syrup D_2 2.5ml /day.

The syrup administered to the study neonate in two groups were prepared by Orion Laboratories Ltd. drug manufacturing company. Syrup D_1 2.5ml contains zinc 5mg was given to A group and Placebo (D_2) for B group. The two syrups were indistinguishable in taste and color and code of syrup 'D_1' and 'D_2' was kept strictly confidential with the pharmacist.

The parents or care giver were instructed to feed syrup D_1 2.5ml or syrup D_2 every morning at 10 am to their neonate up to 28 days.

Measurement of weight of case and control without cloth before feeding at 9a.m after 3 days, 7 days, 14 days, 21 days and 28 days and recorded in a record form. The overall supervision was maintained by researcher. At the end of the study the code of syrup was decoded and found 'D_2' for Placebo and D_1 for zinc. Data were analyzed by using statistical software SPSS.

Result : Among the study subjects 54% of them were male and 46% were female, of them 78% were preterm, and were 22% IUGR. The mean (±SD) birth weight was 1789.50 ± 228.89gm is for cases and controls. Three days after birth, weight decreases to (1610.50 ± 255.38gms) in cases and to (1613.00 ± 215.04 gms) in controls. More weight gain in cases than controls was observed after 7 days of birth. Highly significant weight gain after 21 days (2261.50 ± 296.14 gms) in cases than controls (2165.50 ± 243.47 gms) and 28 days (2665.00 ± 331.52 gms) in cases observed than controls (2374.00 ± 410.07 gms). So mean weight after 21st and 28th days of cases was significantly higher ($P<0.05$) than that of control group respectively.

Mean weight gain (31.37 ± 6.91 gm/day) of cases was significantly higher ($P<0.000$) than the mean weight gain (21.63 ± 5.67 gm/day) of control group. Mean weight of final follow up of zinc group was 2665.00 ± 331.52 and placebo group was 2374.00 ± 4107. ($P<0.000$) when compared with mean birth weight.

Linear curve of effectiveness of the program on weight for age z-score by follow up days. It was found that increment of effectiveness in Zinc group was higher than that of placebo group. Eighty four percent of cases gained weight more than control group. Problems like physiological Jaundice, infection, convulsion, were less in zinc group compared to control group.

Conclusions : Neonatal mortality in Bangladesh is high as experienced by causes of death during Neonatal period due to low birth weight. The result of the study provide evidence that zinc supplementation in low birth weight enhanced more weight gain and experienced less problems like infection, convulsion and Jaundice. There was no adverse effect in zinc supplementation groups. Therefore, we conclude that zinc supplementation to LBW neonates is beneficial to combat curse of low birth weight.

CHAPTER – 9

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CHAPTER – 10

APPENDIX

Appendix 10.1 shows Ethical clearance from BMRC

BMRC

বাংলাদেশ চিকিৎসা গবেষণা পরিষদ
Bangladesh Medical Research Council

Ethical Review Committee

Dr. A. K. M. Aminul Haque
Associate Professor
Deptt. of Paediatrics
Sher-e-Bangla Medical College,
Barisal.

Subject: Ethical Clearance

With reference to your application on the above subject, this is to inform you that your Research Proposal entitled **"The Effect of Zinc Supplementation on Weight Gain in Low Birth Weight Neonate"** has been reviewed and approved by the Ethical Review Committee of Bangladesh Medical Research Council (BMRC).

You are requested to please note the following ethical guidelines as mentioned at page 2 (overleaf) of this memo.

(Prof. Harun-Ar-Rashid)
MD, MSc, MPH, PhD, FRCP Edin
Director

Appendix 10.2 shows information leaflet

জিংক প্রয়োগে স্বল্প ওজনের নবজাতকের ওজন বৃদ্ধিতে প্রভাব শীর্ষক গবেষণা

অবহিত পত্র

পরিসংখ্যানে দেখা যায় যে, বাংলাদেশে প্রায় ৩০ - ৫০% নবজাতক স্বল্প ওজন (জন্ম ওজন ২.৫ কেজির কম) নিয়া জন্মগ্রহণ করে। এ স্বল্প ওজনের নবজাতকের প্রথম চার সপ্তাহে বিভিন্ন ধরণের ইনফেকশন, খিচুনী, জন্ডিস সহ বিভিন্ন ধরণের সমস্যা দেখা দেয়। অল্প ওজনের শিশুদের শরীরে মিনারেলস, ভিটামিন কম থাকে। তাই তাদের রোগ প্রতিরোধ ক্ষমতা কম থাকে বলে অনেক নবজাতক মারা যায়। নবজাতকের শরীর বৃদ্ধি ও রোগ প্রতিরোধের জন্য মায়ের দুধের সাথে প্রথম চার সপ্তাহে সাপ্লিমেন্ট হিসাবে ভিটামিন কে, ই, মাল্টি ভিটামিন দেয়া হয়।

দেশে-বিদেশে অসংখ্যক গবেষণায় দেখা যায় জিংক শিশুদের রোগ প্রতিরোধ ও শরীর বৃদ্ধিতে সাহায্য করে। বিশ্ব স্বাস্থ্য সংস্থা ও ইউনিসেফ শিশুদের ডায়রিয়া চিকিৎসায় জিংক প্রদানের সুপারিশ করেছেন।

বিভিন্ন দেশে গবেষণার তথ্যে পাওয়া যায় যে গর্ভ অবস্থায় অনেক মায়ের শরীরে জিংক কম থাকে বলে গর্ভের চার মাস থেকে ডেলিভারী পর্যন্ত এই সব গর্ভবতীদের জিংক দেয়ার ফলে ডেলিভারী জনিত জটিলতা কম হয় এবং নবজাতকের জন্ম ওজন বেশী হয়। আমরা আপনাদের স্বল্প ওজনের শিশুর বেশী ওজন বৃদ্ধির ও সমস্যা কমানোর জন্য জন্মের পর থেকে ২৮ দিন পর্যন্ত চিকিৎসা কল্পে একটি নতুন পরীক্ষামূলক প্রকল্প হাতে নিয়েছি, যাতে আপনাদের স্বতঃস্ফূর্ত অংশগ্রহণ প্রয়োজন। ভক্ষণযোগ্য জিংক সিরাপ ২.৫ এম.এল (৫ মিলিগ্রাম) প্রতিদিন সকালে ২৮ দিন বয়স পর্যন্ত খাওয়াতে হবে। এ চিকিৎসা প্রকল্পে অংশগ্রহনের জন্য আপনার সম্মতি প্রয়োজন। জিংক প্রয়োগ প্রকল্পে অংশগ্রহণকারী নবজাতকদের গবেষক প্রতিদিন পর্যবেক্ষণ করবেন। এতে আপনার নবজাতকের কোন ক্ষতি হবে না।

আমরা আশা করছি যে, এ চিকিৎসায় আপনার নবজাতক উপকৃত হবে এবং এর প্রাপ্ত ফলাফল ভবিষ্যতে স্বল্প ওজনের নবজাতক চিকিৎসায় সাফল্য বয়ে আনবে।

Appendix 10.3 shows consent form

জিংক প্রয়োগে স্বল্প ওজনের নবজাতকের ওজন বৃদ্ধিতে প্রভাব শীর্ষক গবেষণা

সম্মতি পত্র

অবহিত পত্রে উল্লেখিত তথ্যাদি জানার পর এবং বুঝার পর আমি স্বজ্ঞানে আমার অল্প ওজনের নবজাতকের জিংক গবেষণায় অংশগ্রহণে রাজী আছি।

স্বাক্ষর ও তারিখ

নবজাতকের অভিভাবকের নাম-

ঠিকানা-

গবেষকের স্বাক্ষর ও তারিখ
(ডাঃ এ.কে.এম. আমিনুল হক)
সহযোগী অধ্যাপক (শিশু)
শের-ই-বাংলা মেডিকেল কলেজ
বরিশাল

Appendix 10.4 shows Questoaire form

বিসমিল্লাহির রাহমানির রাহিম

QUESTIONNAIRE FOR STUDY OF "THE EFFECT OF ZINC SUPPLEMENTATION ON WEIGHT GAIN IN LOW BIRTH WEIGHT NEONATES".

Serial No. ☐ Date ☐☐☐☐

Name of the Neonate _____

A. Sex : (1) Male (2) Female

Father's & Mother's Name _____

Address : _____

B. Administration of syrup : D_1 ☐ D_2 ☐ Group A ☐ Group B ☐

C. Weight :

1. Birth weight _____ gms
2. Weight after 72 hours _____ gms
3. Weight after 7 days _____ gms
4. Weight after 14 days _____ gms
5. Weight after 21 days _____ gms
6. Weight after 28 days _____ gms
7. Total weight gain at end of study _____ gms
8. Average weight gain _____ gms/ days
9. More weight gain that controls (i) Yes (ii) No

C. Gastational Age _____ weeks

D. Types of low birth weight (1) Preterm (2) IUGR

E. Types of feeding (1) 10% dextrose + Express breast milk by NG tube + breast feeding (2) Formula feeding + Express breast milk + Breast feeding

(3) Exclussive Breast feeding by suckling

F. Problems / Complication during study (1) Jaundice

(2) Infection (3) Convulsion (4) Apnea.

G. Outcome (1) Good (2) Death.

Comments : _____

_____

_____

_____

_____

Signature of investigator

Appendix 10.5 shows the formula use for statistical analysis.

(II) The Formula use for statistical analysis:

1. Arithmetic mean (X)

$X = \frac{\Sigma X}{n}$ Where ΣX = Summation of individual observations.

n = number of observations.

2. Standard deviation (SD).

$$SD = \sqrt{\frac{\Sigma(X - X)2}{n-1}}$$

3. Chi – Square test (x^2)

$x^2 = \Sigma\frac{(O-E)^2}{E}$ Where O = Observed value

E = Expected value

Formula of $E = \frac{Rowtotal \times Column\ total}{Grand\ total}$

d. f = (Row – 1) (Column – 1)

4. Odds Ratio (OR).

Suppose that groups of cases and controls are studied to assess exposure to a suspected causal factor. The data can be tabulated as follows :

	Exposed		
Study group	Yes	No	Total
Cases	a	b	a+b

Controls	c	d	c+d
Total	a+c	b+c	n

An approximate estimate of the relative risk for the disease associated with exposure to the factor can be obtained from a case-control study through the odds ratio.

The odds ratio (OR) is given as :

$$OR = \frac{ad}{bc}$$

A confidence interval for the population value of OR can be constructed using several methods which vary in their case and accuracy. The exception t this is when any of the numbers a, b, c, or d is small, when a more accurate but complex procedure should be used if suitable computer facilities are available.

The logit method uses the normal approximation to the distribution of the logarithm of the odds ($\log_e$ OR) in which the standard error of $\log_e$ OR is :

$$SE(\log_e OR) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$$

A 100 (1 - α) % i.e. 95% confidence interval for the population value of OR is found by first calculating the two quantities:

$$Y = \log_e OR - (N1\ \alpha/2 \times SE\ (\log_e OR)$$

Where NI - ω2 is the appropriate value from the standard normal distribution for the 100 (1 - α/2) percentile.

The confidence interval for OR is then given by exponentiating Y and Z as:

$$e^Y \text{ to } e^Z.$$

Worked example

The ABO secretor state was determined for 114 patients with spondyloarthropathies and 334 controls with the following results:

ABO secretor state

Study group	Yes	No	Total
Cases	54	60	114
Controls	89	245	334
Total	143	305	448

The estimated odds ratio is $OR = \frac{54 \times 245}{60 \times 89} = 2.48$. The standard error of $\log_e$ OR is :

$$\text{SE}(\log_e \text{OR}) = \sqrt{\frac{1}{54} + \frac{1}{60} + \frac{1}{89} + \frac{1}{245}} = 0.2247$$

For a 95% confidence interval

$$Y = \log_e 2.48 - (1.96 \times 0.2247) = 0.4678$$

and

$$Z = \log_e 2.48 + (1.96 \times 0.2247) = 1.3487.$$

The 95% confidence interval for the population value of OR is then given as: $C^{0.4678}$ to $e^{1.3487}$ that is, form 1.59 to 3.85.