STUDY OF THE MATERNAL NUTRITIONAL ANEMIAS–ADVERSE BIRTH OUTCOME ASSOCIATION

Thesis

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By:

Nermeen Farouk Mahmoud

M.B.B.Ch, (2008, Ain Shams University)

Supervised by

Prof. Dr. Mohammed Sami El-Shimi

Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Dr. Abeer Salah ELdin ElSakka

Assistant Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain-Shams University

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بسم الله الرحمن الرحيم

قالوا سبحانك لا علم لنا الا
ما علمتنا انك أنت العليم
الحكيم. صدق الله العظيم

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List of Abbreviations

AGA: Appropriate for gestational age

ANC: Antenatal care

ELBW: Extremely Low birth weight

GA: Gestational age

CRH: Corticotropin-releasing hormone

DNA: Deoxy ribo-nucleac acid

EPI: Expanded Program in Immunization

Hb: Hemoglobin

Hcy: Homocysteine

IUGR: Intrauterine growth retardation

IDA: Iron deficiency anemia

LMP: Last menstrual period

NHANES: National Health and Nutrition Examination Survey

NTDs: Neural tube defects

PT: Preterm birth

PPROM: preterm premature rupture of membranes

SGA: Small for gestational age

TfR: Transferrin receptor

TSAT: Transferrin saturation

THF: Tetrahydrofolate

TIB: Total iron binding capacity

List of tables

List of Figures

Introduction

Anemia, as measured by low hemoglobin or hematocrit, affects nearly one quarter of the worldwide population. Worldwide prevalence is highest in preschool children (47.4%), reproductive age women (30.2%) and women who are pregnant (41.8%) ***(McLean et al., 2008).***

The etiology of anemia is multifactorial-including hemoglobinopathies, acute infections, chronic inflammation, and diet poor in nutrients such as folate, B12, along with iron, the most commonly recognized nutritional cause ***(Scoll, 2011).***

In pregnant women, moderate to severe deficiencies of iron and folic acid have been shown to increase risk of low birth weight, perinatal mortality and morbidity ***(Kolte et al., 2009).***

Supplementation with iron is generally recommended during pregnancy to meet the iron needs of both mother and fetus. When detected early in pregnancy, iron deficiency anemia (IDA) is associated with a > 2-fold increase in the risk of preterm delivery ***(Scholl, 2005).***

The low maternal vitamin B12 status is associated with intrauterine growth retardation in infants ***(Muthayya et al., 2006).***

As regards folic acid, folate plays a crucial role in the one carbon metabolism for physiological nucleic acid synthesis, cell division, and neurotransmitter synthesis ***(Djukic, 2007).***

Folate requirements are 5 to 10 folds higher in pregnant than in non-pregnant women ***(Antony, 2007).***

Less than optimal folate status has been associated with many negative reproductive outcomes such as an increased risk of neural tube defects, anemia in pregnancy and low infant birth weight ***(Sherwood et al., 2006).***

AIM OF THE WORK

The aim of the study was to assess the relationship between maternal folic acid, vitamin B12 and iron deficiency anemias with pregnancy outcomes as regards length of gestation and newborn anthropometric measures.

REVIEW OF LITERTURE

1. Normal Micronutrients supplement

A. Definitions:-

Micronutrients which referred collectively to vitamins and minerals are essential for growth. And its deficiency, whether clinical or sub-clinical, may affect growth, cognition, and reproductive performance (***Ahmed et al., 2011***).

Nutrition plays a major role in maternal and child health. Poor maternal nutritional status has been related to adverse birth outcomes; like preterm and intrauterine growth retardation (IUGR). However, the association between maternal nutrition and birth outcome is complex and is influenced by many factors; like biologic, socioeconomic, and demographic factors. Understanding the relation between maternal nutrition and birth outcomes may provide a basis for developing nutritional interventions that will improve birth outcomes and long-term quality of life and reduce mortality, morbidity, and hospitalization costs (***Villar et al., 2003).***

Micronutrients are essential for growth and development of newborns, and maternal micronutrient deficiency, frequently multiple in developing countries, may be an important cause of IUGR. Supplementation of undernourished mothers with micronutrients has several benefits but there is little hard evidence of improved fetal growth. Maternal energy and protein deficiency are clearly associated with IUGR. Likely, other forms of under nutrition as micronutrients deficiencies are associated with IUGR. Recent interest has turned to micronutrients as possible limiting factors for fetal growth. Some micronutrients are structural components of body tissues. Others are essential for the process of growth, including energy and protein metabolism, gene transcription, endocrine function and nutrient transport ***(Caroline et al., 2003).***

Studies found around 30% reductions in childhood mortality due to maternal antenatal/postnatal supplementation with iron-folic acid plus vitamin A especially in developing countries where maternal iron deficiency anemia and maternal anemias in general are common. These prove the long-term effect of maternal iron-folic acid supplementation and give a global policy for pregnant women to take regular vitamin supplementation for childhood survival and better life. Also it is found that maternal supplementation with iron, folic acid plus zinc resulted in an increased child length ***(Christian et al., 2009).***

The World Health Organization recommends iron and folic acid supplementation to women during pregnancy as part of routine antenatal care. Also sufficient food supplementation to women during early pregnancy reduces early childhood malnutrition, especially short stature. These effects on postnatal growth suggest programming effects in early fetal life ***(Khan et al., 2011).***

There are 3 main strategies for increasing maternal intake of multiple micronutrients. The first is to improve dietary quality, which in many situations might require increasing consumption of animal source foods, fruits, and vegetables. A number of studies have reported an association between poor maternal diet and a greater risk of pregnancy complications. Also, other studies have showed that provision of micronutrient-rich foods can improve pregnancy outcome. In some situations well-designed nutrition education programs can improve dietary quality and pregnancy outcome. An easier and more common approach is to provide multiple micronutrient supplements to women on their first clinic visit. Studies showed women who started taking supplements in their first trimester, there was a substantial reduction in preterm, very preterm, low birth weight and very low birth weight deliveries. If supplements were started in the second trimester, a similar pattern of response was observed, although reduction in complications was somewhat less substantial. The supplement that contained most micronutrients reduced neural tube defects by 90 %, and birth defects by 50%, compared with the trace element supplement. When the micronutrients were consumed before pregnancy, menstrual periods were more regular, time to conception was shorter, and the rate of conception was increased by 7% ***(Allen, 2005).***

The supplements containing multiple micronutrients were no more effective than iron in improving maternal hemoglobin at 1 month postpartum, birth weight or gestational age, or mortality of the infant in the first 6 month of life. In contrast, other studies have showed multiple micronutrients supplementations reduce low birth weight by 44%, preterm delivery by 39%, and IUGR by 43%. Although multiple micronutrient supplementations are theoretically preferable to supplementation with iron and folic acid alone, especially in developing countries where multiple deficiencies are prevalent, more data needs to be collected to determine the advantages of different multiple micronutrient formulations for pregnant and lactating women ***(Christian et al., 2003).***

Antenatal supplementation with multiple micronutrients especially iron and folic acid were associated with longer gestation, increased birth weight and a reduction in early neonatal mortality. Pregnant women in developing countries need sufficient doses of iron in nutrient supplements to maximize reductions in neonatal mortality ***(Zeng et al., 2008).***

There is little causal evidence on the effect of maternal micronutrient supplementation on pregnancy outcome and infant health and survival in the developing world. Although prenatal multivitamin and mineral supplements are commonly consumed in developed countries, this practice is less common in developing countries, in which existing antenatal iron-folate programs achieve low coverage and have been ineffective in reducing maternal anemia. Infant mortality reduction remains a major public health goal throughout the developing world. Post neonatal mortality has declined globally, in contrast with neonatal mortality, which constitutes one-half of all infant deaths in many developing countries. In general, populations with high infant mortality also have a high prevalence of low birth weight (less than 2.5 kg), a condition that predisposes newborns to increased neonatal mortality and morbidity ***(Yip, 1996).***

A significant evidence supports a causal relationship between iron deficiency and deficits in work productivity and child development, and between severe anemia and maternal and child mortality. Causal evidence is contradictory for iron deficiency and low birth weight, and for mild-to-moderate anemia and child or maternal mortality ***(Stoltzfus, 2001).***

Worldwide ≈4 million infants die every year in the neonatal period (ie, the first 28 d of an infant's life. The use of antenatal iron/folic acid supplements is an important intervention to reduce neonatal mortality. Studies found around 47% reduction of the risk of early neonatal deaths in mothers who taking iron/folic acid supplements during pregnancy ***(Titaley et al., 2010).***

Fetal growth depends on the uptake of nutrients, which occurs at the end of a complex maternal supply line that begins with the mother's intake (appetite, diet, absorption). Nutrients arriving at the placenta depend on the mother's intermediary metabolism and endocrine status; her partitioning of nutrients among storage, use and circulation; the capacity of circulating transport proteins; and cardiovascular adaptations to pregnancy, such as plasma volume expansion, which determine uterine blood flow. These are of course influenced by her nutritional status. Nutritional factors are also likely to influence placental function, including vascular structure; the efficiency of placental transport systems; and the partitioning of nutrients among mother, placenta and fetus ***(Harding, 2001).***

Although prenatal multiple micronutrients can improve fetal growth, their benefit on postnatal health remains uncertain. Improved fetal growth with continuation into early life is enhanced by the effect of the prenatal multiple micronutrients on infant nutritional status with additional follow-up to assess long-term effects. The prenatal multiple micronutrients supplements reduce the stunting rate by 27% during infancy. Moreover, the effect of the prenatal multiple micronutrients supplements on weight-for-length and head circumference is still effective till the end of the first year of life ***(Roberfroid et al., 2012)***.

Studies showed that prenatal supplement of multiple micronutrients starting in the first or the second trimester was associated with a diminished risk of very preterm delivery (less than 33weeks) and very low birth weight (VLBE) (less than1.500g) infants. However, among first trimester users, it is likely that increased nausea may have interfered with supplement use, and vaginal bleeding reduced circulating levels, especially for ferritin. Diminution in risk of very preterm delivery was greater with first trimester use (four- to six folds reduction), compared with a two- to fourfold decrease when use of prenatal supplements began in the second trimester. Risk of VLBW was decreased seven folds with a first trimester start and six folds when prenatal supplements were started in the second trimester. No influence of pre-conceptional supplement use on these outcomes was detectable. The finding that prenatal supplement use is associated with a decreased risk of poor outcomes among low income is consistent with a growing literature on the influence of maternal micronutrient intake on the course and outcome of pregnancy. Recently, use of periconceptional folic acid-containing multivitamin/mineral supplements (400ug/day) was recommended for all women in their reproductive years because of the reduced risk of occurrence and recurrence of neural tube defects ***(Scholl et al., 1997).***

Maternal multiple micronutrients improve fetal growth, and that gain would be sustained as such during early life. For instance, zinc, contained in the multiple micronutrients formula is a necessary component for placental alkaline phosphatase and a regulator of insulin-like growth factor I activity in osteoblast formation. Such properties can affect fetal bone growth. Also vitamin A and D which are contained in the multiple micronutrients formula could play a role in a better linear growth in the fetal period ***(Prawirohartono et al., 2011).***

Maternal multiple micronutrients is required for enzymatic, hormonal, or immunologic pathways that are important for fetal growth. Prenatal zinc may reduce diarrheal morbidity during infancy and hence, may protect the infants from growth faltering episodes of infectious origin. Prenatal zinc might also be important to ensure hyperplasia in muscle cells that will later grow in size. Finally, greater stores at birth could also trigger the production of more growth hormones, such as insulin-like growth factor I, in early life. Prenatal selenium and vitamin A could also play a role in postnatal growth ***(Iannotti et al., 2010).***

There is evidence of the inverse association between positive effect of maternal multiple micronutrients supplements on linear growth and blood pressure, cardiovascular risk factors, and metabolic disorders ***(Gaskin et al, 2000).***

In developing countries increased use of antenatal iron-folic acid supplements will reduce deaths of children less than 5 y of age, especially in the first year of life. Also reduce risk of low birth weight and preterm delivery ***(Dibley et al., 2012).***

Pregnancy is a period of increased metabolic demand, when nutritional status directly influences the infant size and also the main determinant factor for the growth and development of the offspring. During this period, inadequate store or intake of nutrients can have adverse effects on pregnancy and even death of the mother. Furthermore; the fetus can be affected resulting in still-birth, preterm delivery, IUGR, congenital malformation, reduced immune competence or abnormal organ development. So; nutritional status during pregnancy has a direct influence upon birth weight of newborn and adequate supply of micronutrient is very important in pregnancy (***Ahmed et al., 2011).***

Previously, multiple micronutrients have shown no effect or modest effects on birth weight. But recent studies showed a significant 18% reduction in early infant mortality (less than 3 months of age) that was attributed to antenatal/postnatal micronutrient supplementation ***(Christian et al., 2009).***

There is strong evidence for the benefits of maternal supplementation with iron, folic acid, and vitamin D and iodine. There is also some evidence that high quality diets and or multiple micronutrient supplements are beneficial for pregnant women even in industrialized countries. More efficacy trials are needed to test the benefits of neglected nutrients, such as B-vitamins, in both industrialized and developing countries ***(Allen, 2005).***

B: Components of micronutrients:-

Fat-soluble vitamins.

Supplementation of pregnant women with their recommended daily intake of vitamin A reduced maternal mortality by 40%. Supplementation with B-carotene reduced mortality by 49%. The apparent cause of the reduced mortality risk was less susceptibility to infection. An additional advantage of vitamin A supplementation of pregnant women is that it can increase