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Micronutrients: Its role in intrauterine growth restriction

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Abstract:

Objective: To find out the role of micronutrients in intrauterine growth restrictions.

Methodology. Desktop review of articles from the year 1986 till 2005 March using key words, Micronutrients AND Intrauterine Growth Restriction.

Results: 13.7 million infants are born annually with fetal growth restriction (IUGR) comprising 11% of all births in developing countries affecting up to 40% in some of developing countries varying from 14-38.8% for Nepal. Public health officials have recognized the urgent need for interventions aimed to prevent IUGR as this higher percent is likely due to protein calorie malnutrition, known to be the second leading cause of perinatal morbidity and mortality.

The identification of IUGR is crucial because proper evaluation and management can result in a favourable outcome. Sixty five percent of IUGR are not identified until after delivery. More over, it is unrealistic issue to assume that extra nutrient taken for few months during pregnancy would replace the under nutrition that has been prevalent for over decades in terms of reproductive performance.

Conclusion: Although it is frustrating that, most of the interventions aimed to prevent or treat impaired fetal growth have hardly shown any beneficial effect on short-term perinatal outcomes, long term benefit may be rewarding with significant impact. Hence provision of energy supplementation for two (or more, if they occur) consecutive pregnancies must be focused rather than during single pregnancy.

Key words: micronutrients, intrauterine growth restriction, malnutrition.

Objective

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Introduction.

Intrauterine growth restriction (IUGR) is of public health importance as it is prevalent in developing countries. The highest rates are in South Asia and parts of sub-Saharan Africa affecting about 40% as compared to less than 10% in most developed countries.¹The

prevalence of low birth weight in Nepal from various studies and surveys varied from 4-38%. IUGR has adverse consequences for future generations.

Fetal under nutrition affects large numbers of infants in developing countries, with adverse consequences for their immediate survival and lifelong health. It manifests as intrauterine growth restriction (IUGR).²

Intrauterine growth restriction (IUGR), fetal growth restriction (FGR), small for gestational age (SGA), and low birth weight (LBW) are all terms used to describe small babies. The most common definition of fetal growth restriction refers to a weight below the 10th percentile for gestational age, although other definitions employing a variety of criteria have been advocated. This definition is controversial because it does not make a distinction among fetuses that are constitutionally small and growth restricted and small,

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and growth restricted but not small. Seventy percent of fetuses who weigh below the 10th percentile for gestational age are small simply due to constitutional factors such as female sex or maternal ethnicity, parity, or body mass index. They are not at high risk of perinatal mortality and morbidity. Thus, there is a possibility of misclassifying a normally nourished, healthy, but constitutionally small, neonate as growth restricted. By comparison, a malnourished fetus whose birth weight is slightly greater than the 10th percentile may be misclassified as appropriately grown and at low risk of adverse perinatal outcome, even though its weight may be far below its genetic potential.

IUGR is associated with short and long term negative outcome in fetuses, infants and children. It may be associated with development of disease in adult life. IUGR also has adverse consequences for future generations. It forms part of an intergenerational vicious cycle of deprivation.³ For example the poor postnatal growth of low-birth-weight girls increases their own risk of producing low-birth-weight infants.

Fetal growth restriction is the second leading cause of perinatal and childhood morbidity and mortality followed only by prematurity. Intrauterine growth restriction (IUGR) is a problem that affects approximately three percent of all pregnancies in the United States. The incidence of IUGR is estimated to be approximately 5 percent in the general obstetric population. In assessing perinatal outcome by weight, newborns who weigh less than 2,500 g (5 lb, 8 oz) at term have a perinatal mortality rate that is five to thirty times greater than those whose birth weights are at the 50th percentile. The mortality rate is 70 to 100 times higher in newborns who weigh less than 1,500 g (3 lb, 5 oz). Newborns with IUGR are five to ten times more likely to die in the first year of life than average gestational age (AGA) newborns. Perinatal asphyxia involving multiple organ systems is one of the most significant problems in growth restricted newborns.⁴

Neonatal complications found to be associated with IUGR include hypoglycemia, hypothermia, hypocalcemia, polycythemia, necrotizing enterocolitis, meconium aspiration, and persistent fetal circulation. IUGR frequently appears to be due to an unexplained intrinsic disorder. It is estimated that 13.7 million infants are born annually with IUGR, comprising 11% of all births in developing countries.

While the incidence of low birth weight is widely varied, the lowest being reported as 13.8%. Christian. P et al. reported the prevalence of LBW as high as 38.8% in a double blind randomized community trial study conducted to see the effects of alternative maternal micronutrients supplements on LBW in rural Nepal. A multi central hospital based study conducted in four regions of Nepal by UNICEF/MIRA in June 2000, reported the prevalence of LBW as 27.2%. Various

studies conducted by Nepal Family Health Survey (NFHS) in 1996 and by NMIS in 1998 reported the prevalence of LBW as 25% and 19% respectively. Hospital based studies conducted by Dali et al (1989) in Tribhuvan University Teaching Hospital and Manandhar et al (1997) in Maternity Hospital, Kathmandu reported the LBW prevalence as 20% and 32% respectively. In a study conducted by WHO/SEARO in Chitwan district and Maternity Hospital, Kathmandu in 1990, the LBW prevalence was 14% and 22% respectively. David Osrin and co-workers report their randomised trial of the effect on birth weight of a daily multiple micronutrient supplement given to Nepalese women during pregnancy. The investigators found an average increase in birth weight of 77gms and a 25% reduction in the rate of low birth weight compared with the controls who received iron and folate.⁵ The circumstances that lead to under nutrition are frequently associated with multiple micronutrient deficiencies.

The increased risk of adult chronic disease (cardiovascular disease and type 2 diabetes) had been attributed to permanent changes in structure and metabolism resulting from undernutrition during critical periods of early development (the fetal origins of adult disease hypothesis). An inadequate supply of nutrients forces the fetus to adapt, down-regulate growth and prioritize the development of essential tissues. Adaptations include preferential blood flow to the brain and reduced flow to the abdominal viscera, altered body composition (reduced muscle mass) and reduced secretion of and sensitivity to the fetal growth hormones (insulin-like growth hormone and insulin). These adaptations enhance immediate survival but may carry a long-term price. An association between low birth weight and later insulin resistance, a strong risk factor for both cardiovascular disease and type 2 diabetes, is a consistent finding in a number of populations in both adults and children in India⁶, China⁷ and Jamaica⁸. Low birth weight has also been linked to higher blood pressure in children and coronary heart disease in adults in developing countries. The combination of low birth weight followed by obesity in later life appears to carry the greatest risk of insulin resistance. The persisting high incidence of IUGR, along with a worldwide increase in obesity, may therefore contribute to the epidemic rise of cardiovascular disease and type 2 diabetes.⁹

Maternal nutrition and micronutrients for fetal growth

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; 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 influenced by her nutritional status and infection load in ways that are poorly understood. 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. Thus the link between maternal nutrition and fetal nutrition is indirect; they are not the same.

Zinc

Zinc supplementation of 25 mg/day seems to have a tendency towards reducing term-LBW, mainly reflecting the effect observed in the Alabama trial.¹⁰ Women in this trial had relatively low plasma zinc concentrations in early pregnancy and most of the effect is concentrated among women with a body mass index less than 26 kg/m². In conclusion, there are 4 RCTs including 1400 women on this subject and the available data provide no convincing case for routine zinc supplementation during pregnancy.

Some supplementation trials have shown that supplementation increases birth weight, reduces the prevalence of small for gestational age, reduces the incidence of preterm delivery, increases gestational duration, and improves APGAR scores. Again, however, other studies demonstrate no effect on birth weight, small for gestational age, preterm, gestational duration, or APGAR scores. It is possible that beneficial effects would only be seen in poorer populations: a Cochrane review of five trials¹¹ finds that reductions in the prevalence of low birth weight and small for gestational age were only significant in groups selected for low zinc status.

It is conceivable that gestational zinc supplementation could have longer-term effects on mortality because of benefits to immunocompetence. In the short term, however, two supplementation studies in poor US populations found no effect on perinatal deaths, stillbirths, neonatal deaths or admission for special care.

Magnesium

Dietary assessment suggests that magnesium intake is positively associated with birth weight. While some studies show no association of maternal plasma magnesium or cord plasma magnesium with low birth weight, one study suggests that higher serum magnesium levels are seen in mothers of growth retarded infants. Lower serum magnesium levels have also been questionably associated with preterm labour.

Some magnesium supplementation studies have shown benefits to rates of preterm birth; others have not. Some studies have shown benefits for low birth weight and small for gestational age; others have not. Supplementation seems to have no effect on APGAR scores or admission for special care.¹²

The available evidence suggests that magnesium supplementation at doses of 15 mmol/day may have beneficial effects in preventing IUGR, however, the data are currently insufficient to justify routine magnesium supplementation during pregnancy. In view of the methodological limitations of the two available trials, it is important that further, better-designed trials be conducted to assess whether the current evidence reflects bias or a real beneficial effect. The suggestion that in-utero exposure to magnesium sulphate could be protective against cerebral palsy in very low birth weight infants is encouraging and further evaluation is justified¹³.

A Cochrane review of six controlled trials (heavily weighted by two studies¹⁴⁻¹⁵) concludes that supplementation starting before the third trimester results in a lower incidence of preterm birth and a lower prevalence of low birth weight and small for gestational age.

Iron

Gestational iron supplementation improves haematological indices is not in question. The U-shaped relation of gestational anaemia with fetal outcome makes assumptions about benefits questionable, however, and the ethics of placebo-controlled trials where supplementation is routinely recommended cloud the subject further. A recent trial of supplementation showed reductions in both fetal loss and neonatal mortality, but a Cochrane review of routine iron supplementation in pregnancy cannot draw conclusions about either beneficial or harmful effects to mother or baby.¹⁶

Concerning antianemic supplements, there seems to be no evidence currently to recommend routine as opposed to selective iron supplementation in well-nourished populations and there are inadequate data from populations where iron deficiency is common; thus, it is urgent that it be adequately tested in anemic populations or in populations where anemia is believed to contribute to perinatal morbidity and mortality. Unfortunately, considering the widespread use of iron supplements, it is unlikely that a placebo controlled trial can be ethically justified in such populations. Furthermore, iron supplements are indicated for maternal reasons in populations with high prevalence of anemia.¹⁷

Folate

The key role of folate in DNA synthesis means that deficiency is associated with dysfunction in rapidly dividing cells. The relationship between periconceptual folate deficiency and neural tube defects is now well established, as is the benefit of supplementation. Observational studies have suggested that lower maternal serum folate levels are associated with low birth weight and preterm birth. A large US study suggests an association between higher maternal serum folate at 30 weeks gestation and lower risk of intrauterine growth restriction, higher birth weight and higher Apgar scores. Two Brazilian studies, however, suggest a lack of relation between serum or erythrocyte folate and intrauterine growth restriction¹⁸⁻¹⁹. An early supplementation trial suggested that folate supplementation might have an effect on birth weight in malnourished women. There is some evidence that supplementation prolongs gestation. A Cochrane review of trials in non-anaemic women finds no association between folate supplementation and stillbirth or preterm delivery.

Folate supplementation seems to reduce the incidence of term-LBW despite the methodological limitations of the trials. There are plausible mechanisms through which such an effect could operate and the evidence therefore deserves further testing. Where there is evidence that megaloblastic anemia in pregnancy is a common problem, routine supplementation with folate may well be justified. However, better controlled trials in populations in which folate deficiency is common are needed before any firm recommendations in this regard can be made. In developing countries folate supplementation could be important because folate deficiency frequently co-exists with iron deficiency, and it may be relevant to antimalarial chemoprophylaxis studies or programs.²⁰

Iodine

Iodine-dependent thyroid hormones increase cell proliferation, synapse formation and microtubular assembly. The beneficial effect of iodine supplementation on endemic cretinism and goitre has been well established, and deficiency disorders are now understood to manifest across a spectrum. A trial in Zaire suggested improvements in birth weight and infant mortality as well.

Iodine carries out its function in the body as a part of the hormones, thyroxine (T_4) and triiodothyronine (T_3) produced by the thyroid gland. However, initially the fetus cannot utilize iodine directly: it is dependent on the mother for T_4 but after about 18–22 weeks the fetus gradually becomes more independent of the mother as

it starts to synthesize its T_4 from iodine supplied via the placenta.²¹ This is because the thyroid and pituitary responsible for the production of T_4 and thyroid-stimulating hormone respectively develop by 12 weeks, while the hypothalamus, responsible for the production of thyrotropin-releasing hormone, develops from the 10th to the 30th week. However, newborns incapable of synthesizing their own thyroid hormones due to genetic defects have cord serum T_4 values of 20–50% of those of normal newborns indicating that transplacental transfer of maternal T_4 continues until birth.²² When the iodine supply to the thyroid gland is limited, the gland produces relatively more T_3 than T_4 . When T_4 levels are low, target tissues also convert T_4 to T_3 . However, the brain can only take up T_4 but not T_3 , so brain function is affected when T_4 levels are low even though there may be sufficient T_4 and T_3 to carry out the function of thyroid hormones in other organs/tissues. This is particularly important for the fetus in the first half of pregnancy. If maternal T_4 levels are low, the fetal brain will be exposed to low T_4 levels, and this will result in brain damage.

Selenium

Selenium has been found to be a component of various deiodinases thus explaining why selenium deficiency can contribute to the development of iodine deficiency disorders in areas where both iodine and selenium are deficient.

Selenium participates in antioxidant cellular protection and energy metabolism. Frank deficiency is associated with a juvenile cardiomyopathy and a chondrodystrophy. Maternal serum selenium does not correlate with birth weight, length or head circumference. Cord serum selenium has been found to be lower in low birth weight infants, and plasma selenium has been found to be higher in preterm than term infants.²³ There is presently little evidence for direct effects of deficiency on the fetus, other than in conjunction with iodine deficiency.²⁴

Vitamin D

Because of its relationships with parathyroid hormones and calcium homeostasis, maternal cholecalciferol status might affect fetal growth. A non-randomised trial of third trimester supplementation in India was associated with increases in birth weight and length. This was supported by a trial in UK Asians, which suggested a reduced prevalence of low birth weight²⁵, but not by another study²⁶. Routine supplementation has not been an issue: the focus has generally been on populations at risk of neonatal hypocalcaemia. A Cochrane review includes two trials, and supports the administration of cholecalciferol to vulnerable groups in later pregnancy.²⁷

Conclusion

In contemporary obstetrics timely diagnosis and management of IUGR is one of the major achievements. If the growth-restricted fetus is identified and appropriate management instituted, perinatal mortality can be reduced, underscoring the need for assessment of fetal growth at each prenatal visit.

While majority of the literature linking maternal micronutrient intake with fetal growth is dominated by studies of single micronutrients and the evidence relating to each vitamin or mineral, the circumstances that lead to undernutrition are frequently associated with overall multiple micronutrient deficiencies. Thus, for developing countries, the reductionist approach seems illogical.

As most interventions aimed to prevent or treat impaired fetal growth do not show significant effects on short-term perinatal outcomes. It is unrealistic to assume that chronic under nutrition during two or three decades of life will be overcome, in terms of reproductive performance with only a few months of extra nutrient intake. Energy supplementation was seen to be more effective on birth weight if it was provided for two consecutive pregnancies rather than during only one pregnancy.

There is no such thing as a key micronutrient, and a single micronutrient supplement would be expected to produce an effect only if it were the sole nutrient limiting fetal growth. We therefore conclude with a review of current evidence for multiple micronutrient supplementations with either pharmaceutical preparations or micronutrient-dense foods.

It is surprising how limited data are supporting the effectiveness of nutritional interventions during pregnancy, some of which are of widespread use even in women without nutritional deficiencies. However, it is obvious that women manifesting nutritional deficits can only benefit from reversing such situation. On the basis of the evidence reviewed, only balanced protein/energy supplementation has additional potential beneficial effects on reducing the incidence of IUGR.

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