

Micronutrients and Pregnancy Outcome

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Table of Contents

Table of Contents	1
Summary	2
Introduction	3
Iron.....	4
Maternal Mortality and Anaemia	4
Maternal Haemoglobin Concentrations and Birth Weight	4
Maternal Iron Deficiency Anaemia and Duration of Gestation	5
Vitamin A	6
Folic Acid	8
Zinc	9
Iodine	10
Magnesium	11
Calcium	12
Vitamin C	13
Vitamin B1 (Thiamine), Vitamin HB6, (Pyridoxine), Vitamin B12 (Cobalamin)	14
Discussion	15
References	18

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Summary

The present paper reviews the available evidence on the effects of micronutrient deficiencies on pregnancy outcome. The largest possible effects are noted on neonatal outcome in terms of low birth weight, preterm delivery, miscarriages and higher risks of morbidity in the first year of life. Evidence is accumulating that a deficiency in β carotene, magnesium, zinc, vitamin C and possibly the B vitamins increase the risk of pre-eclampsia. Whether supplementation on a population based scale will yield improvements in pre-eclampsia incidence remains to be seen. Iron deficiency negatively affects birth weight, increases the chances of prematurity and it is highly likely that there are more complications during delivery for mother and child. Whether there is a direct effect on maternal mortality remains unclear. Iron supplementation during pregnancy is a widely accepted strategy and it will be impossible to set up placebo controlled studies. It is clear that supplements are needed in most regions where the prevalence of iron deficiency is high. It is not so clear whether supplementation is needed in situations where the prevalence is low. The present review supports the view that no single strategy will yield important improvements in birth outcome and that a solution must be sought to improve, in general, the nutritional status of pregnant women.

Introduction

Creating offspring is one of man's most cherished achievements and joys. For many it is the main drive for life and the reason to be. Unfortunately this act of procreation is also in many countries the most dangerous period in life. Maternal mortality remains high in many developing countries and pregnancy is beset with high incidences of miscarriages, pre-term deliveries, low birth weight and birth trauma, which endanger the chances of survival of the newborn.

The high associated mortality risk of pregnancy together with a low survival chance of the child makes pregnancy a major investment for many women.

During pregnancy the foetus is entirely dependent on his mother for his growth and development. Her general physical status can therefore profoundly affect the health status of the neonate at birth and so his survival chances. It is long known that a low energy intake during pregnancy affects birth weight. During the winter hunger in Holland (Lumey 1988, Lumey 1992) and the siege of Leningrad (Antonov 1947), at the end of the second world war, food rations decreased considerably. Babies born in that period had a birth weight 338 gr lower than before the famine. However, birth weight was little affected if the food ration stayed above 1500 Kcal per day. These findings led to enthusiastic implementation of supplementary food programs during pregnancy in a wide variety of settings. The results were unfortunately rather disappointing. Birth weight increased on average 50 gr. With a few exceptions where the higher increase in birth weight was probably due to the addition of a mineral supplement. These studies also highlighted the existence of adaptation mechanisms. During pregnancy, metabolic changes occur that protect the mother and her pregnancy through an increased metabolic efficiency. The foetus is also relatively protected at the cost of the nutritional status of the mother (Prentice *et al.* 1983, Lechtig *et al.* 1975a, Lechtig *et al.* 1975b, McDonald *et al.* 1981, Adair & Pollit 1985, Mora *et al.* 1979, Mardones-Santander *et al.* 1988). For micronutrients, similar mechanisms seem to be in place. In a deficiency state of the mother, the foetus will be in part protected with a higher stress on the mother.

Since micronutrient deficiencies can affect maternal morbidity and mortality, and are also essential for foetal development, it is difficult to separate the effect of a deficiency between mother and child. Recent research even suggests that after the period of infancy, the health of the child and even the adult can be influenced by the foetal period. Coronary heart disease, hypertension and type 2 diabetes are thought to originate, in part, from impaired intra-uterine growth and development. These diseases may be a consequence of "programming" whereby a stimulus or insult at a critical, sensitive period early in life has permanent effects on structure physiology and metabolism (Godfrey & Barker 2000). Maternal mortality is also very difficult to measure and relate to interventions. More proxy indicators on morbidity can give an idea if an effect on mortality can be suspected.

The present review combines therefore the effects of a deficiency on mortality, maternal morbidity and effects on the newborn.

Iron

The provision of iron supplements in pregnancy is one of the most widely practised public health measures, yet surprisingly little is known about the benefits of supplemental iron for the mother or her offspring during foetal and postnatal life. A high proportion of women in both industrialised and developing countries become anaemic during pregnancy. Estimates are that 35% to 75% of pregnant women in developing countries and 18% of women in industrialised countries are anaemic (WHO/FAO 1992). The prevalence of anaemia in women increases usually with 15 to 20% during pregnancy. A normal pregnancy needs an investment of 840 mg of iron with the highest needs in the second half. Iron is needed for the placenta, the increase in uterine size, expansion of the red blood cell mass and the foetus. The daily iron needs in the second half of pregnancy are estimated to be 6.7 mg per day even increasing up to 10-12 mg in the last month of pregnancy (Beard 2000, Hallberg 1988). With a normal average diet the absorption of non-haem iron needs to increase to 50% in order to cover the increased needs (Allen 2000a). Absorption efficiency seems to increase during pregnancy but the studies vary considerably in estimates from 14.3% to 66% at 35 weeks gestation (Svanberg *et al.* 1976, Barrett *et al.* 1994). After pregnancy the absorption returned to values comparable with those before pregnancy. Given the large discrepancies between the studies is it difficult to conclude whether the needs during pregnancy can be met by the increased absorption. There is definitely a mobilisation of iron reserves during pregnancy and it is most likely that notwithstanding the increased absorptive capacity, stored iron will need to be used. It appears that on average extra iron is needed during pregnancy.

Maternal Mortality and Anaemia

In a recent review article Allen (Allen 2000a) looked at the evidence for a relationship between maternal mortality and anaemia. Most of the papers describing the relationship do so on the basis of retrospective studies or on associations between haemoglobin levels and outcomes. In most of the studies the relationship was not corrected for health status, environment, nutritional status and health care provision. Many of the authors also believe that the relation of maternal mortality with anaemia reflects the underlying pathology, which also causes anaemia. This causality is more complex than iron deficiency alone and high prevalences of an associated hookworm infection or megaloblastic anaemia due to folic acid deficiency are usually diagnosed. Many of the authors concluded that mortality was not caused solely by anaemia but that it was a contributing factor (Chi *et al.* 1981, Llewellyn-Jones 1965). Associations are not proof for a causal relationship and need to be substantiated by intervention studies. There are unfortunately no controlled supplementation studies documenting the effect on maternal mortality. Since iron supplementation during pregnancy is a widely accepted public health strategy, it would be not ethical anymore to perform placebo-controlled trials. No conclusive evidence exists on the benefits of iron supplementation in reducing maternal mortality (Steer 2000, Allen 2000a).

Maternal Haemoglobin Concentrations and Birth Weight

Changes in haemoglobin values during pregnancy make it difficult to determine anaemia. The plasma volume changes during pregnancy and there is a drop in osmolarity, which reduces blood viscosity and enhances the blood flow in the intervillous space of the placenta. Enhanced blood flow improves foetal growth. Failure to reduce adequately blood viscosity with resulting high haematocrit values impairs foetal development.

The relation between maternal anaemia and birth weight was reviewed extensively (Steer 2000, Ramakrisham *et al.* 1999, Scholl & Hediger 1994) recently, and shows a U shaped relation with risk of low birth weight. Low and high haemoglobin values are associated with an increased risk of low birth weight, with an optimum range in between. In a recent review Steer (Steer 2000) analysed the haemoglobin values of 153 602 pregnancies collected in the Northwest Thames region (UK) between 1988 and 1991. The highest mean birth weight was found in association with a haemoglobin concentration of 85-95 g/L. The minimum incidence

of low birth weight (<2.5 kg) and of preterm labour (< 37 weeks gestation) occurred in association with a haemoglobin concentration of 95-105 g/L. These values are below the WHO proposed cut-off values of 110 g/L, to define anaemia in pregnant women (WHO 1968).

In a multivariate analysis of data from 691 women in Nepal, neonatal weight also followed a U shaped relation with haemoglobin concentrations. Lower and higher haemoglobin values increase the odds for low birth weight in a dose related fashion (Dreyfuss 1998) reported in (Allen 2000b). This U shaped relationship between haemoglobin values and birth weight and preterm delivery was also documented in a study of 44,000 pregnancies from Cardiff, Wales (Murphy *et al.* 1986).

The evidence from controlled supplementation studies is less straightforward. 20 controlled supplementation studies were reviewed in a Cochrane study. They looked at diverse pregnancy outcomes and the authors had to conclude that: *“supplementation improved haematological indices in women receiving the supplement. No conclusion can be drawn in terms of any effects, beneficial or harmful, on outcomes for mother and baby as data are available from single trials only”* (only two trials reported on birth weight as an outcome). The inclusion criteria for participating in the studies were also very selective (Hb > 10 g/L) and did not include severely anaemic women (Mahomed 2000). Very few studies included women of developing countries.

Maternal Iron Deficiency Anaemia and Duration of Gestation

This issue of preterm delivery was extensively reviewed recently in a number of reviews (Allen 2000b, Ramakrisham *et al.* 1999, Steer 2000, Allen 2000a, Scholl & Hediger 1994). There seems a consistency in the findings that iron deficiency anaemia, but not other forms of anaemia increase the risk of preterm deliveries and associated low birth weight. Allen concludes: *“The results are consistent with an association between maternal iron deficiency anaemia in early pregnancy and a greater risk of preterm delivery”*. The association disappears in the third trimester of pregnancy.

All the above evidence supports the notion that that iron deficiency anaemia affects pregnancy outcome. What the effect on maternal mortality is will most probably never be established given the wide accepted practices of iron supplementation during pregnancy and the inability to do controlled supplementation studies. Normal haemoglobin values and correction of iron deficits improves neonatal health and justifies the correction of the deficits during pregnancy. The exact cut-off values to consider a woman anaemic during pregnancy are, however, not so clear. It is possible that the extend of the problem of anaemia during pregnancy has been overestimated. There is definitely an association between low haemoglobin values and low birth weight, but the anaemia is often either a shared cause or a sign of an underlying pathology. Correcting anaemia might yield better results. The effects of a supplement are probably higher when the supplement is given in the first half or in early pregnancy.

Vitamin A

Retinol metabolites play essential metabolic roles. They maintain night vision and the integrity of the cornea. The metabolite, retinoic acid has been shown to play a fundamental role in embryonic development. Retinoic acid receptors have been identified, which activate transcription of genes. In animals, a vitamin A deficient diet induces malformed offspring, mostly affected by microphthalmia and anophthalmia associated with cardiac, lung, and urogenital system defects (Azaïs-Braesco & Pascal 2000). In the light of these findings, a higher incidence of malformed babies would be expected in areas of endemic vitamin A deficiency, but this is not the case.

On the other hand there is now a considerable consensus that vitamin A deficiency, even marginal, can affect survival in children, probably by reducing morbid periods or their effects (Beaton *et al.* 1993). This has triggered supplementation studies in other population groups. In a large vitamin A supplementation trial in Nepal, 44 646 women were followed (West Jr *et al.* 1999). They received either a weekly dose of vitamin A, or placebo. During the follow up period 22 189 pregnancies were recorded. Deaths during pregnancy and up to 12 weeks postpartum were recorded. The mortality was 704 (n=51), 426 (n=33) and 361 (n=36) per 100 000 pregnancies in the placebo, vitamin A and β carotene group respectively. This study has raised quite an interest but caution is necessary in the interpretation. All types of deaths were used in the comparison, even if there is no functional explanation to do so. Death due to accidents and chronic illness contributed to a large number of deaths in the placebo group. If one excludes them, the number of deaths in the different groups change (placebo 43 deaths with RR 1.0, vitamin A 33 deaths with RR 0.45-1.18 and β carotene 23 deaths RR 0.31-0.94). Only the carotene group shows significant differences. The period of follow was also much longer than the usually accepted six weeks postpartum. Taking the usual definition of pregnancy related deaths, the results are also no longer significant (Sachdev 1999, Ronsmans *et al.* 1999, Azaïs-Braesco & Pascal 2000). Overall, the evidence is not conclusive enough to warrant a vitamin A supplementation during pregnancy.

The latest theories on the role of oxidative stress in the pathophysiology of pre-eclampsia and eclampsia have triggered the interest in the direct role of β -carotene during pregnancy. Free radicals are proposed as the toxic elements that negatively affect maternal vascular function. Reactive radicals start peroxidation of lipids on cell membranes changing the structure of the cell wall and secondarily the normal function of the cell (Halliwell 1994). Markers of lipid peroxidation are increased in plasma of women with pre-eclampsia, and the low concentrations of water-soluble and lipid-soluble antioxidants in plasma and placenta further suggest a state of antioxidant stress (Yanik *et al.* 1999, Shaarawy *et al.* 1998, Mikhail *et al.* 1994). In these studies lower levels of vitamin E, C and β carotene were also found to be associated with a higher risk of pre-eclampsia. A recent randomised trial seems to confirm this oxidative stress theory as a cause of pre-eclampsia. Participants either received a placebo or a dose of vitamin E and C. In the intention to treat cohort, pre-eclampsia occurred in 24 (17%) of the 142 women in the placebo group and 11 (8%) of the 141 in the vitamin group (adjusted odds ratio 0.39, p=0.02). In the cohort who completed the study, the odds ratio for pre-eclampsia was 0.24 (0.08-0.70, p=0.002). It needs to be remarked that all the participating women were recruited on the basis of an abnormal uterine artery Doppler at 18-22 weeks of gestation and represent a selective population (Chappell *et al.* 1999). Effects of a supplementation on a population basis will be much smaller.

Vitamin A and β carotene levels in the third trimester or at birth have also been found to be predictive of low birth weight and prematurity (Ramakrishnam *et al.* 1999). So far no supplementation studies during pregnancy are available to determine a causal relationship. In the Nepal study (West Jr *et al.* 1999) these parameters were included but they have not yet been published.

Because of its accepted effects on morbidity and mortality, vitamin A has recently been investigated in relation to HIV infections. Some studies documented an association between serum retinol levels of the mothers and the risk of mother to child transmission of

HIV (Greenberg *et al.* 1997). This has triggered controlled supplementation studies in Tanzania (Fawzi *et al.* 1998) and South Africa (Coutsoudis *et al.* 1999). In Tanzania 728 HIV pregnant women received either a daily vitamin A (with β carotene) supplement or a placebo. There was no difference in the risk of HIV infection by 3 months of age between the two groups, nor were there differences in foetal mortality rates. However, vitamin A seemed to protect against pre term deliveries, and the pre term delivered babies were also less likely to be HIV infected. In South Africa, 1075 HIV pregnant women were assigned to either a vitamin A group, a multivitamin group, a multivitamin with vitamin A group or a placebo. In the group who received multivitamins less foetal deaths were recorded giving a relative risk for foetal deaths of 0.61 (0.39-0.94). The multivitamins also decreased the risk of low birth weight by 44%, severe pre term birth ((34 weeks gestation) by 39% and small size for gestational age at birth by 43%. Vitamin A supplementation alone had no significant effects on these variables. Multivitamins but not vitamin A, resulted in a significant increase in CD4, CD8 and CD3 counts.

What the exact effect is of a vitamin A deficiency on pregnancy remains up to now unclear. Although there is a theoretical framework to explain the negative effect of a deficiency no studies have been conducted that show beyond doubt that a supplementation program has a benefit on maternal mortality, birth weight or prematurity. In women at risk of pre-eclampsia a supplement does have a benefit. In situations where women are deficient it is warranted to correct the deficit to protect the newborn in the first months of life.

Folic Acid

Folate is critically important for foetal development. It is a cofactor essential in the nucleotide biosynthesis and in the metabolisation of homocysteine to methionine. Methionine is used in the methylation process of DNA, proteins and lipids with the production of homocysteine as end product (Botto & Yang 2000).

Interference with DNA synthesis gives rise to abnormal cell division. Rapidly dividing cells, such as those in the haematopoietic system, are the most susceptible to irregularities in DNA production. One of the clinical manifestations of folate deficiency is macrocytic anaemia (Scholl & Johnson 2000).

There is no doubt that folic acid deficiency is directly linked to neural tube defects. A recent review studied 35 published studies and found in concordance with a Cochrane review (Lumley *et al.* 2000) that periconceptual folate supplementation reduced the incidence of neural tube defects by as much as 70% (odds 0.28 C.I. 0.15-0.53). The reduction is similar for occurrent as recurrent defects. The relationship of folate with risk of abortions, preterm delivery and birth weight is not very clear. Many observational studies of folate during pregnancy suggest a potential benefit of good folate status with improvement of birth weight and gestational age. Unlike observational studies, randomised trials of folic acid supplementation have shown less uniform benefit (Scholl & Johnson 2000, Lumley *et al.* 2000).

Folate deficiency increases homocysteine concentrations. Women with habitual abortions had a higher prevalence of hyperhomocysteinemia as compared to controls (Wouters *et al.* 1993, Nelen *et al.* 1998), which is also confirmed by later studies (Scholl & Johnson 2000). Folate supplements reduced significantly the homocysteine concentrations. Homocysteine levels are also higher in women who have given birth to offspring with neural tube defects.

Although dietary intake is directly responsible for folate levels, the interactions with homocysteine are also mediated through a genetic predisposition. A thermolabile reductase has been identified which decreases the metabolisation of folic acid and thus hampers the conversion of homocysteine to methionine. The homozygote frequency ranges from 1% in American blacks to 20% or more among Italians and US Hispanics. Homozygote defects in mothers are associated with a higher risk of neural tube defects. Heterozygote rates range from 5 to more than 40%. It is believed that the both homo- and heterozygotes have increased need of folic acid. The need for a folic acid supplement is thus determined by the prevalence of the genetic defect in the population. We have no information on what this prevalence might be in developing countries. The folic acid supplement needs also to be given in the periconceptual period, which is not a very vulnerable period in operational terms. Improvement in food quality and the use of fortified products seem the only effective strategy.

Zinc

Studies of experimental animals and in humans indicate that severe zinc deficiency can have profound effects on pregnancy outcome. Severe zinc deficiency causes prolonged labour, teratogenesis, and embryonic or foetal death. Acrodermatitis enteropathica is an autosomal genetic recessive defect in zinc metabolism and causes a marked inhibition of zinc absorption (Van Wouwe 1989). The outcomes of pregnancies with acrodermatitis enteropathica ended in spontaneous abortion, anencephaly, achondroplastic dwarfism and low birth weight infants (Hambidge *et al.* 1975). When these patients were given high dosages of oral zinc to maintain normal plasma zinc concentrations throughout gestation, pregnancy outcomes were normal.

Several studies have documented the relation between maternal zinc status and pregnancy outcome. The results are mixed and several adverse effects have been associated with low zinc status. These include congenital anomalies, reduced birth weight for gestational age and preterm delivery. Maternal complications include pregnancy-induced hypertension, pre-eclampsia, intrapartum haemorrhage, infections, and prolonged labour (King 2000). A review (Tamura & Goldenberg 1996) analysed 41 studies of maternal zinc status and birth weight published between 1977 and 1994. Seventeen of the 41 studies recorded a significant relation between and indicator of maternal zinc status and birth weight. To date there are 12 randomised, controlled supplementation studies published (Jameson 1993, Hunt *et al.* 1984, Hunt *et al.* 1985, Mahomed *et al.* 1989, Cherry *et al.* 1989, Nielsen *et al.* 1992, Fawzi *et al.* 1997, Sautier 1991, Jonsson *et al.* 1996, Osendarp *et al.* 2000). Of the 12 trials 6 found no effect of the zinc intervention on pregnancy outcome. In many of the studies documenting the association between zinc status and maternal health very little confounding has been taken into account. Overall the available evidence points in the direction that zinc deficient women might have a higher risk for themselves and for their offspring. Firm evidence to warrant a supplement during pregnancy is, however, still lacking.

Iodine

Iodine is an essential substrate for synthesis of thyroid hormones. When the physiological requirements of iodine are not met in a given population, a series of functional and developmental abnormalities occur and, when iodine deficiency is severe, endemic goitre and cretinism, endemic mental retardation, decreased fertility rate, increased perinatal death and infant mortality. Endemic cretinism knows a neurological and a myxoedematous form, with mixed forms. In affected populations one finds mental retardation, deafmutism, spastic diplegia, squint, hypothyroidism and dwarfism (Delange 1994). Although the best known clinical sign of iodine deficiency is goitre, this does not represent the mayor health problem. Iodine deficiency during pregnancy is responsible for development defects of the foetus and the pathologies associated with endemic goitre. Iodine supplementation studies have shown beyond doubt that supplementing iodine during pregnancy can reverse the described abnormalities (Pharoah 1993). Maternal health seems not directly affected by iodine deficiency. Salt fortification is now widely practised throughout the world with an impressive decrease in associated morbidity (Delange 1998).

Magnesium

Magnesium is an essential mineral needed in relatively large amounts by humans. In a number of retrospective studies magnesium levels during pregnancy were found to be associated with the risk of seizures in pre-eclampsia, prematurity and low birth weight (Ramakrisham *et al.* 1999, Makrides & Crowther 2000). This promising association has triggered a number of controlled supplementation studies, which have been reviewed lately (Makrides & Crowther 2000). The authors of the Cochrane review concluded that there is at present not enough evidence to show that dietary magnesium supplementation during pregnancy is beneficial. No studies are available on magnesium supplementation in developing countries, where the deficiency might be more important.

Calcium

High blood pressure with or without proteinuria is a major cause of maternal and perinatal morbidity and mortality worldwide. Preterm birth, a common association with hypertensive disorders, is the leading cause of early neonatal death and infant mortality, particularly in low-income countries. A number of observation studies led to the hypothesis that an increase in calcium intake during pregnancy might reduce the incidence of high blood pressure and pre-eclampsia among women with low calcium intake (Atallah *et al.* 2000). To date 12 randomised placebo controlled calcium supplementation trials during pregnancy have been published (Belizan *et al.* 1991, Villar *et al.* 1987, Purwar *et al.* 1996, Lopez-Jaramillo *et al.* 1997, Sanchez-Ramos *et al.* 1994, Lopez-Jaramillo *et al.* 1990, Lopez-Jaramillo *et al.* 1989, Villar & Repke 1990, Herrera *et al.* 1998, Crowther *et al.* 1999). 10 of them were analysed in a Cochrane review (Atallah *et al.* 2000) and the two more recent, in a recent discussion paper (Villar & Belizan 2000). In the Cochrane analysis, there was a slight reduction in blood pressure with calcium supplementation (RR 0.81 C.I. 0.74-0.89). In women at risk of hypertension and with low calcium intakes the effects were more marked with a RR of 0.35 (C.I. 0.21-0.57) and 0.49 (C.I. 0.38-0.62) respectively. The risk of pre-eclampsia also decreased after calcium supplementation (RR 0.70 C.I. 0.59-0.83). Here again the risk decrease was more important when women were either at risk of pre-eclampsia or when they had lower baseline calcium intakes with a RR of 0.22 (C.I. 0.11-0.43) and 0.32 (C.I. 0.21-0.49) respectively. There was no evidence that supplements decreased preterm delivery, although there was a reduction in risk among women at risk of hypertension. There was no effect of calcium supplementation on stillbirth or death before discharge from the hospital, but here were fewer babies with a low birth weight. Most of these findings have been replicated in the two more recently published trials (Herrera *et al.* 1998, Crowther *et al.* 1999). The present evidence supports the concept that calcium supplements during pregnancy can reduce pre-eclampsia when given to women with deficient calcium intake or when they are at risk for pre-eclampsia. The expected effect of supplementation might however be overestimated given that the total number of participants with low calcium intakes in all the analysed studies was rather small. There remains a need to conduct larger scale studies in calcium deficient populations. Calcium supplements during pregnancy seem however also to have a more sustained effect in the neonatal period and infancy. 591 children of a mean age of 7 years were followed up after their mothers were randomly assigned to a calcium supplement or a placebo group during pregnancy. The systolic blood pressure was lower in the children from the calcium supplemented group than in the placebo group. This effect was highest between the children who had a body mass index above the median of the population (Belizan *et al.* 1997).

Vitamin C

A few studies have shown that vitamin C deficiency plays a role in some pregnancy complications, such as premature rupture of membranes (PRM) and pre-eclampsia (Casanueva *et al.* 1991). Recent evidences from two, randomised, double-blind, placebo-controlled trials show how vitamin C (and other natural antioxidants) could be effective in decreasing the oxidative stress and thereby improving the course of pre-eclampsia (Gülmezoglu *et al.* 1997). The proportion preterm deliveries was higher in the placebo group (22/29) than in the antioxidant group (14/27), yielding a relative risk of 0.68 (0.45-1.04). Better results were achieved by Chappell and co-workers (Chappell *et al.* 1999): in the cohort who completed the study (81 placebo and 79 vitamin group) they found that the odds ratio for pre-eclampsia was 0.24 (0.08-0.70). These findings support the hypothesis that oxidative stress is responsible for the characteristic endothelial dysfunction of pre-eclampsia, as has been described by Roberts *et al.* (Roberts & Redman 1993, Roberts & Hubel 1999). A multicentre trial with large numbers of patients is needed, however, before introducing ascorbic acid in the clinical management of either pre-eclampsia or PRM as routine.

Vitamin B1 (Thiamine), Vitamin B6, (Pyridoxine), Vitamin B12 (Cobalamin)

Plasma levels of the B vitamins have been related to diverse pregnancy outcomes with varying results. The recognised potential of homocysteine in playing a role in pre-eclampsia has also triggered research in the role of vitamin B12 in pregnancy. To date no controlled supplementation studies are available to prove that supplements are needed during pregnancy unless in situations where there is clinical evidence of a specific deficiency where the treatment is needed to correct the clinical picture. Table 1 gives an overview of the available evidence.

Discussion

As can be seen from table one, there is a large body of evidence supporting the concept that deficiencies in micronutrients adversely affect maternal health and pregnancy outcome. It is important to underline here that not one micronutrient alone is responsible for this adverse effect. It is therefore very unlikely that the supplementation or correction of one deficiency will yield high effects, as long as other deficiencies remain. There is no magic bullet to improve maternal and child health through a single nutrition supplement. What the possible effect would be of a multivitamin-mineral supplement, which would cover all needs of pregnant women, is at present impossible to tell. So far no controlled supplementation studies have published their results, and few are under way (Scholl & Reilly 2000).

A second consideration is that most of the described effects and results of supplementation relate to overt deficient subjects. It is therefore difficult to translate the effect of a supplementation to the general population or to make generalisations for all populations. Most of the controlled supplementation studies have also been performed in populations of industrialised countries where deficiency states are less frequent. The observed effects might thus be an underestimation of what one could expect in a developing country. So far very few studies are available in these population groups.

Table 1. Overview of the effects of micronutrients on pregnancy outcome

Micronutrient	Maternal mortality	Birth weight	Preterm delivery	Delivery complications	Pre-eclampsia	Remarks
Iron	Possible	Yes, U shaped relation	Yes, U shaped relation	Probable	No info	Lack of controlled supplementation studies
Vitamin A	One study only Not clear	Possible	Possible	Hiv transmission risk decreased	B carotene	
Iodine	Not documented	Yes	Yes	Not documented	Not documented	Important congenital malformations
Zinc	Not documented	Yes	Yes		Yes	Effect is clear in deficiency states
Folate	Not documented	Not documented	Not documented	Abortions Congenital malformations	Not documented	The need for a minimal dietary intake to protect congenital malformations is clearly established
Magnesium	Not documented	Possible	Possible	Decrease documented	Not clear	No evidence enough to support a general supplementation
Calcium	Not documented	Possible	Possible	Possible	yes	Effects found in risk groups or groups with low calcium intake
Vitamin C	Not documented	Not documented	Possible	Abruptio?	Possible	Very few studies
Thiamine B1	Not documented	IUGR?	Not clear	Not clear	Not clear	Very few studies
Pyridoxine B6	Not documented	possible	Possible	Better Apgar scores	Possible	Very few studies
Cobalamin B12	Not documented	Not documented	Not documented	Not documented	Possible	Very few studies

For some deficiencies the maximum effect of a correction is found when this happens in early pregnancy. For folic acid the supplement should ideally be given before conception and the highest effects of an iron supplement can be expected when taken in the first trimester. This, however, has major repercussions on the implementation strategies. In developing countries, women usually don't consult for a pregnancy until well in the second half of pregnancy. This is often too late to correct a deficit and find a consequent improvement in maternal and child health. Providing supplements also means that the health system must be able to provide the supplements on a regular basis and with certain continuity. The experience with iron supplements has demonstrated that this is usually where the strategy is flawed. Drug availability is often erratic and health services are not always accessible throughout the year.

The cost of a supplement is also not negligible and varies from 1 to 8 US dollars for iron supplementation programs, according to the study and the way the costs are calculated.

The effect of a supplement of iron is also mitigated by the confusion between iron deficiency and anaemia itself, which has a much wider causality. Often the underlying causes of anaemia, other than iron, are poorly addressed and many of the studies suggest that the confounding might be more important than iron deficiency. Low haemoglobin values during pregnancy should be first addressed with a strategy to correct anaemia in a broad sense in which iron deficiency is only one of the many possible factors. It is highly likely that effects on maternal health will be much more important than with provision of iron alone.

It seems thus that apart from an iodine fortification program, there is little scope for improving the micronutrient status of pregnant women with supplementation programs alone. Hope of achieving an improvement must lie in upgrading the nutritional status of women of childbearing age in general and providing nutritional advice during pregnancy. A nutrition approach should be integrated in ante natal care programs. The challenge will be how to define the role of the health services in both specific activities during the ante natal care program, as in a more development directed approach. Judging from the experiences so far, the results will be slow in coming, and they will need an intersectoral approach given the multicausal nature of the problem. It would be good if an intermediate solution could be found. This will need to be found in a supplementation of all micronutrients needed in pregnancy. Since no results of such studies are available, there is an urgent need to do a large scale controlled supplementation intervention study.

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