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Review: Effects of maternal micronutrient supplementation on placental function

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ABSTRACT

Pregnancy is a physiological challenge that may require additional nutritional support. Suboptimal micronutrient intakes and micronutrient deficiencies during pregnancy are a global problem, often leading to poor maternal and child outcomes. Micronutrient supplementation is commonly recommended during pregnancy to support and enhance maternal metabolism. Recent studies suggest that the use of multiple micronutrient supplements may be of benefit during a normal pregnancy and may significantly reduce the risk of preeclampsia, preterm delivery, gestational diabetes, and improve pregnancy outcomes. Given the crucial role that the placenta plays in mediating pregnancy outcomes, it is important to consider the impact of micronutrient supplementation on the mechanisms associated with placental function, as well as maternal and fetal homeostasis. This review will consider the role of key micronutrients in supporting pregnancy and the possible mechanisms by which multiple micronutrients influence placental function and modulate placental oxidative stress and inflammation.

Contents

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1. Introduction

Micronutrients are defined as elements and compounds required in very small quantities to exert physiological effects and include numerous vitamins and minerals derived from the diet. Micronutrients are essential for cellular metabolism, optimal tissue function and growth, due to their involvement in the production of enzymes, hormones, signalling molecules, and the regulation of differentiation and apoptosis [1,2]. An adequate supply of micronutrients during pregnancy facilitates the successful development of the fetus, and supports maternal and placental homeostasis as physiological demands increase across gestation [3,4].

Throughout the course of pregnancy, the requirements of the growing fetus may lead to an increased risk of micronutrient deficiency [5]. Maternal micronutrient deficiencies can have long-term impacts for offspring, including effects on cognition and increased risk of cardio-metabolic disease, in addition to the risk of adverse complication during pregnancy and fetal and maternal mortality [5]. In the developing world, micronutrient deficiencies during pregnancy are common; poor nutrition is associated with both suboptimal perinatal outcomes [6,7], and deficiencies in several key micronutrients linked with the inflammatory processes involved in preterm labour and preeclampsia [7]. Antenatal micronutrient supplementation has been shown to improve birth outcomes in areas of inadequate dietary intake [8].

As the site of micronutrient transfer, the placenta is central to the provision of resources to the fetus. Placental transport capacity will adapt across gestation to supply the variable resource demands of the developing fetus [9,10]. Several micronutrients are actively transported across the placenta, and fetal nutrient supply can be maintained by the up-regulation of transporters when maternal availability is limited [10]. In addition to nutrient transport, the placenta has key roles in the modulation of inflammation and oxidative stress that are also affected by micronutrient sufficiency [11]. This review will consider the evidence to support multiple micronutrient preparations and the role of essential micronutrients including iron, iodine, zinc, folate, and selenium in supporting placental function and healthy pregnancy. The role of vitamin A will also be considered due to its importance in supporting fetal development despite its absence from pregnancy specific preparations.

2. Micronutrients

2.1. Multiple micronutrient preparations

In most developed nations, pregnancy specific multiple micronutrient supplements are widely available and in common use. In a recent study conducted in Australia, it has been estimated that as many as 100,000 pregnant women could be consuming these products per annum [12]. The majority of supplements available on the market contain a combination of B group vitamins (niacin, riboflavin and thiamine, B12, B6), vitamins D, E and C, folate, iron, iodine, copper, selenium, and zinc. In addition to this core group of components, a wide variety of vitamins, minerals and herbal preparations are also added with significant variability in formulations evident [12].

Retrospective cohort analysis has suggested that the use of multiple micronutrients during pregnancy may significantly reduce the risk of developing disorders of pregnancy including preeclampsia [13–15], preterm delivery [7] and other complications [16]. However, despite these findings, and mechanistic evidence of plausible materno-fetal health advantages, varied results have been noted upon systematic review of supplementation trials [6]. Such variability may be linked to specific population contexts and resultant supplementation responses [6].

A recent Cochrane review however, analysed 19 trials across low and middle-income countries and concluded that there was a strong basis from which to replace iron and folic acid supplements with multiple micronutrient preparations for pregnant women [8]. Such evidence highlights, that although significant advancements in the understanding of micronutrient affects during pregnancy have been made across the past 20 years, there remains gaps in our understanding of the interaction effects of multiple micronutrient supplements and the preparation formulations required for greatest efficacy - which warrant further investigation.

2.2. Iron

Globally, iron is one of the most prevalent micronutrient deficiencies and is estimated to affect 32 million pregnant women [17]. During pregnancy, iron is required in high levels to support fetal development with supply facilitated by the active transport from the maternal to the fetal circulation against the concentration gradient by the placenta [10]. With fetal demand increasing significantly during late gestation, maternal requirements also elevate and as such the risk of anaemia increases with advancing gestation [17].

In total, the placenta transports approximately 270 mg of iron to the fetus each day, with the iron stored during in utero development the major iron source for the first six months of life [18]. Iron uptake is facilitated via maternal diferric-transferrin binding to and being endocytosed by placental transferrin receptors (TfR) found on the apical syncytiotrophoblast [18]. Iron is then released by the acidification of vesicles and reduced by ferrireductases, which are then transported into the cytoplasm by divalent metal transporter 1 (DMT1). Iron can be stored in the cytoplasm as ferritin or transported to the fetal circulation via ferroportin and oxidised by ferroxidase zyklopen/hephaestin like-1 [18].

Placental iron transport can adapt to maternal and fetal iron levels. In women with iron deficiency, placental transport of iron is increased [10], possibly through the increased expression of placental TfR [19]. Indeed, increased expression of TfR leads to increased iron uptake in BeWo cells [19]. Low iron status in rat dams has been evidenced to lead to increased expression of TfR and DMT1, and an increased activity of copper oxidase [19]. Low fetal iron levels can also lead to the up-regulation of the placental TfR and DMT1 [18]. The human placenta is thought to rely primarily on the uptake of non-heme iron, however there is some evidence that the placenta may also be able to utilise iron of heme origin [19]. The placenta expresses proteins involved in heme iron uptake and heme scavenger receptors [19]. Despite the up-regulation of

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