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Multiple micronutrient supplementation and birth outcomes: The potential importance of selenium

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ABSTRACT

A healthy diet and lifestyle is a pre requisite to a healthy pregnancy, however this is often not the case. Many pregnant women are overweight or clinically obese and this has been shown to increase their risk of major complications of pregnancy such a preeclampsia, intrauterine growth retardation, preterm birth and gestational diabetes. An adequate and balanced diet is important, as is the balance between macronutrients such as carbohydrates, fats and protein and the vitamins and essential trace elements needed to support metabolism. In this review, we look at the use of micronutrient supplements during pregnancy and examine the recommendations currently in place to guide the use of these products. We also present evidence that broad-spectrum micronutrients may have a beneficial effect in pregnancy and lower the incidence of preeclampsia and preterm labour, especially in overweight and obese women. Finally we focus on the essential trace element Selenium and present a strong case for its importance in maintaining mitochondrial function during oxidative stress which is generated in the placentae of women experiencing these complications of pregnancy. It can no longer be assumed that women are consuming an adequate and well balanced diet during pregnancy and the use of micronutrient supplements may potentially have positive effects on a healthy start to life. Globally, millions of women are currently taking these products each year and an opportunity exists to systematically determine their beneficial effect.

1. Introduction

The global sale of prenatal multivitamins is a rapidly expanding billion-dollar industry. In North America alone, product sales equate to approximately $700 million annually and are increasing at a rate of 3%. In Australia, sale of multivitamin pregnancy supplements earn companies approximately $50 million per annum, however annual sales growth is much larger than that of the US at 14% [1]. When considering that the annual birth rate in Australia is approximately 300,000 and estimates that 50–60% of women are taking multivitamins supplements during the course of gestation, it raises interesting questions as to the benefits of broad-spectrum micronutrient supplementation in pregnancy and the potential impacts on birth outcomes.

The motivation to consume these products stems from important discoveries in the 1980's of the role of folic acid in preventing neural tube defects and reducing the incidence of spina bifida [2]. Folic acid is the major constituent of all leading prenatal micronutrient brands, with between 500 and 800 μg per tablet in a once a day dose [Table 1]. The benefit of multivitamin supplements is that the combination of a range of vitamins and minerals make it convenient for women to support their bodies during pregnancy. In addition to folate, these products routinely contain a range of vitamins (B group, C, D and E), omega 3 fatty acids in addition to trace elements such as iron, calcium, iodine, zinc and selenium all of which have been shown to be important during pregnancy.

Many studies have established the importance of multivitamins and trace elements in pregnancy and correlations have been drawn between adverse pregnancy outcomes and micronutrient deficiency, however less is known regarding baseline dietary intakes of essential multivitamins. It is assumed that by following the general recommendation that pregnant women eat a balanced healthy diet that they will have a sufficient intake of essential vitamins and minerals. However this is not routinely tested and as a result it is difficult to assess the necessity for supplementation in western

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Table 1
Micronutrient and trace element content of five leading pregnancy supplements available on the Australian market.

Ingredient	RDI[a]	Upper Limit[a]/day	Product 1 (1/day)	Product 2 1/day	Product 3 (1/day)	Product 4 (1/day)	Product 5 (1/day)
Folic Acid	600 μg	1000 μg	500 μg	800 μg	500 μg	500 μg	500 μg
Vitamin D3 as cholecalciferol	5 μg	80 μg	10 μg	5 μg	5 μg	15 μg	5 μg
Vitamin B1	1.4 mg	None	1.5 mg	1.4 mg	1.5 mg	1.4 mg	5 mg
Vitamin B2	1.4 mg	None	1.5 mg	1.4 mg	1.5 mg	1.4 mg	5 mg
Vitamin B3	35 mg	900 mg	20 mg	18 mg	10 mg	18 mg	20 mg
Vitamin B5	5 mg	None	4.6 mg	10 mg	10 mg	4.6 mg	10 mg
Vitamin B6	1.9 mg	50 mg	50 mg	1.9 mg	75 mg	1.6 mg	50 mg
Vitamin B12	2.6 μg	None	50 μg	2.6 μg	4 μg	2.6 μg	50 μg
Vitamin A	4.2 mg	18 mg	1.5 mg		1.5 mg	6 mg	5 mg
Vitamin C	60 mg	1000 mg	200 mg	85 mg	80 mg	67.5 mg	62 mg
Vitamin E	7 mg	300 mg	147 mg	18.7 mg	10 mg	10.5 mg	
Vitamin K	60 μg	None				60 μg	
Biotin	30 μg	600 μg	100 μg	30 μg		30 μg	
Coenzyme Q10			60 mg				
Omega 3- FA	1 g	None	500 mg	500 mg	500 mg	500 mg	500 mg
Iron	27 mg	45 mg	24 mg	60 mg	5 mg	5 mg	5 mg
Calcium	1000 mg	2500 mg	59 mg	125 mg	80 mg		20 mg
Magnesium	350 mg	350 mg	200 mg	100 mg	42 mg	20 mg	10 mg
Selenium	65 μg	400 μg	65 ug	50 μg		65 μg	40.6 μg
Iodine	220 μg	1100 μg	197 μg	220 μg	200 μg	250 μg	250 μg
Zinc	11 mg	40 mg	15 mg	11 mg	12 mg	11 mg	12 mg
Copper	1.3 mg	10 mg	1.3 mg	1 mg		1.3 mg	
Manganese	5 mg	5 mg	5 mg	1.9 mg			1 mg
Chromium	30 μg	1 mg			20 μg	30 μg	2.5 μg

[a] National Health & Medical Research Council Recommendations [32].

populations [3,4]. The lesson learnt through the findings with folic acid suggest that supra-nutritional supplementation may offer an applicable and safe way to prevent serious complications of pregnancy and support at risk women such as those with abnormal metabolism or high BMI to maintain homeostasis.

1.1. Prenatal micronutrients and complications of pregnancy

Physiologically, micronutrients play a vital role in supporting pregnancy through the modulation of maternal and foetal metabolism, reductions in inflammation and oxidative stress, and through the support of placentation [5]. To this end significant research has been undertaken to evaluate the effectiveness of individual and limited combinations of vitamins/minerals on pregnancy outcomes. Randomised controlled trial supplementation with vitamin C [6], vitamin E [7], vitamin D [8] and calcium [9] have yielded mixed results and raised a hypothesis that it is unlikely to be one single micronutrient that will be beneficial in these complicated pregnancies and rather that more can be gained by comprehensively supporting maternal homeostasis through multiple-micronutrient supplementation.

Recently, the Royal Australian College of Obstetrics and Gynaecology (RANZCOG) reviewed the use of vitamin and mineral supplements in pregnancy and made several key recommendations [10]. The first and central recommendation is that pregnant women should eat a healthy balanced diet before and during pregnancy, however this assumes that women have a healthy metabolism and a BMI between 18.5 and 30. RANZCOG guidelines do not make a special recommendation for undernourished women or those that are clinically obese. The second recommendation is that all women should take at least 400 μg per day of folic acid to aid in the prevention of neural tube defects. The remainder of the recommendations relating to Vitamin B12, D, K and the trace elements iron, calcium and iodine are similar in that if women are below a defined level of each they should be recommended a supplement [5].

In reality however, the majority of women are not measured for levels of these micronutrients pre-pregnancy, at conception or routinely across pregnancy and whilst women may assume that their diets contain these elements, modern food is highly processed and soils are becoming depleted of key trace elements [11]. Recent evidence suggests that the Australian population may be particularly vulnerable to micronutrient deficiency with reductions in thiamin, vitamin A, folate, vitamin D, calcium, iron, magnesium and zinc observed [5], so perhaps micronutrient screening or routine supplementation is warranted.

The growing number of women choosing to take a prenatal supplement may protect against this baseline reduction in micronutrient status. However when one considers the prenatal supplements available on the market much variability exists in specific formulations (Table 1). Across all prenatal supplements, vitamins and minerals such as folate, iron, zinc, calcium, B group vitamins and vitamin D are present, however dosage and composition variability means that not all supplements are the same, meet nutritional requirements or contain key trace elements of importance such as selenium.

Several important studies have reported positive associations between multivitamin use preconception and during pregnancy and a reduction in risk of preeclampsia, preterm labour and small for gestational age babies [12–14]. A recent meta-analysis of 13 studies also confirmed beneficial effects of multinutrient supplementation in reducing the risk of low birth weight [15]. Some of these studies are based on large multicentre populations such as the Danish National Birth Cohort which comprises more than 100,000 births of which 48,000 accurately report weekly consumption of multivitamins [16]. In these studies there was a significant decrease in adverse birth outcomes in women reporting multivitamin use during pregnancy. Similar observations have been made in a US birth cohort where the use of multivitamins during pregnancy was associated with a 45% reduction in the risk of developing preeclampsia [17]. Interestingly, these positive effects of multinutrient supplementation in these populations appeared to be limited to women of normal BMI and were lost in women with BMI >25 kg/m^2. It is widely acknowledged that incidences of both hypertensive disorders of pregnancy and preterm labour are higher in overweight women and these data allude to metabolic

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