



The
Fertility Society
of Australia

Pre-Conception Health Special Interest Group



Micronutrient (folic acid, iodine and vitamin D) supplements pre-conception and during pregnancy

The evidence relating to the use of folic acid, iodine and vitamin D supplementation to improve reproductive outcomes is reviewed.



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Evidence review

Folic acid

Women

There is good quality evidence from meta-analysis of several large multicentre randomised controlled trials (RCTs) that daily supplementation with folic acid, taken alone or as part of a multivitamin preparation during the periconception period reduces the risk of neural tube defects (NTD) in the babies [1]. Folic acid doses between 0.36 mg (360 mcg) and 4 mg (4000mcg) appear to be safe. Precipitation of vitamin B12 deficiency has been reported with high dose folic acid supplements but is rare. Folic acid doses of 2mg and 4 mg showed evidence of benefit in trials investigating the prevention of recurrent NTD [1]. Folic acid with multivitamins versus folic acid alone has not been compared in sufficiently large populations so neither can be recommended over the other in primary prevention of NTD. There is insufficient evidence that periconceptual folic acid reduces other birth defects such as cleft lip/palate, congenital heart disease, or miscarriage.

Obese women (BMI > 29kg/m²) were more likely to have a baby affected with a NTD than women of lower BMI despite similar usage of vitamins and folic acid in the periconception period and this risk increased in obese women who were smokers [2]. Obese women taking folic acid supplementation are more likely to have low serum folate levels than normal weight women [3]. The RCOG, on the basis of these studies, has recommended that women with a BMI >30 kg/m² should take high dose folic acid when planning a pregnancy. This has provoked controversy as maternal hyperglycemia may be a confounding factor in the findings. Women with genetically abnormal metabolism of folic acid may theoretically benefit from the administration of 5 methyl-tetrahydrofolate (5MTHF) but there have been no RCTs to confirm the benefit of this. Furthermore, there have been no RCTs with NTD and birth defects as outcomes of interest comparing weekly and daily folic acid supplementation.

Men

One small RCT compared the effect of folic acid and placebo on seminal parameters and found no difference in fertile and infertile men [4]. The same study showed that folic acid in combination with zinc was associated with improved total sperm count. Folic acid in combination with other agents in men undergoing ART for male factor subfertility improved embryo morphology but not live birth rate [5]. Another study found that folic acid in combination with zinc only improved seminal parameters in men who were wild type for the C677T methylenetetrahydrofolatereductase polymorphism [6]. There is insufficient evidence to justify widespread use of folic acid supplementation to augment seminal parameters and fertility in men.

Iodine

Women

Severe maternal iodine deficiency is associated with stillbirth, miscarriage, congenital abnormalities including but not limited to the clinical picture of "cretinism" which is characterised by intellectual impairment, diplegia and deaf mutism [7-8]. Lesser degrees of maternal iodine deficiency have been associated lower IQ scores in the offspring in several population based studies and this appears to be corrected with maternal iodine supplementation [9-10].

In 2009 a committee of NHMRC recommended that pregnant and breast feeding women take 150mcg iodine supplementation per day regardless of the fact that some areas in Australia, as determined by epidemiological studies, are iodine replete [11]. There are no data of the effects of iodine supplementation in iodine replete populations such as Western Australia and Queensland. It is suggested that cross sectional research over time in school-age children in both iodine deficient and iodine replete areas be conducted following implementation of NHMRC guidelines.

A committee of the WHO published guidelines for supplementation of iodine for women and recommended that women of childbearing age should take 150 mcg of iodine per day and women who are pregnant or lactating should take 250 mcg of iodine per day [11].

Men

There are no data on the role of iodine supplementation in men with infertility. The association between abnormal thyroid function and male infertility is uncertain.

Vitamin D

Vitamin D facilitates the transfer of calcium to the fetus, particularly during the third trimester of pregnancy. Vitamin D deficiency in neonates can result in hypocalcemic tetany and reduced bone growth including rickets. There are reports of rickets in neonates born to women with vitamin D deficiency in Australia [13, 14]. A systematic review of observational studies of women with vitamin D deficiency (<50nmol/l) suggested that this was associated with increased risk of adverse obstetric outcome such as preeclampsia, gestational diabetes mellitus, preterm birth and being small for gestational age [15]. An observational study suggested respiratory disease in the baby was reduced when the cord levels of vitamin D level were higher [16].

Vitamin D is obtained from two sources: the major source is through the action of ultraviolet radiation on the skin (D3 or cholecalciferol) and the lesser source is from food (D2 or ergocalciferol). The recommended daily intake is the same for pregnant and non-pregnant women (5 mcg per day). There is lack of agreement on the definition of vitamin D deficiency both in pregnancy and in non-pregnant women and defining the upper limit of the reference range has been particularly controversial [17-19]. In Australia a position statement issued by a Working Group in 2005 defined severe deficiency as <12.5nmol/l, moderate deficiency as 12.5-25nmol/l, mild deficiency as 25.1-50nmol/l [20]. The Working Group did not specifically address the issues of vitamin D in pregnant women but provided good advice on skin exposure applicable to Australia and New Zealand and the best oral supplements to use. Risk factors for vitamin D deficiency are: having dark skin, being veiled, suffering malabsorption syndromes, taking anticonvulsants and using sunscreen. Winter exacerbates the risk of vitamin D deficiency [21].

Routine screening of pregnant women for vitamin D deficiency has been recommended [22]. However, results of RCTs of the effect of maternal antenatal vitamin D supplementation on neonatal outcomes are conflicting and inconclusive. A Cochrane review found only four trials involving only 623 women comparing Vitamin D supplements to placebo during pregnancy [23]. The review concluded that there was insufficient evidence of adequate quality to recommend vitamin D supplementation in pregnancy. Furthermore, another comprehensive review concluded that only severe deficiency should be treated during pregnancy [24].

The role of vitamin D in infertility is uncertain. One study conducted in Turkey measured vitamin D levels in follicular fluid at IVF and found that higher levels were associated with an increased chance of IVF success [25]. However the study was small and did not control for a number of confounders including race.

There is need for further research into the role of vitamin D deficiency preconceptually and in infertility in both women and men.

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Summary

There is evidence that folic acid, iodine and vitamin D are important for reproductive outcomes. Folic acid and iodine supplementation is recommended for women planning to conceive and in pregnancy. Vitamin D supplementation is recommended only for women with vitamin D deficiency.

There is insufficient evidence to justify recommending the use of folic acid, iodine and vitamin D to improve reproductive outcomes for fertile and infertile men and further research should be conducted in this area.

Recommendations

Folic acid

The recommended dose of folic acid for women without special considerations planning to conceive is 400-500 mcg.

The recommended dose of folic acid for women with special considerations is 2-5 mg per day. The special considerations requiring the higher dose of folic acid are:

1. Personal history (self or past pregnancy) of neural tube defect (NTD)
2. A first degree relative with a pregnancy with a NTD
3. Use of sodium valproate
4. Body mass index greater than 30 kg/m²
5. Diabetes mellitus (type 1 or type 2)

Iodine

Women planning a pregnancy, including those with thyroid disease, should take iodine supplements in the dose of 150 mcg per day prior to and during pregnancy.

Vitamin D

There is insufficient evidence to justify routine supplementation of vitamin D for all women who are pregnant or planning a pregnancy. However, it is prudent to recommend measurement of vitamin D levels in women planning a pregnancy who are at risk of vitamin D deficiency including those who are veiled, have dark skin, have a malabsorption syndrome, take anticonvulsants, or regularly use sunscreen or avoid exposure to sunlight. The optimal level of vitamin D during pregnancy is uncertain but it would seem reasonable to offer supplementation for severe (<12.5nmol/l) and moderate deficiency (12.5-25nmol/l) to prevent neonatal rickets. Mild deficiency (26 -50nmol/l) can be adequately treated with increased sun exposure. There is insufficient evidence to allow extrapolation of the clinical use of the high doses of vitamin D prescribed for treatment of osteoporosis and osteopenia to women in the preconceptional period and during pregnancy.

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