The Impact of Preconceptional Multiple-Micronutrient Supplementation on Female Fertility

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ABSTRACT: In industrialized countries, fertility has declined in recent years to the lowest recorded levels. Identifying modifiable factors that influence human fertility, such as diet, is therefore of major clinical and public health relevance. Micronutrient status is a modifiable risk factor that may have an impact on female fertility, as essential vitamins and minerals have important roles in the physiological processes that are involved. Adequate levels are important for oocyte quality, maturation, fertilization, and implantation, whereas antioxidants are vital to reduce oxidative stress, a process known to impair fertility. In women who are diagnosed as infertile, lower than recommended levels of certain micronutrients have been reported. A similar scenario has been found in a proportion of women of childbearing age in general, some of whom may be struggling to conceive. Supplementation studies with multiple micronutrients are still scarce, but the literature suggests that supplementation before conception can help restore micronutrient status to recommended levels and reduce oxidative stress when antioxidants are included. Overall, supplementation has a small but beneficial effect on fertility in healthy and infertile women, including a shorter time to pregnancy and an increased chance of becoming pregnant. Nevertheless, many studies are small or observational, and adequately powered randomized controlled trials of supplementation with multiple micronutrients are necessary to confirm any definite effects on fertility. This review substantiates the potential benefits of micronutrient supplementation beyond the prevention of neural tube defects, the traditionally viewed value of prenatal vitamin use.

KEYWORDS: female, fertility, industrialized countries, multiple micronutrients, preconceptional, supplementation

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Background

Over the last few decades, fertility has declined globally to unprecedented low levels.[1] The lowest levels are in Europe, at 1.6 children per woman compared with the global rate of 2.5 children per woman.[1] In more than 70% of couples, a problem with ovulation cannot be identified, motivating the identification of potentially modifiable risk factors.[2,3] In developed countries, particularly Europe, Australia, and North America, an increasing number of women delay childbearing because of further education, career priorities, or financial concerns, for example—sometimes unaware that fertility declines with older age, and that assisted reproductive techniques are less successful in older women.[1,4] Smoking and obesity also adversely affect fertility, as may caffeine, alcohol consumption, and environmental pollutants.[4]

Micronutrients have numerous roles in fertility

Micronutrients are essential vitamins and minerals that are required in small quantities as dietary components. Although these micronutrients do not provide energy to the human body, they are essential for catabolic and anabolic processes and need to be supplied externally. The importance of good nutrition has already been established during pregnancy, influencing embryonic and fetal development, and thus pregnancy outcomes.[5,6] Micronutrient deficiencies in pregnant women can result in pre-eclampsia, pre-term deliveries, neural tube defects of the brain or spinal cord (such as spina bifida), and other congenital abnormalities (eg, cardiovascular or urinary system related), as well as babies who are born small-for-gestational age or with a low birthweight.[5] An inadequate supply of micronutrients during pregnancy may also have long-term effects into adulthood, increasing the risk of non-communicable diseases.[7,8]

Much less is known about the influence of micronutrient status on female fertility, and human studies are scarce. Nevertheless, it is apparent that micronutrients have vital roles at various stages involved in fertility. For example, adequate folate levels are important for oocyte quality, maturation, fertilization, and implantation,[6,9,10] whereas zinc has been implicated in ovulation and the menstrual cycle.[9] Sufficient vitamin A levels are a factor in oocyte quality and blastogenesis.[11] DNA synthesis, which is fundamental to the development of oocytes, is dependent on zinc and certain B vitamins.[9] Apoptosis (ie, normal cell death), essential for regulation of follicle atresia, degeneration of the corpus luteum, and endometrial shedding, is influenced by folate and zinc.[6,9] The risk of luteal phase deficiency, where inadequate progesterone secretion by the corpus luteum makes the endometrium less receptive to implantation, may be increased in women with inadequate selenium levels, putting them at a greater risk of infertility (ie, failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse).[12] Vitamin D receptors are distributed throughout reproductive tissues, and vitamin D has an important role in fertility.[13,14] Folate, vitamins B_6, B_{12}, and D, and iron all have roles in mechanisms that could affect fertility, including homocysteine metabolism, inflammation, oxidative stress, and embryogenesis.[15] Oxidative stress, which occurs when the balance between pro-oxidant molecules such as reactive oxygen species (ROS) and the body's antioxidant defense mechanism is upset, is also known to impair fertility.[6,9,16] Although ROS are necessary for normal cell functions, excessive ROS production (which can occur with smoking, alcohol use, extremes of body weight, exposure to environmental toxins, advanced maternal age) can impair physiological female reactions such as oocyte maturation, ovulation, luteolysis, and follicle atresia[9]; this can lead to infertility and conditions that may reduce fertility, such as polycystic ovary syndrome (PCOS) and endometriosis.[16] Oxidative stress is exacerbated when antioxidant reserves within the body are low.[17] Antioxidants such as vitamins C, E, and A help defend against ROS, as do micronutrients that either have antioxidant properties (eg, folate, zinc) or are involved in the formation or activity of superoxide dismutases (eg, copper, manganese, zinc), which counteract the effects of ROS.[9,18] Antioxidants protect DNA and other vital molecules against oxidative damage that would otherwise induce apoptosis.[9] When combined with low antioxidant status, oxidative stress may be associated with infertility of both known and idiopathic origin.[19]

It seems that women who struggle to conceive do have lower than recommended levels of certain micronutrients. For example, insufficient vitamin B_{12} levels have been reported in more than half of infertile women.[20] Other studies have also found associations between vitamin B_{12} deficiency and female subfertility.[21,22] Women who are infertile appear to have lower vitamin B_6 levels than fertile women.[23] Women may be less likely to conceive if their vitamin D intake is below recommended levels, or if serum 25-hydroxyvitamin D levels are at risk for inadequacy or deficiency.[24] Vitamin D deficiency is also associated with conditions that decrease fertility, such as PCOS, and can adversely affect the outcome of infertility treatment such as in vitro fertilization (IVF).[13,14] It has been reported that the total antioxidant status is lower in the serum of women with PCOS,[25] as well as in the peritoneal fluid of women with idiopathic infertility.[26] In industrialized countries, a proportion of women of childbearing age in general have lower than currently recommended levels of micronutrients (especially folate, vitamin B_{12}, vitamin D, calcium, iodine, iron, and selenium),[27] and the physiological environment for conception and pregnancy may be suboptimal.

Considering the importance of certain micronutrients (eg, folate, vitamins B_6 and B_{12}, vitamin D, antioxidants) on various aspects of fertility,[6] it seems reasonable to presume that restoring micronutrients to recommended levels may have a positive impact on fertility. In women with fertility problems, a healthy balanced diet during preconception improved fertility and was associated with a greater probability of pregnancy.[28] Improvements in the preconception diet is also associated with increased chances of an ongoing pregnancy in such women.[29] A healthy diet positively correlates with red blood cell (RBC) folate levels,[28] and higher serum folate levels appear to be beneficial for fertilization[10] and for mature oocyte counts in women undergoing infertility treatment.[30] One study has indicated that vitamin D levels may also predict the outcome of IVF, as higher serum and follicular fluid vitamin D levels were associated with a greater chance of clinical pregnancy after fertility treatment.[31] It has been suggested that women with below-recommended intakes of vitamin D may be less likely to conceive and might benefit from increased vitamin D intake to achieve adequate levels.[24]

However, it can be difficult to consume a healthy diet, even in countries with easier access to fresh, nutritious foods. Social, economic, educational, ethnic, cultural, and genetic factors can all affect the preconception diet, leaving many women of childbearing potential with a suboptimal micronutrient status.[27] Thus, there is a rationale to supplement with multiple micronutrients (MMNs) before conception, to help restore micronutrients to recommended levels and potentially have a positive impact on fertility.

Supplementation With Micronutrients May Improve Fertility

Although few randomized controlled trials (RCTs) have been performed, there is evidence to suggest that supplementing with micronutrients may beneficially affect female fertility.[23,32] For example, the risk of ovulatory infertility was reduced in women who used a supplement containing MMNs at least 3 times a week, and frequent MMN use (ie, ⩾6 tablets per week) was associated with an even lower risk of ovulatory infertility.[2,33] Some of the association between MMN use and the lower risk of ovulatory infertility was thought to be explained by the presence of B vitamins, particularly folate.[33] Studies using either single micronutrient supplements or MMN supplements have demonstrated positive results on fertility in healthy women and in those already having problems conceiving (see Supplementary Table).

Effect on fertility in healthy women

A double-blind RCT assessed the use of an MMN supplement containing 800 µg folic acid (Elevit, Bayer) in women planning a pregnancy, with the main objective of preventing neural tube defects; the trial was also used to evaluate the impact of supplementation on fertility.[34] Use of the MMN supplement for at least 1 month before conception and throughout the first trimester resulted in a significantly higher number of confirmed pregnancies compared with a supplement containing trace elements (Cu, Mn, Zn, vitamin C) (64.6% vs 62.3% of women, respectively), corresponding to an odds ratio of 1.1. The time to conception was shorter with the MMN supplement (3.8 menstrual cycles) compared with trace elements (4.0 cycles), leading to the suggestion that MMN supplementation can result in a slight (5%), but significant increase in fertility in healthy women. A prospective cohort study has evaluated the effects of folic acid supplementation (usually 400 μg/day), used alone or in combination with MMN, on fecundability (ie, the probability of conceiving during a single menstrual cycle with unprotected intercourse).[35] Increased fecundability was reported after the use of folic acid compared with non-use. The fecundability ratio (FR), which represents the cycle-specific probability of conception among exposed women divided by that among unexposed women, was 1.15; an FR > 1 indicates enhanced fecundability among folic acid supplement users relative to non-users.[35] The greatest increases in fecundability were observed in women with irregular (FR 1.35), short (FR 1.36), or long (FR 1.24) menstrual cycles.[35]

Effect on fertility in women undergoing infertility treatment

Impact on micronutrient levels. Restoring micronutrient levels to recommended levels in women who are having fertility problems could beneficially affect the mechanisms involved in fertility. For example, supplementation with vitamin D in women with PCOS and hypovitaminosis D may improve menstrual frequency and metabolic disturbances.[14]

Both RBC folate and vitamin B_{12} are biomarkers involved in the homocysteine pathway, and an insufficiency of either may affect fertility.[36,37] In infertile women attending an IVF clinic, it has been found that both RBC folate and vitamin B_{12} levels were inadequate overall.[20] However, in those who used a folic acid supplement, there was a significantly greater likelihood of achieving the threshold for folate sufficiency (RBC folate > 906 nmol/L to protect against neural tube defects)[38]; although few women in the folic acid group were replete (<30%), the proportion was nearly negligible in women who did not use any supplement.[20] In a study analyzing the levels of trace elements in women undergoing IVF,[39] serum and follicular fluid selenium and zinc, and follicular fluid copper levels, were significantly lower in IVF patients compared with controls. However, follicular fluid levels of aluminum and iron were significantly higher in IVF patients than in controls, which may reflect increased oxidative stress (known to enhance non-heme iron absorption).[39] In the IVF group, women who received MMN supplementation compared with those that did not had significantly higher serum and follicular fluid levels of copper, zinc, selenium, and aluminum, and higher serum magnesium levels, but lower follicular fluid iron levels.[39] A later placebo-controlled RCT also demonstrated that levels of trace elements could be restored using an MMN supplement (Elevit, Bayer) during preconception in IVF patients.[40] At baseline, serum copper and zinc were significantly lower in IVF patients compared with controls; after MMN supplementation, serum and follicular fluid copper and zinc, and serum manganese, were significantly higher compared with placebo, whereas the levels of iron in follicular fluid were significantly lower.[40] Thus, MMN supplementation in women with fertility problems can help normalize trace element levels, which may have a positive impact on the quality of the microfollicular environment, and thus on oocyte and embryo quality, implantation, and live birth.[41]

Impact on antioxidant defenses, oxidative stress, and fertility. Antioxidant levels, including vitamins A and C and glutathione peroxidase (GSH-Px), have been shown in an RCT to be significantly lower in women receiving IVF compared with controls, whereas lipid peroxidation (which results in cell damage when oxidants attack lipids in cell membranes and is an indicator of oxidative stress) was significantly higher in serum and in follicular fluid.[42] Supplementation with MMN (including antioxidants such as vitamins A, C, and E, folate, zinc, and copper) in these women during preconception led to significant increases in serum levels of vitamins C and E and GSH and follicular fluid levels of vitamin C and GSH-Px compared with placebo.[42] There was also a reduction in lipid peroxidation in serum and follicular fluid in the supplemented women.[42] This indicates that increased antioxidant intake can help strengthen the antioxidant defense system and thus reduce oxidative stress, with a potential beneficial role in female fertility.[17]

The effects of supplementing with micronutrients that have antioxidant effects (eg, vitamins B_2, B_6, C, and E, copper, manganese, zinc, selenium) on levels of oxidative stress and subsequent outcomes of IVF in older women (⩾39 years) have been evaluated in an open pilot study.[43] Use of the MMN supplement (Elevit, Bayer) before IVF cycles significantly increased the total antioxidant capacity in serum and follicular fluid and protected proteins against oxidative damage compared with untreated controls.[43] The outcome of IVF in these older women also improved with MMN supplementation, with a significant increase in the mean number of good-quality oocytes retrieved (the result of decreased oxidative stress) and an ongoing pregnancy rate of 17.7%.[43] Recently, it has been determined that MMN supplementation can significantly improve embryo quality in older women (>35 years) undergoing intracytoplasmic sperm injection (ICSI)/IVF.[44] Use of the MMN supplement resulted in a significantly higher fertilization rate compared with folic acid only (42.9% vs 66.7%, respectively) and a higher proportion of women with at least 1 good-quality embryo (58% vs 36%, respectively), supporting a beneficial effect of MMN supplementation on female fertility that may be due to the effects of the antioxidants within the formulation.[44] In women with unexplained infertility undergoing controlled ovarian stimulation, supplementation with vitamin E significantly increased endometrial thickness compared with no supplementation.[45] Supplementation was thought to improve the endometrial response via the antioxidant effects of vitamin E (which has been shown to reduce oxidative stress) and its anticoagulant effects (by increasing endometrial and follicular blood supply).[45]

It should be noted that not all studies assessing the effects of antioxidants on fertility have had positive results. An RCT evaluating the effect of daily supplementation with the antioxidants vitamins A, E, and C, zinc, molybdenum, selenium, biotin, and mixed bioflavonoid on the outcomes of fertility treatment (ICSI/IVF) in women with unexplained subfertility did not find any significant differences compared with similar women who did not receive the supplement.[46] The authors suggested that the lack of a significant difference could be caused by the fact that ROS can develop in the culture media used in assisted reproductive technology, and that the lack of follicular fluid antioxidants during IVF may disturb the oxidant-antioxidant balance, rendering the culture less protected against oxidation.[46] Oxidative stress triggered by culture media can partially deplete oocyte GSH content, enhancing the effect of sustained oxidative stress and thus risking oocyte fertilization and viability.[46] The timing of therapy may also have contributed.[46]

Impact on the time to pregnancy and chances of becoming pregnant. An increased antioxidant intake can result in a shorter time to pregnancy and is positively associated with female fertility; use of supplements rather than relying on diet alone helped women to achieve the increased intake necessary to elicit an effect.[47] A study in women being treated for unexplained infertility found that the antioxidants had different effects, depending on the body mass index (BMI) and age of the supplemented women.[47] The time to pregnancy was used to calculate the hazard ratio (HR), where an HR > 1 indicates that the variable was associated with a shorter time to pregnancy.[47] Results showed that a shorter time to pregnancy occurred with increasing vitamin C in women of normal weight (BMI < 25 kg/m^2, HR 1.09), with increasing β-carotene in overweight women (BMI ⩾ 25 kg/m^2, HR 1.29), with increasing β-carotene and vitamin C in women < 35 years (HR 1.19 and 1.10, respectively), and with increasing vitamin E in women ⩾ 35 years (HR 1.07).[47]

The number of women who become pregnant may also increase after vitamin supplementation. For example, use of a folic acid supplement in women undergoing IVF helped optimize the homocysteine pathway in follicular fluid, which was associated with better embryo quality and a greater chance of becoming pregnant; a 2-fold increase of monofollicular fluid folate was associated with a 3.3 times greater chance of becoming pregnant.[48] There may be an increased likelihood of twins associated with increased plasma folate and RBC folate levels in IVF,[49] but this may be reduced if single embryo transfer is performed using a good-quality embryo, without having an impact on the overall pregnancy rate.[50] In a pilot study of women who had tried unsuccessfully to conceive for 6 to 36 months, use of a nutritional supplement that also contained multiple vitamins and minerals resulted in one-third of women becoming pregnant compared with none in the group that received placebo.[51] These results were later confirmed in a double-blind RCT in similar, nutritionally adequate women,[52] where significant increases in progesterone levels and in the average number of days with luteal phase basal temperatures > 98°F were found in the supplement group, as well as normalization of short or long cycles; in contrast, no such changes were noted in the placebo group. After 3 months, 26% of women in the supplement group were pregnant compared with none in the placebo group, whereas another 32% conceived after 6 months of supplement use.[52] It was suggested that the use of an MMN supplement as a first step, before more invasive therapies, may improve key physiological factors essential to fertility.[52] A later study has also looked at the pregnancy rate in women struggling to conceive after using an MMN supplement compared with folic acid alongside fertility treatment.[53] The pilot study found that the cumulative clinical pregnancy rate was significantly higher in the MMN group compared with folic acid alone (66.7% vs 39.3%), as was the ongoing pregnancy rate (60.0% vs 25.0%, respectively). Furthermore, significantly fewer attempts to become pregnant were necessary in the MMN supplementation group compared with folic acid alone. These results suggest that the use of an MMN supplement in women susceptible to micronutrient deficiencies may help optimize their reproductive health.[53]

Risk of adverse events with preconceptional MMN supplementation. To date, virtually no studies have reported any adverse events after using an MMN supplement in women trying to conceive. One trial did report a low incidence of some side effects, including slight nausea when taking the supplement on an empty stomach, constipation, headache, and spotting, but these were not considered significant compared with placebo.[51,52] Another study indicated a potentially increased risk of multiple pregnancy with a supplement that contained a whole range of vitamins and minerals (although the risk may be reduced by single embryo transfer),[34] but this association was not seen when only oral antioxidants were evaluated.[46] It should be noted that none of the MMN supplements used in women trying to conceive contained vitamins or minerals in doses higher than those recommended for use during pregnancy. Available safety data from the use of vitamins and/or minerals during preconceptional use indicate that supplementation is well tolerated,[54–56] although gastrointestinal adverse events have been reported with MMN supplementation.[54]

Conclusions

Micronutrients have essential roles in fertility, and inadequate levels can have an adverse impact on the ability to conceive. It has been reported that a proportion of women of childbearing age in general, as well as those who struggle to conceive, have lower than recommended levels of certain micronutrients. Thus, there is a rationale to supplement with vitamins and minerals before conception to optimize nutritional status and perhaps positively affect fertility. Although data on the effects of supplementation with multiple micronutrients are scarce, there is evidence to support a small but positive impact of

MMN supplementation in both healthy women and those having difficulties conceiving. Micronutrient supplementation can enhance the reproductive environment by helping restore micronutrients to recommended levels and strengthening the antioxidant defense system, thus ameliorating oxidative stress, with the clinical benefits of improving oocyte and embryo quality, reducing the time to conception, and increasing the chances of becoming pregnant. Supplementation with MMNs may be a good strategy to adopt in healthy women trying to conceive and in those with fertility problems. However, large, prospective, randomized, rigorously controlled trials are required to provide robust evidence for the benefits of MMN supplementation on fertility in such women.

Author Contributions

ES devised and conceived the data review. DN wrote and reviewed the data review.

Supplemental Material

Supplemental material for this article is available online.

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