Commentary: Multivitamins and early pregnancy loss

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Multivitamins containing folate, or folate-alone supplements, are widely recommended for women contemplating pregnancy or in the early weeks of gestation, because of incontrovertible evidence that folate reduces the risk of neural tube defects (NTDs).1,2 In this issue of IJE, Nohr et al.3 report a study of 35,914 women in the Danish National Birth Cohort in which consumption of folate-containing multivitamin preparations in the periconceptional period was associated with a modest, but increased, risk of miscarriage in the early weeks of pregnancy, when compared with women who took no supplements.

As concluded by the authors, it is critical that the data are not interpreted by health professionals or women contemplating pregnancy, or already pregnant, as evidence against current recommendations for folate supplementation. Neither is there strong enough reason to conclude that folate-only supplements should be preferred over multivitamins. Whereas the authors found no evidence that the use of supplements restricted to folate alone was associated with early fetal loss compared with women taking no supplements, there was less confidence in this result because of the small percentage of women taking the single supplement (6.2% compared with 62.1% taking multivitamins). Perhaps of most concern, not mentioned by the authors, was the high percentage of the Danish cohort (31.7%) not taking any form of folate supplementation during the periconceptional period, and the potential influence on the occurrence of NTDs.

Reports such as this of increased risk of early fetal death associated with pregnancy micronutrient supplementation, however modest, are obviously concerning. As noted by Nohr et al., they are not alone in...
observing this relationship. Czeizel’s original observation of an increase in miscarriage in Hungarian women, in a randomized controlled trial (RCT) of multivitamins containing 800 µg folic acid, was confirmed by Windham et al.5 in a Californian population, also using a mixture of vitamins. In contrast, data from a folic acid (400 µg) intervention study in China provided strong evidence against increased risk of miscarriage in 23,806 women,6 and a study from Sweden,7 of a population-based, matched, case-control study of women with spontaneous abortion, reported no association with the supplement use.

Nohr et al. have acknowledged two potential causes of supplement-related miscarriage suggested previously: first, that periconceptional multivitamin/folate supplements may increase the risk of twin pregnancies which, in turn, heightens the risk of early fetal loss; and, second, that normally unviable pregnancies may be prolonged, leading to excess risk of death after 8 weeks of gestation. As no information was available on twin pregnancies before 28 weeks of gestation or on early abortions, these potential causes could not be addressed in the present analysis. The relationship with increased twinning has nonetheless been widely disputed, owing to confounding by increased maternal age and the related use of assisted reproductive technologies associated with heightened occurrence of multiple pregnancy.8

Assumption of causality is always difficult in observational studies, but Nohr et al. obtained detailed information on potential confounders (parity, previous miscarriage, waiting time to pregnancy, use of infertility treatment, BMI, smoking and social status) in the majority of women, finding that the adjusted risk for early pregnancy loss was unaffected. This sub-group of women, however, showed a 5% bias towards those who had experienced fetal death, but adjustment only modestly reduced the risk of miscarriage. The authors ‘ran out of’ potential confounders to explain the relationship, although they acknowledge that an absence of detailed dietary information and physical activity could lead to residual confounding.

The reported protective influence of multivitamin supplements on later fetal death, although supported by potential benefits of folic acid on maternal disease of placental origin—for example, pre-eclampsia—is, in contrast to the influence on miscarriage, far less convincing and presents a rather confused picture. Appropriately, this is not highlighted by the authors.

The major strength of the study by Nohr et al. lies in the large size of the cohort, and the benefit of the detailed dataset afforded by the extraordinary depth and breadth of the Danish National Birth cohort. The lack of statistical confidence in the apparent absence of miscarriage risk in folate-only users leaves the reader wondering, without any strong evidence, whether there could be something peculiarly deleterious in multivitamin preparations. Without measurement of blood folate, differences in folate status between groups could be a factor. Indeed, the dose of folate in the multivitamin supplements generally used (200 µg) in the Danish National Birth Cohort was lower than that recommended for folate-alone supplements (400 µg). Is it possible that women taking multivitamins rely on the vitamins for a ‘healthy diet’ and eat a poorer diet leading to worse folate status than those taking no supplements? The dietary data available were not adequately detailed to address this, but alone it could hardly account for the increased risk of miscarriage. None of the components of multivitamin supplements are likely to be directly harmful; the daily doses are within accepted recommendations, and because no other explanation springs to mind, one is led back to the possibility of residual confounding. A study of vitamin A supplementation in women in Nepal reported an increase in twin pregnancies,9 but the doses were an order of magnitude higher than those in the Danish women. The authors are rather alarmist in writing that although ‘studies have shown that supplements of vitamins in well-nourished people may increase the risk of cancer and overall mortality’…‘women are advised to take multivitamins when planning to conceive believing it can do no harm’. Perhaps this could have been qualified by adding that studies suggesting harm used high, non-physiological, doses of vitamins.

In conclusion, as in many observational studies, the authors rightly recommend that further studies are needed. These should include well-designed RCTs which compare pregnancy outcomes, particularly early fetal loss, in women taking multivitamins in the periconceptional period and in pregnancy with those taking folate alone, including measurement of folate status. In the meantime, the data should be assimilated into meta-analyses, and supplements should be taken in accordance with current clinical guidelines.

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References


