Few factors have been identified as causes of multiple births.\(^1\) Ovulation-inducing drugs are known to substantially increase the rate, but this is likely to explain only a minority of all occurrences. A number of other conditions have been found to be associated with multiple birth, including seasonality at birth, maternal age, social class, and diet.\(^1\) However, the evidence relies nearly exclusively on observational studies, since very few randomized interventions have been undertaken in the periconceptual period which are large enough to enable the study of a rare outcome such as multiple birth.

Until recently there was only evidence available from one such trial with a dietary intervention which was conducted in Hungary and published in 1992.\(^2\) More than 4000 women were randomized to receive either a supplement containing different vitamins, minerals and trace elements or a supplement containing the trace elements only plus minute amounts of vitamin C, from at least one month prior to conception until the second missed menstrual period or later. The authors found a reduced occurrence of neural tube defects in the vitamin/mineral group (0 versus 6 cases), a finding which has contributed to current policies for preventing neural tube defects. A few years later, and more relevant to this commentary, the authors published results showing a significantly higher rate of twins in the group receiving vitamins and minerals, 3.8% versus 2.7%, which was an unexpected finding.\(^3,4\) The statistical power to differentiate between effects on dizygotic and monozygotic twin rates was limited, but both twin types tended to be increased in the intervention group. These results prompted an analysis based on five observational data sets collected in the US, where periconceptual use of dietary supplements had been assessed retrospectively after birth. In this exploratory analysis, published in 1997,\(^5\) four of the five studies exhibited a positive association between the twin rate and use of multivitamins from 1 month before to 3 months after conception. When exposure was defined as only comprising post-conceptional supplement use, the associations got weaker or disappeared, a pattern which was interpreted to reflect an effect on twinning rather than an effect on viability of twin pregnancies.

Katz’s et al.’s report\(^6\) in this issue of the journal is based on a mega-trial conducted in a poor rural area of Nepal. The main finding of this randomized trial was a lower incidence of maternal deaths within 12 weeks of delivery in the two groups receiving vitamin A and beta-carotene compared to the placebo group (33, 26, and 59 deaths, respectively) which opened novel

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**Commentary: Does use of food supplements influence the twin rate? New evidence from a randomized controlled trial**

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and promising perspectives for prevention of maternal mortality and also created some controversy.\textsuperscript{7,8} In the present paper the authors focus on multiple birth as an outcome. They describe a relatively high rate of multiple births in this population of Nepal (12 per 1000 births in the control group), whereas mortality patterns among twins and triplets were similar to what could be expected from earlier studies. These data contribute important information to the epidemiology of multiple births. The most intriguing finding, however, is the differential occurrences of twin births seen across the intervention groups. Thus, twins occurred at a higher rate in the groups receiving retinol (99/5591) and beta-carotene (89/5148) than in the placebo group (65/5146). As in the Hungarian trial, it was not possible to say if the increased twin rate was due to generation of more twin conceptions or to greater survival among twin conceptions, and neither did the data permit a differentiation between effects on monozygotic versus dizygotic twin rates.

Which substance(s) could be the causative factor(s)? The observational study focused on multivitamins in general,\textsuperscript{9} whereas the common denominator of the two trials was retinoids. In the Nepal trial 23 300 IU of pre-formed vitamin A and 42 mg of all trans beta-carotene were given per week to the women in the two intervention groups, respectively.\textsuperscript{7} In the Hungarian trial, 4000 or 6000 IU (in first and latter part of the trial, respectively) of pre-formed vitamin A was given per day (along with a number of other vitamins and minerals).\textsuperscript{2–4} It may also be that it was an unspecific effect of dietary supplementation rather than an effect due to a particular component of the supplement.

Two other trials\textsuperscript{9,10} are worth mentioning, which together with the Hungarian trial,\textsuperscript{2} provide strong evidence regarding the preventive effect of peri-conceptional folic acid against neural tube effects. The MRC trial, published in 1991, recruited women who had had a baby with neural tube defects in an earlier pregnancy, and who wanted to get pregnant again.\textsuperscript{9} Two placebo-controlled regimens were tested simultaneously in a factorial design, 4 mg folate per day, and a cocktail with (other) vitamins and minerals until week 12 of gestation; the cocktail included 4000 IU pre-formed vitamin A per day. Folate substantially reduced the recurrence risk of neural tube defects. Later, the authors showed a non-significant difference in the twin rate in the folate versus non-folate groups, 7/593 versus 5/600 (P = 0.76) (no data were presented regarding the vitamin/mineral cocktail).\textsuperscript{11} A meta-analysis of the Hungarian and the MRC trial, plus another smaller randomized trial, exhibited an odds ratio of 1.40 (95% confidence interval 0.93–2.11) of twin pregnancies after peri-conceptional folic acid supplementation.\textsuperscript{12} The recent China-US Collaborative Project for Neural Tube Defect Prevention, where more than 200 000 Chinese women participated in a non-randomized intervention with periconceptional folic acid, is likely to provide decisive evidence regarding the impact of 0.4 g folate on the twin rate.\textsuperscript{10} Clarification of this matter is essential since, in many countries today, women who wish to get pregnant are advised to take this amount of folic acid to prevent neural tube defects.

In recent years large observational pregnancy cohorts have also been established in several countries. The Danish National Birth Cohort is by far the largest: it intends to recruit 100 000 pregnant women, and at the time of writing 65 000 women had been recruited. Peri-conceptional use of food supplements is recorded at recruitment, which typically takes place in week 6–10 of gestation. The data are likely to contribute important information regarding several of the issues discussed here.

Acknowledgement

The author is supported by the Danish National Research Foundation and the March of Dimes Birth Defects Foundation.

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