

Periconceptional intake of vitamins and fetal death: a cohort study on multivitamins and folate

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Background Women planning to conceive are often advised to take multivitamins. Whether this affects the survival of the fetus is not known.

Methods We used data from 35 914 women in the Danish National Birth Cohort who at recruitment had reported the number of weeks of supplement use during a 12-week periconceptional period. A telephone interview provided information about maternal characteristics and data on fetal death came from registers. The associations between periconceptional multivitamin or folate-only use and early (<20 weeks) and late (\geq 20 weeks) fetal death were estimated by hazard ratios (HR) with 95% confidence intervals (CI). Follow-up started at 8 completed weeks of gestation, and comparisons were made with no supplement use at any time during the periconceptional period.

Results Any multivitamin use was associated with a small increased crude risk of fetal death [HR 1.12 (1.01–1.25)], which was restricted to early losses [HR 1.18 (1.05–1.33)] compared with late losses [HR 0.82 (0.62–1.10)]. Adjustment for maternal factors increased this excess risk further. Whereas regular users of multivitamins (4–6 weeks of 6) before conception had more early losses [HR 1.29 (1.12–1.48)], a decreased risk of late losses was indicated when use started after conception [HR 0.65 (0.39–1.09)]. Folate-only use was not associated with fetal death.

Conclusions Multivitamin use was associated with a modest increased risk of early fetal death. For late fetal death, regular supplement use after conception may decrease risk, but numbers were small. Further studies on preconceptual multivitamin use are needed to guide public health recommendations.

Keywords Multivitamins, folic acid, dietary supplements, fetal death, stillbirth, spontaneous abortion, cohort study

Introduction

Conception, implantation and early development of the fetus and placenta require energy and micronutrients, including vitamins,^{1–5} but the optimal doses and combinations are still largely unknown. Previous studies of periconceptional use of multivitamins in well-nourished women indicate a beneficial effect on the incidence of preeclampsia,^{6,7} intrauterine growth restriction and preterm birth,^{8,9} possibly operating by affecting the early development and function of the placenta.^{10–12} If so, it may be hypothesized that periconceptional use of multivitamins also lowers the risk of late fetal death,^{13–17} as several studies indicate that late fetal death shares a common underlying aetiology related to early placental dysfunction with these outcomes.^{15,17–19}

Supplementation with folate, either as a single supplement or included in a multivitamin product, is recommended before and early in pregnancy, mainly because the protective effect on neural tube defects is believed to require more folate than is provided by a prudent diet.^{20–22} However, justification of periconceptional multivitamin use is still controversial, partly due to the possible increased risk of twinning.^{23,24} Also, some studies,^{25,26} but not all,^{27,28} indicate a modest increased risk of fetal death after periconceptional multivitamin use which seems unrelated to the content of folate.^{29,30} A Cochrane review stated that multivitamin use during pregnancy was not associated with either increased or decreased risk of fetal death,²³ but only few included studies allowed assessment of periconceptional use and the power to evaluate stillbirth risk was low.

Several studies in the general population have shown that supplements of vitamins in well-nourished people may increase the risk of cancer^{31–33} and overall mortality.^{33–35} Nevertheless, women are advised to take multivitamins when they plan to conceive, believing it can do no harm. It is therefore of importance to estimate any effects of early multivitamins on the entire range of pregnancy outcomes. We used data from the Danish National Birth Cohort (DNBC) to examine the association between periconceptional multivitamin or folate-only use and risk of early and late fetal death, accounting for timing of use and important maternal factors.

Methods

Study population

The DNBC is a nationwide study of 100 419 pregnancies among 92 374 women recruited in 1996–2002. In the second round of enrolment, women completed a revised version of the recruitment form where they were asked about supplement use week by week (45 040 pregnancies). Women with an uncertain recruitment date or who joined the cohort before 5 weeks of gestation were excluded ($n=505$) as were

women with unknown pregnancy outcome ($n=9$). Women who reported only single supplement use (other than folate) or did not report weeks of use were also excluded ($n=8550$). Finally, we excluded 64 pregnancies that were aborted before follow-up started at 8 completed weeks of gestation. The final study population consisted of 35 914 pregnancies among 35 172 women.

Measures

The recruitment form was returned at approximately 11 weeks of gestation (interquartile range 9–14 weeks). It provided a form with week by week boxes to report supplement use by type and frequency from 4 weeks before the last menstrual period (LMP) through 14 weeks after the LMP. We defined the periconceptional period in weeks as LMP–4 through LMP+8, and this period was further categorized as a 6-week preconception period (LMP–4 to LMP+2) and a 6-week postconception period (LMP+3 to LMP+8) (Figure 1). For the 3308 women recruited during gestation weeks 5, 6 and 7, we imputed supplement use for the remainder of the periconceptional period based on use reported during the week of enrolment. The contents of the most commonly used multivitamin use in the study period are provided in Table 1. The recommendations regarding folate-only use was 400 µg/day.

Use of multivitamins was defined as any use in each of the 12 weeks comprising the peri-conceptional period. We also computed duration of multivitamin use for the pre- and post-conception periods as the reported number of weeks of use, which was categorized into non-users and users in 1–2 weeks, 3–4 weeks, and 5–6 weeks relative to the 6 weeks comprising each of these periods. Finally, we defined women with different patterns of multivitamin use based on either no use, partial use (1–3 weeks) or regular use (4–6 weeks) in either the pre or post-conception period. This led to the following categories (pre/post use): regular/regular; partial/regular; no/regular; no or partial/no or partial; no/no (reference). For folate-only users, we generated the same variables.

A fetal death was defined as a non-deliberate demise of an intrauterine pregnancy and included

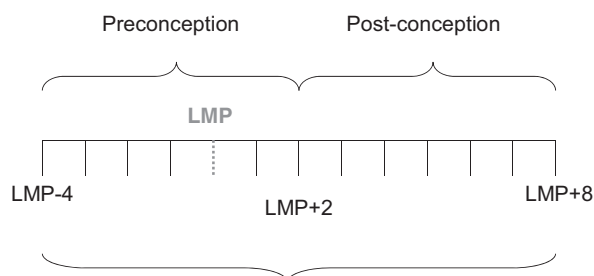


Figure 1 Periconceptional exposure period

Table 1 Contents of the most commonly used multivitamin supplement, Danish National Birth Cohort 1996–2002

Nutrient	Content (unit)
Vitamin A	800 mcg
Thiamin (B ₁)	1.4 mg
Riboflavin (B ₁₂)	1.6 mg
Vitamin B ₆	2 mg
Vitamin B ₁₂	1 mcg
Folic acid	200 mcg
Niacin	18 mg
Pantothenic acid	6 mg
Vitamin C	60 mg
Vitamin D	5 mcg
Vitamin E	10 mg
Iron	14 mg
Zinc	15 mg
Copper	2 mg
Iodine	150 mcg
Manganese	2.5 mg
Chromium	50 mcg
Selenium	50 mcg
Molybdenum	150 mcg

spontaneous abortions and stillbirths leading to hospital admission. These were identified together with live births, induced abortions, ectopic pregnancies and hydatidiform mole by linking the Civil Registration Register, the National Birth Register and the National Hospital Discharge Register using the mother's civil registration number. The estimate of gestational age was based on the LMP as reported by the woman at recruitment and was validated in case of unlikely estimates.

At recruitment, women agreed to participate in four telephone interviews. The first took place at approximately 17 weeks of gestation (interquartile range 14–21 weeks), and it was possible to reach 92.5% of the women in the present study. If the woman was no longer pregnant, she was offered a slightly modified interview, which was accepted by 766 women. From these two interviews, we defined pregnancy-related covariates including parity, previous miscarriages, waiting time to pregnancy, use of infertility treatment, prepregnancy body mass index (BMI, kg/m²), smoking and social status (Table 2).

A second interview at approximately 30 weeks of gestation provided information about nausea in the first 8 weeks of pregnancy, and from 185 women with fetal death (mainly late) we had the same information reported retrospectively. For women who were still pregnant in mid-pregnancy, including 87 with late fetal death, dietary data were available from a

mail-distributed and validated food frequency questionnaire.³⁶ Diet was characterized as 'Western' (high-fat dairy and red meat), 'health conscious' (intake of fruits and vegetables, poultry and fish) and 'intermediate' as previously reported.³⁷

Statistical analysis

To illustrate risk of fetal death over duration of gestation, we first calculated rates of fetal death according to use of multivitamins and folate-only supplements for the following periods: 8–11 weeks, 12–19 weeks, 20–27 weeks and 28 weeks+. Follow-up started at gestational day 56 (8 completed weeks) and ended at the time of fetal death, live birth, induced abortion, hydatidiform mole or emigration. Multiple pregnancies ($n=766$) were coded as live births if all ($n=761$) or just one ($n=5$) baby were born alive.

The risk of fetal death associated with any periconceptional multivitamin or folate-only use was estimated as hazard ratios with 95% confidence intervals using Cox regression with gestational days as the underlying time variable. When fetal death was divided into an early and late period at ≥ 20 completed weeks of gestation, which is in accord with the threshold used in other studies,²³ we found interaction between any multivitamin use and gestational age (crude analysis; $P_{\text{interaction}}=0.02$). In some models we therefore included an interaction term to present estimates for early fetal deaths (<20 weeks) and late fetal death (≥ 20 completed weeks) separately. Based on previous studies,^{7,9} we also examined for interaction by maternal weight (BMI ≥ 25), but this was not found.

We also evaluated the duration and timing of multivitamin use by entering pre- and post-conception use as categorical exposure variables, which were mutually adjusted to account for the fact that most women with preconception use were also users in the post-conception period. Next, we used the exposure variable for different patterns of multivitamin use. Non-users at any time were the referent for all models. These analyses were also carried out for folate-only use.

In adjusted analyses, we controlled for age, parity, prepregnancy BMI, smoking and social status. Because women with fertility problems or previous miscarriage may more often be early multivitamin users, we also adjusted for waiting time to pregnancy, infertility treatment and previous miscarriage.

In supplementary analyses, we restricted the analyses to nulliparous women with spontaneous pregnancies, a waiting time to pregnancy <6 months and no previous miscarriage. We also repeated all analyses after excluding 5024 pregnancies among multivitamin users where intake of single supplements other than folate was reported. Finally, we added adjustment for nausea and mid-pregnancy

Table 2 Maternal characteristics across patterns of periconceptional multivitamin and folate-only supplement use

	Total <i>n</i>	%	Non-users (<i>n</i> = 11 393) %	Multivitamin users (<i>n</i> = 22 285) %	Folate-only users (<i>n</i> = 2236) %
Total population	35 914		31.7	62.1	6.2
Early fetal death	1346	3.8	3.4	4.0	3.4
Late fetal death	206	0.6	0.7	0.6	0.6
Age at conception					
<25	4715	13.1	17.2	11.3	10.7
25–29	14 950	41.6	38.7	43.2	41.2
30–34	11 717	32.6	31.1	33.2	35.1
35+	4532	12.6	13.0	12.4	13.0
Parity					
Primiparous	16 503	49.9	44.1	52.2	55.2
Multiparous	16 587	50.1	55.9	47.8	44.8
Missing	2824				
Prepregnancy BMI					
<18.5	1416	4.4	4.3	4.4	4.5
18.5–24.9	21 530	66.1	62.9	67.5	67.5
25.0–29.9	6559	20.1	21.8	19.4	19.2
30+	3066	9.4	11.0	8.7	8.8
Missing	3343				
Waiting time to pregnancy					
Not planned	3900	11.8	18.4	9.1	6.3
Less than 6 months	19 982	60.5	57.2	61.9	63.6
6–12 months	4696	14.2	13.0	14.8	15.1
More than 12 months	4427	13.4	11.4	14.3	15.0
Missing	2909				
Infertility treatment					
No	30 916	93.4	96.6	92.0	92.6
Yes	2175	6.6	3.5	8.1	7.4
Missing	2823				
Previous miscarriage					
No	26 916	81.4	83.5	80.5	79.9
Yes	6147	18.6	16.5	19.5	20.1
Missing	2851				
Multiple pregnancies					
No	35 148	97.9	98.5	97.5	98.0
Yes	766	2.1	1.5	2.5	2.0
Social status					
High	17 555	53.3	43.9	57.2	60.7
Middle	12 245	37.2	42.5	35.1	31.4
Low	3150	9.6	13.7	7.7	8.0
Missing	2964				

(continued)

Table 2 Continued

	Total <i>n</i>	%	Non-users (<i>n</i> = 11 393) %	Multivitamin users (<i>n</i> = 22 285) %	Folate-only users (<i>n</i> = 2236) %
Smoking in pregnancy					
Non smoker	27 801	84.1	78.4	86.5	88.9
0–10 cig/day	4008	12.1	15.6	10.7	9.0
>10 cig/day	1245	3.8	6.0	2.8	2.1
Missing	2860				
Nausea in the first 8 GA weeks					
No	14 981	48.5	52.1	47.0	45.8
Yes	15 898	51.5	47.9	53.0	54.2
Missing	5035				
Maternal diet pattern					
Western	3559	15.5	20.1	13.4	13.8
Intermediate	15 140	65.9	67.0	65.5	63.7
Health conscious	4290	18.7	13.0	21.1	22.5
Missing	12 925				

Percentages are column percentages except for the first three rows. Columns percentages do not include missing values.

diet and restricted the analysis to women with prospectively collected information about confounders.

We used a correction for within-cluster correlation (robust standard errors) since 742 women contributed more than one pregnancy to the study. STATA 9.1 Special Edition (Stata Corporation, College Station, TX) was used for all statistical analyses.

Results

Overall, any multivitamin use was reported in 22 285 pregnancies (62.1%), folate-only supplementation in 2236 pregnancies (6.2%) and in 11 393 pregnancies (31.7%) no use of multivitamins, folate-only or any other single supplementation was reported during the periconceptional period (Table 2). Compared with non-users, multivitamin and folate-only users were more likely to be nulliparous, 25–35 years old and to have lower BMI. They reported more often planned pregnancies, a longer waiting time to pregnancy, more frequent use of infertility treatment and a history of miscarriage. They were less likely to smoke and to be of lower social status. Nausea in the first 8 weeks of pregnancy was more common among multivitamin and folate-only users who were also more likely to report a diet classified as health conscious. They had more multiple births, but not when infertility-treated women were excluded (1.20% in non-users, 1.26% in multivitamin users and 1.04% in folate-only users).

We observed 1552 fetal deaths in the study population [1346 early (<20 weeks) and 206 late (\geq 20 weeks)]. Rates of fetal death decreased steeply

across gestation from 49.8 per 10 000 weeks in weeks 8–11, 22.9 in weeks 12–19, 3.3 in weeks 20–27 and 2.8 from week 28 onwards (Figure 2). Compared with non-users, multivitamin users had higher rates before 20 weeks of gestation and lower rates thereafter, but with overlapping confidence intervals in the late period. Fetal death rates for folate-only users did not provide any clear pattern and was omitted from the figure.

For the entire period, multivitamin use was associated with a 12% increased crude risk of fetal death, restricted to early losses before 20 weeks of gestation [HR 1.18 (1.05–1.33)] as compared with losses thereafter [HR 0.82 (0.62–1.10), $P_{\text{interaction}}=0.02$] (Table 3). In the analysis restricted to women with confounder information, the crude risk of fetal death in multivitamin users was slightly higher than in the full sample, and this excess risk increased further after adjustment. The association between multivitamin use and late fetal death seemed slightly stronger in lean women [HR 0.79 (0.52–1.18)] and not present in overweight women [HR 1.17 (0.71–1.94)] with a ratio of hazard ratios of 1.49 ($P=0.23$). Thus, we had restricted power to examine this issue. Folate-only users had no excess risk at any time, but associations were estimated with large imprecision.

To examine the robustness of these findings, we repeated the analysis after excluding multivitamin users with single supplement use other than folate ($n=5024$). This decreased the risk of fetal death slightly [crude HRs 1.10 (0.98–1.23) for all fetal death; 1.15 (1.00–1.30) and 0.85 (0.63–1.15) for

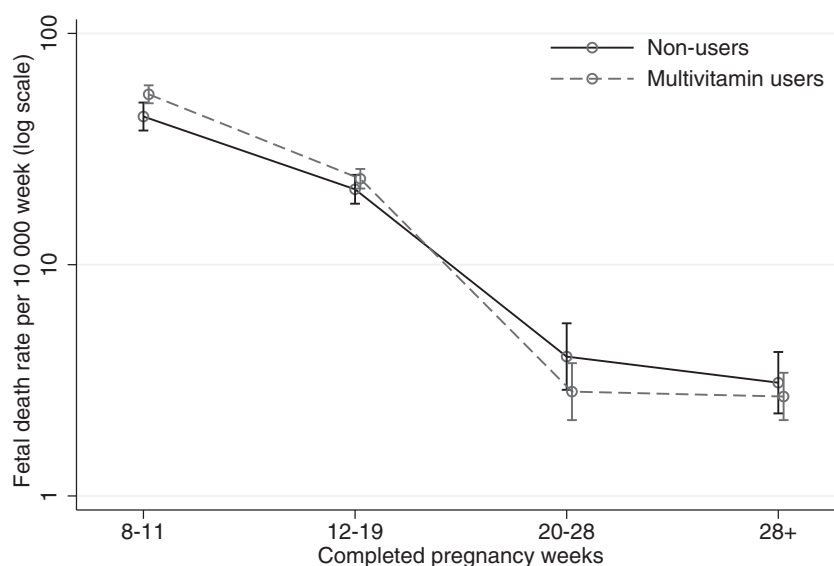


Figure 2 Events / 10 000 weeks according to any periconceptional use of multivitamins, i.e. expected number of fetal deaths when 10 000 women were followed for one week. $n=33\,678$; 1271 early and 193 late deaths

Table 3 Risk of fetal death according to any periconceptional multivitamin or folate-only supplement use

	Full population ($n=35\,914$; 1552 deaths)			Population with information about confounders ($n=32\,285$; 1018 deaths)		
	fetal death (n)	Crude HR	95% CI	Crude HR	Adj HR ^a	95% CI
All Fetal death (8 weeks+)						
Non user	461	1.00	ref	1.00	1.00	ref
Multivitamin user	1003	1.12	1.01; 1.25	1.18	1.23	1.06; 1.42
Folate-only user	88	0.98	0.78; 1.23	1.02	1.06	0.80; 1.40
Early Fetal death (8–20 weeks)						
Non user	385	1.00	ref	1.00	1.00	ref
Multivitamin user	886	1.18	1.05; 1.33	1.24	1.29	1.10; 1.52
Folate-only user	75	0.99	0.78; 1.27	1.03	1.07	0.78; 1.47
Late Fetal death (20 weeks +)						
Non user	76	1.00	ref	1.00	1.00	ref
Multivitamin user	117	0.82	0.62; 1.10	0.94	0.97	0.70; 1.35
Folate-only user	13	0.90	0.50; 1.62	0.98	1.01	0.53; 1.92

^aAdjusted for age, parity, pre-pregnancy BMI, socio-occupational status, smoking in pregnancy, waiting time to pregnancy, infertility treatment, and previous miscarriage.

early and late fetal death, respectively]. We also restricted the analysis to fertile nulliparous women with short waiting time to pregnancy and no previous miscarriage, but the excess risk in multivitamin users remained at the same or even higher levels. Adjustment for maternal diet pattern had no influence on the estimates, but could only be investigated in a sample where late fetal deaths accounted for 92% of cases. Adjusting for nausea in the first 8 weeks of pregnancy did not alter the observed associations although nausea in itself, as expected, was strongly

associated with a decreased risk of fetal death [adjusted HR 0.61 (0.44–0.83)].

In subsequent analyses, we examined risk of fetal death according to duration and pattern of multivitamin use. Compared with non-users and women with 1–2 weeks of preconception multivitamin use, risk of early fetal death increased slightly with increasing preconception use [crude HRs 1.23 (0.93–1.61) and 1.32 (1.09–1.60) for 3–4 and 5–6 weeks, respectively; $P_{\text{test for trend}}=0.002$] (Table 4). For post-conception multivitamin use, risk of early fetal death was

Table 4 Risk of fetal death according to timing and duration of multivitamin use in the pre- and post-conception periods (6 weeks + 6 weeks)

	Full population (<i>n</i> = 33 678; 1464 Fetal deaths).			Population with information about confounders (<i>n</i> = 30 241; 959 Fetal deaths)		
	At risk (<i>n</i>)	Crude HR ^a	95% CI	Crude HR ^a	Adj HR ^b	95% CI
Early Fetal death (8–20 weeks)^c						
No use at any time	10 905	1.00	ref	1.00	1.00	ref
Preconception use						
1–2 weeks	1604	0.96	0.71; 1.30	0.97	0.97	0.66; 1.43
3–4 weeks	1831	1.23	0.93; 1.61	1.16	1.18	0.83; 1.66
5–6 weeks	8602	1.32	1.09; 1.60	1.32	1.31	1.03; 1.66
Post-conception use						
1–2 weeks	3732	0.99	0.81; 1.21	1.13	1.17	0.92; 1.49
3–4 weeks	4933	1.28	1.08; 1.51	1.32	1.38	1.12; 1.71
5–6 weeks	12 550	0.94	0.77; 1.15	0.98	1.02	0.79; 1.31
Late Fetal death (20 weeks +)^c						
No use at any time	10 959	1.00	ref	1.00	1.00	ref
Preconception use						
1–2 weeks	1601	1.36	0.68; 2.73	1.44	1.44	0.68; 3.08
3–4 weeks	1795	0.53	0.18; 1.56	0.53	0.53	0.15; 1.85
5–6 weeks	8397	1.49	0.90; 2.47	1.86	1.83	1.11; 3.03
Post-conception use						
1–2 weeks	3691	1.18	0.78; 1.80	1.43	1.48	0.94; 2.32
3–4 weeks	4794	0.73	0.46; 1.15	0.85	0.88	0.54; 1.45
5–6 weeks	12 334	0.57	0.34; 0.96	0.53	0.55	0.32; 0.95

^aPre- and post-conception use are not exclusive and are mutually adjusted.

^bAdjusted for age, parity, pre-pregnancy BMI, socio-occupational status, smoking in pregnancy, waiting time to pregnancy, infertility treatment, and previous miscarriage.

^c1271 early fetal deaths and 193 late deaths in the crude analysis.

increased in women with 3–4 weeks of use compared with non-users [crude HR 1.28 (1.08–1.51)], but not in women with either lower or higher intensity of use. For late fetal death, a decrease in risk was seen across the two highest categories of post-conception use [crude HRs 0.73 (0.46–1.15) and 0.57 (0.34–0.96) for 3–4 and 5–6 weeks of use, respectively] but not with 1–2 weeks of use [crude HR 1.18 (0.78–1.80); $P_{\text{test for trend}} = 0.02$ across all four exposure groups]. Adjustment had very little effect on the crude estimates.

In the group of multivitamin users (62.1%), the following patterns of use were observed. Regular multivitamin use throughout the entire period was reported by 24.5%, 6.6% reported partial use before conception followed by regular post-conception use and 12.2% had no use before conception followed by regular use. Finally, 18.8% reported some combination of no use/partial use during the two periods. Compared with women with no use, only regular use throughout the periconceptional period was associated with increased risk of early fetal death [crude HR 1.29 (1.12–1.48)] (Table 5). For late fetal death, especially women where

regular multivitamin use was initiated after conception, seemed to have reduced risks of about 35–60%, but number of deaths was small. Again, adjustment had only minor effect on the crude estimates.

When the above analyses of duration and pattern of use were repeated in the much smaller sample of folate-only users compared with non-users, hazard ratios were estimated with large imprecision and no clear pattern (results available on request).

Discussion

We found a modest but consistent increased risk of early fetal death in multivitamin users, especially in women with a regular preconceptional intake. For late fetal death, we observed some indication of a beneficial effect of multivitamin use in women with regular use after conception, but interpretation should be made with caution due to the few cases in these analyses. Folate-only use was not associated with fetal death, but our ability to examine this exposure was limited by a relatively small number of users.

Table 5 Risk of Fetal death according to patterns of periconceptional multivitamin use

		Full population (<i>n</i> = 33 678; 1464 Fetal death).				Population with information about confounders (<i>n</i> = 30 241; 959 Fetal death)		
		At risk (<i>n</i>)	Fetal death (<i>n</i>)	Crude HR	95% CI	Crude HR	Adj HR ^a	95% CI
Early Fetal death (8–20 weeks)								
Preconception ^b	Post-conception ^b							
–	–	10 905	385	1.00	ref	1.00	1.00	ref
++	++	8578	380	1.29	1.12; 1.48	1.33	1.38	1.15; 1.66
+	++	2284	76	0.95	0.74; 1.23	0.96	1.02	0.73; 1.40
–	++	4260	168	1.14	0.95; 1.37	1.17	1.22	0.96; 1.54
– or +	– or +	6577	262	1.15	0.98; 1.35	1.27	1.32	1.08; 1.61
Late Fetal death (20 weeks +)								
Preconception ^b	Post-conception ^b							
–	–	10 959	76	1.00	ref	1.00	1.00	ref
++	++	8375	49	0.89	0.62; 1.27	1.03	1.06	0.71; 1.57
+	++	2270	6	0.40	0.17; 0.92	0.43	0.45	0.18; 1.13
–	++	4184	18	0.65	0.39; 1.09	0.66	0.69	0.38; 1.24
– or +	– or +	6468	44	0.99	0.68; 1.43	1.17	1.22	0.81; 1.82

^aAdjusted for age, parity, pre-pregnancy BMI, socio-occupational status, smoking in pregnancy, waiting time to pregnancy, infertility treatment, and previous miscarriage.

^bUse in the 6-week interval: – (no use); + (1 to 3 weeks; partial use); ++ (4–6 weeks; regular use).

The increased risk of fetal death in multivitamin users corroborates results from two other studies from affluent countries where periconceptional multivitamin use was associated with a modest increased risk of about 15% in interventional^{38,39} and observational designs.²⁶ Also, the excess risk was slightly higher for use that started prior to pregnancy rather than in pregnancy.²⁶ Another randomized trial in women with previous neural tube defects pregnancies showed no increased risk,^{40,41} but all studies were based on relatively small numbers and results were controversial.^{30,42,43} A Cochrane review from 2011 reported pooled estimates close to one for the association between periconceptional multivitamin use and both early and late fetal death.²³ It included the two randomized studies mentioned above^{37,39} and a small trial from India.⁴⁴

Other studies, based on observational data, reported 40–60% decreased risks of early fetal death in multivitamin users,^{27,28} but findings may well be biased by selection problems and differential recall of use and confounded by healthy behaviours and practices in this group. As expected, we found multivitamin users to be better educated and have healthier diets and lifestyles, all factors that may explain a decreased risk of late fetal death as well as the decreased risks of preeclampsia, small-for-gestational-age (SGA) and preterm birth that we have observed in the same cohort.^{7,9} However, any uncontrolled confounding of this type cannot explain the observed increased risk of early fetal death. Confounding may be present if very

health conscious women with low early weight gain and excessive physical activity or with some kind of morbidity related to poor fetal health more often took multivitamins or folate. We do not think this is the case; on the contrary we found that women with nausea, which is a marker of a healthy pregnancy,^{45,46} were more often multivitamin users. Only when nausea leads to a very poor diet, which is rare, this might be a problem. Users did more frequently report fertility problems and previous miscarriages, which are associated with increased risk of fetal death, but accounting for these factors did not change the results. It has been suggested that more multiple pregnancies in multivitamin users may explain the excess risk of fetal death.⁴⁷ Regrettably, we were not able to identify multiple pregnancies in fetal deaths before 28 weeks of gestation. In women with spontaneous pregnancies, we did not find multivitamin users to have more multiple births, but this does not exclude the possibility that they may have had more multiple pregnancies ending as spontaneous abortions. Some multivitamin users reported use of single supplements within the periconceptional window, typically before they started regular intake of multivitamins. Excluding these women from the analyses had no effect on the estimates either. We ran out of suggestions for confounding factors that may explain the observed association, and our ability to examine those we identified was not always optimal.

Information about use of supplements was provided by the women themselves, but reported prospectively

before the event under study. For some women, we extrapolated information on use from recruitment to the rest of the periconceptional window, but excluding these pregnancies from the analyses did not change the results. Information about most confounders was provided retrospectively for 74% of women with fetal death. We restricted the adjusted analyses to women with prospectively collected information and had similar effects on the crude estimates, indicating that differential recall of confounders was not a problem.

Selection bias of the adjusted estimates should be considered if multivitamin users with fetal death were more willing to participate in the interview than users with a live birth. We did observe a slight tendency in this direction, leading to a positive bias of 5% which means that the adjusted excess risk in multivitamin users should rather be 17% than 23%. For this reason, we chose to focus mainly on the crude estimates derived from the main study population although they may be slightly underestimated. We had close to complete follow-up, but regrettably no information about very early abortions. If multivitamin use delays the termination of less viable fetuses, this would lead to an apparent excess risk of fetal death after 8 weeks of gestation as observed in our study. However, we find this phenomenon less likely.

Although the excess risk of early fetal death that we observed may come with a decreased risk of more rare deaths later in pregnancy, the finding causes concern. With the available data, we were not able to explain why use of multivitamins, especially when taken in the preconception period, should increase risk of early fetal death. Adverse pregnancy outcomes have been observed with large doses of vitamins and other micronutrients,⁴⁸ especially vitamin A in early gestation,⁴⁹ but the concentration of these constituents is much lower in multivitamins. Apart from a decreased risk of low birthweight in multivitamin users, there is no convincing evidence from randomized trials of a

beneficial effect on pregnancy outcomes.⁵⁰ Our findings are based on observational data and need replication, especially in lower socio-economic groups, but they highlight the lack of evidence for periconceptional multivitamin use on risk of miscarriage and stillbirth.²³ It is, on the other hand, important to stress that this study does not provide evidence against use of folate supplements to reduce risk of neural tube defects and it is insufficient to change recommendations regarding multivitamins containing folate. Randomized trials and large observational studies, preferably preconceptional cohorts from different settings, are needed to guide public health recommendations.

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KEY MESSAGES

- Periconceptional multivitamin use (6 weeks before and 6 weeks after conception) has been associated with lower incidence of preeclampsia, of growth restriction and of preterm birth; however, there is evidence indicating a modest increased risk of fetal death after periconceptional multivitamin use.
- Using data from the Danish National Birth Cohort we related the timing and duration of periconceptional multivitamin use to risk of early and late fetal death.
- Regular periconceptional multivitamin use was associated with a modest increased risk of early fetal death (<20 weeks), but regular use after conception may decrease risk for late fetal death (>20 weeks).
- These findings are based on observational data, but highlight the lack of evidence for periconceptional multivitamin use on risk of miscarriage.
- It is important to stress that this study does not affect the recommendations to use folate supplements, either alone or in combination with multivitamins, to reduce risk of neural tube defects.

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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