Original Article

Dan Med J 2020;67(10):A11190665

Multivitamin intake does not affect the risk of preterm and very preterm birth

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Dan Med J 2020;67(10):A11190665

ABSTRACT

INTRODUCTION: The aim of this study was to assess the association between multivitamin intake during pregnancy and the risk of preterm birth and very preterm birth.

METHODS: The study population comprised 15,629 women from the Copenhagen Pregnancy Cohort with data on pregnancy multivitamin intake during their first trimester who gave birth to singletons from October 2012 to October 2016. Data on pregnancy multivitamin intake were linked to the Medical Birth Registry to identify the birth outcome. The main outcome measures were preterm birth before 37 weeks of gestation and very preterm birth before 32 weeks of gestation.

RESULTS: Among the included women, 85.6% had taken daily pregnancy multivitamins during their first trimester. We found no evidence that pregnancy multivitamin intake during the first trimester was associated with a decreased risk of preterm birth (adjusted odds ratio (OR) = 1.01; 95% confidence interval (CI): 0.77-1.33) or very preterm birth (adjusted OR = 1.06; 95% CI: 0.63-1.77). Stratification for BMI into < 25 kg/m^2 and ≥ 25 kg/m^2 did not alter these findings.

CONCLUSIONS: Pregnancy multivitamin intake during the first trimester was not associated with a decreased risk of preterm birth or very preterm birth among women in a high-income population.

FUNDING: none.
TRIAL REGISTRATION: not relevant.

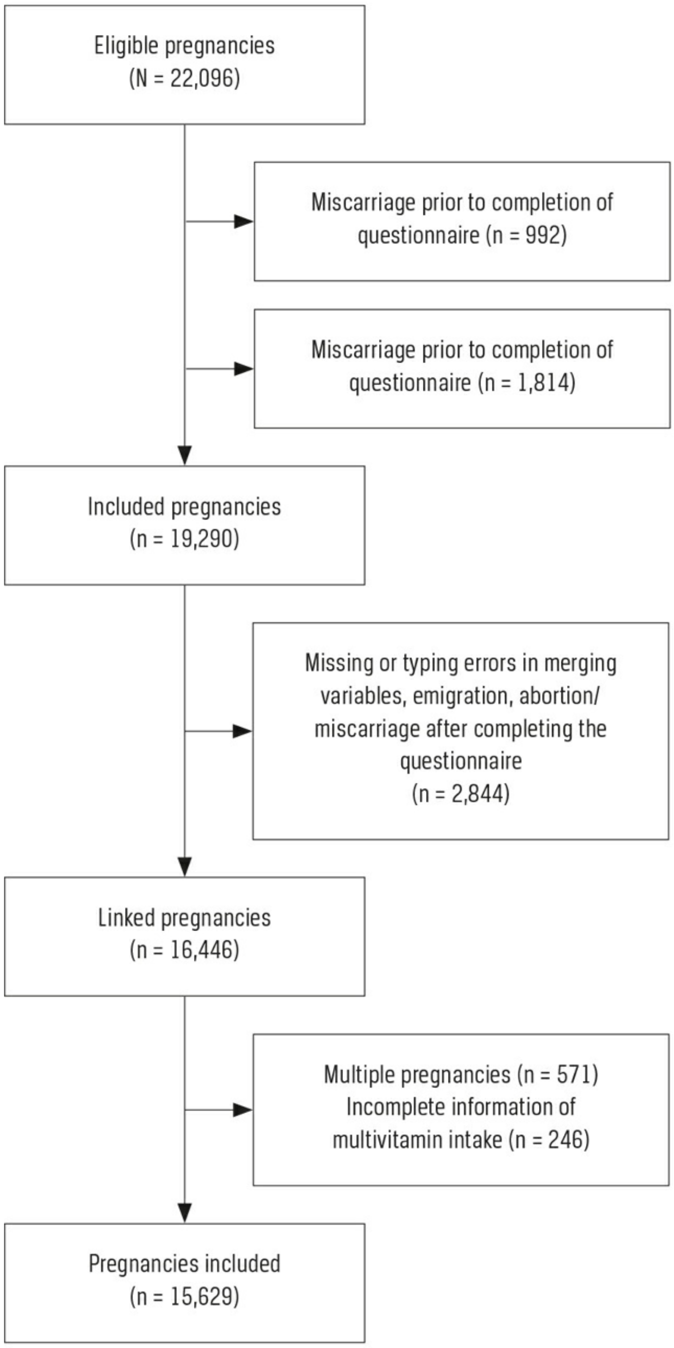
Preterm birth is the leading cause of neonatal morbidity and mortality, and of long-term disability in infants with no congenital malformations [1]. Nutritional status is known to play an important role in the pathogenesis of preterm birth [2]. In high-income countries, a healthy diet is widely available. However, many women tend to consume a low-quality diet with poor nutritional value, which leads to an inadequate vitamin and mineral intake during pregnancy, possibly resulting in preterm birth [3, 4]. A systematic review and meta-analysis found that dietary intakes of pregnant women from high-income countries did not align with the national recommendations [5]. In Denmark, a daily supplement of 400 µg of folic acid prior to pregnancy and until week 12 of gestation to prevent neural-tube defects is recommended [6]. In addition, a daily supplement of vitamin D is recommended throughout the pregnancy and supplementation of iron is recommended from gestational week 10 [6]. A recent systematic review and meta-analysis found that periconceptional multivitamin intake did not prevent preterm birth [7]. However, the authors stressed the need for additional data on multivitamin intake in pregnancy preferably from randomised controlled trials or large cohort studies with multiple confounder controls including BMI, assisted reproductive technology (ART), parity, smoking and use of alcohol and medicine [7]. Therefore, using data from the Copenhagen Pregnancy Cohort, we aimed to assess whether multivitamin intake during pregnancy was associated with a decreased risk of preterm birth. In addition, we aimed to assess whether multivitamin intake during pregnancy was associated with a decreased risk of very preterm birth as this has only been done once before to our knowledge [8].

METHODS

This prospective cohort study was based on analyses of data from the Copenhagen Pregnancy Cohort and reported according to The Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The Copenhagen Pregnancy Cohort represents women who scheduled an appointment for the combined first-trimester screening in the period from October 2012 to October 2016 at Rigshospitalet, Denmark. The department serves as a primary birth facility for women from a local catchment area as well as a tertiary referral hospital for the Eastern part of Denmark. The combined first-trimester screening programme is free of charge in Denmark and was attended by 95% of all women in 2016 [9]. All women who scheduled a combined first-trimester screening at Rigshospitalet in the study period (n = 22,096) received an email with a link to an online questionnaire in Danish and English with questions relating to socio-demographic characteristics, health and lifestyle factors. The information was transferred electronically to the women's medical records. The total response rate was 91.4%. A personal identification number issued to all Danish citizens made it possible to link women in the Copenhagen Pregnancy Cohort to the Medical Birth Registry in order to establish the birth outcome. Women with multiple gestations (n = 571) and women with incomplete information on multivitamin intake (n = 246) were excluded. The final study sample consisted of 15,629 singleton deliveries (**Figure 1**).

The online questionnaire that was pretested in 200 pregnant women using face-validity comprised items on multivitamin intake in pregnancy. Vitamin use was reported as 1) daily intake of a pregnancy multivitamin tablet at the time of conception, 2) daily intake of a pregnancy multivitamin tablet at the time of completing the questionnaire, 3) no intake of a pregnancy multivitamin tablet at the time of conception and 4) no intake of a pregnancy multivitamin tablet at the time of completing the questionnaire. Periconceptional multivitamin intake was defined as daily intake at the time of conception and at the time of completing the questionnaire. Postconceptional intake was defined as daily intake only at the time of completing the questionnaire. Finally, any multivitamin intake was defined as intake in the peri- or postconceptional period. Women without intake of multivitamins at conception or at the time of completing the questionnaire served as reference for all models. Multivitamin intake was self-reported in the first trimester of pregnancy at the time of completing the questionnaire.

FIGURE 1 / Flow chart of the study population.



The primary outcome was preterm birth defined as delivery before 37 completed weeks of gestation. The secondary outcome was very preterm birth defined as delivery before 32 completed weeks of gestation. Gestational age was assessed upon delivery based on ultrasound measurement of crown-rump length in the first trimester. All outcomes were extracted from the Danish Medical Birth Registry, which holds information about all live and in Denmark from 1973 [10].

Statistical analyses were performed using SAS 9.4 software. Descriptive analyses were conducted to assess the distribution of the various confounders across each level of multivitamin intake. We used multivariable logistic regression analyses to test the association between multivitamin intake and preterm birth and very preterm birth adjusting for a priori identified potential confounders including maternal age, pre-pregnancy BMI, maternal educational level, chronic disease (hypertension, heart or lung disease diabetes mellitus, thyroid disorders, rheumatoid arthritis and psychiatric disorder), maternal smoking, maternal diet (conventional, vegetarian, vegan), use of ART and gestational age at recruitment [11-16]. Additionally, we stratified results by maternal pre-pregnancy BMI. We used a robust sandwich covariance matrix estimate to account for possible intra-cluster dependence in our models. This was done because 877 women were recorded with more than one pregnancy in the study. Adjusted risks are reported as odds ratios (ORs) with 95% confidence intervals (CIs). The study was approved by the Danish Data Protection Agency (R. no. RH-2016-202, I-Suite no: 04778) and by the Danish Patient Safety Authority for research purposes (R. no. 3-3013-1802/1/). Ethical approval is not required for registry-based studies in Denmark.

Trial registration: not relevant.

RESULTS

The questionnaire used in the Copenhagen Pregnancy Cohort was completed at a mean (± standard deviation) gestational age of 10.2 (± 2.1) weeks. Maternal characteristics are shown in **Table 1**. Very few women stopped the multivitamin intake once initiated (n = 121; 0.8%). Overall, 85.6% of the included women had taken multivitamins at some point during their pregnancy. Among women with a periconceptional multivitamin intake, 90.7% had a planned pregnancy compared with 67.0% among women with a postconceptional intake. Also, women with a periconceptional multivitamin intake were more likely older and non-smokers than women with a postconceptional multivitamin intake and compared with women without any multivitamin intake (Table 1). Among these women, the proportion of ART conceptions and chronic diseases was higher than in women with a postconceptional multivitamin intake and women without any intake. Women who reported a postconceptional intake of multivitamin differed from women without multivitamin intake by being younger and more often nulliparous. Furthermore, their alcohol intake was lower, and they smoked less, they were less likely to eat a vegetarian/vegan diet, to have planned their pregnancy and to have received ART. Within the cohort, the rate of preterm birth and very preterm birth was 4.9% and 1.3%, respectively.

TABLE 1 / Maternal characteristics of women included from the Copenhagen Pregnancy Cohort.

Indication	Multivitamin intake: periconceptional (n = 4,988)	postconceptional (n = 8,392)	none (n = 2,249)	p-value[a]
Maternal age, %				< 0.05
< 20 yrs	0.1	0.1	0.04	
20-35 yrs	75.4	80.8	76.9	
> 35 yrs	24.5	19.1	23.0	
Nationality, %				0.11
European	92.6	93.4	92.4	
Other	7.4	6.6	7.6	
Educational level				0.19
High school graduation, %	91.1	89.4	89.1	
10-11 yrs of elementary school, %	3.2	3.5	3.6	
7-9 yrs of elementary school, %	5.7	7.1	7.3	
Missing data, n	121	210	397	
BMI, pre-pregnancy				0.09
< 18.5 kg/m², %	5.9	6.1	6.0	
18.5-24.9 kg/m², %	77.8	77.2	77.6	
25-29.9 kg/m², %	12.1	12.4	12.0	
≥ 30 kg/m², %	4.2	4.3	4.4	
Missing data, n	4	14	25	
Assisted reproductive technology, %				< 0.001
Yes	20.8	6.0	8.3	
No	79.2	94.0	91.7	
Chronic disease, %				< 0.001
Yes	11.2	8.5	9.2	
No	88.8	91.5	90.8	
Degree of planning of pregnancy				< 0.001
Planned, %	90.7	67.0	72.7	
Neither planned nor unplanned, %	7.6	21.2	17.3	
Unplanned, %	1.7	11.8	10.0	
Missing data, n	58	105	180	
Maternal smoking status				< 0.001
Non-smoker, %	93.0	86.3	88.1	
Former smoker, %	6.1	12.0	10.1	
Current smoker, %	0.9	1.7	1.8	
Missing data, n	56	70	211	
Current alcohol consumption, %				< 0.001
None	97.8	97.2	95.5	
1-2 drinks/wk	2.1	2.6	4.2	
> 2 drinks/wk	0.1	0.2	0.3	
Dietary pattern				< 0.05
Conventional, diet, %	94.8	95.1	93.1	
Vegetarian/vegan diet, %	5.2	4.9	6.9	
Missing data, n	745	1,450	2,344	

a) χ^2-test.

A daily multivitamin intake any time during first trimester was not associated with decreased odds of preterm birth (OR = 1.01; 95% CI: 0.77-1.33) or very preterm birth (OR = 1.06; 95% CI: 0.63-1.77). This also applied to women with a peri- or postconceptional multivitamin intake (Table 2). When stratifying by BMI < 25 kg/m^2 and ≥ 25 kg/m^2, a trend towards lower odds of preterm birth was seen in the group of women with a BMI ≥ 25 kg/m^2 after postconceptional multivitamin intake (OR = 0.83; 95% CI: 0.54-1.26) (Table 3). In the group of women with a BMI < 25 kg/m^2, we found no associations between multivitamin intake and preterm birth or very preterm birth.

TABLE 2 / Association between multivitamin intake during pregnancy and risk of preterm or very preterm delivery.

		Preterm birth: < 37 wks of gestation			Very preterm birth: < 32 wks of gestation		
Multivitamin intake	N	n (%)	crude OR	adjusted OR (95% CI)[a]	n (%)	crude OR	adjusted OR (95% CI)[a]
None	2,249	106 (4.7)	1.00	1.00	30 (1.3)	1.00	1.00
Periconceptional	4,988	266 (5.3)	1.14	1.02 (0.84-1.25)	67 (1.3)	1.01	1.10 (0.76-1.58)
Postconceptional	8,392	383 (4.6)	0.87	0.98 (0.81-1.19)	103 (1.2)	0.88	0.95 (0.67-1.34)
Any	13,380	655 (4.9)	1.05	1.01 (0.77-1.33)	174 (1.3)	0.99	1.06 (0.63-1.77)

CI = confidence interval; OR = odds ratio.
a) Adjusted for maternal age, pre-pregnancy BMI, chronic disease, maternal diet, maternal educational level, use of assisted reproductive technology, maternal smoking, and gestational age at recruitment.

TABLE 3 / Subgroup analyses stratified on BMI. Association between multivitamin intake during pregnancy and risk of preterm or very preterm delivery.

		Adjusted OR (95% CI)[a]	
Multivitamin intake	n	BMI < 25 kg/m² (n = 12,930)	BMI ≥ 25 kg/m² (n = 2,699)
Preterm birth: < 37 wks			
None	2,249	1.00	1.00
Periconceptional	4,988	1.00 (0.80-1.25)	1.12 (0.72-1.72)
Postconceptional	8,392	1.04 (0.84-1.28)	0.83 (0.54-1.26)
Any	13,380	1.07 (0.79-1.47)	0.82 (0.46-1.48)
Very preterm birth: < 32 wks			
None	2,249	1.00	1.00
Periconceptional	4,988	1.05 (0.68-1.60)	1.21 (0.56-2.61)
Postconceptional	8,392	0.98 (0.66-1.46)	0.91 (0.42-1.97)
Any	13,380	1.04 (0.58-1.88)	1.22 (0.36-4.09)

CI = confidence interval; OR = odds ratio.
a) Adjusted for maternal age, pre-pregnancy chronic disease, maternal diet, maternal educational level, use of assisted reproductive technology, maternal smoking, and gestational age at recruitment.

DISCUSSION

Main findings

This large, prospective observational study yielded three main findings about the intake of pregnancy multivitamins for preterm birth and very preterm birth. First, we found that 85.6% of the included women had taken multivitamins any time during pregnancy. Second, we found that women taking multivitamins in the periconceptional period differed from women without any multivitamin intake and from women with postconceptional intake by being more likely to have received ART, to have planned their pregnancy, to be older and to have a chronic disease. Additionally, they were less likely to drink and smoke. Third, we found no associations between multivitamin intake during pregnancy and the risk of preterm birth or very preterm birth.

Strengths and limitations

The data on multivitamin use were collected during the first trimester which lowers the risk of recall bias. Of note, the data on postconceptional multivitamin use were collected prospectively with no risk of recall bias. Another strength is that in all cases the gestational age was based on ultrasound examination in the first trimester, which makes the diagnosis of preterm birth and very preterm birth very valid. To our knowledge, only two studies investigating the association between pregnancy multivitamin intake and preterm birth have a larger sample size, and these studies failed to adjust for ART [17, 18]. This is important because of the high rate of ART in Denmark, where 8% of the birth cohort in 2016 was born following ART [19]. Limitations include lack of ability to merge all questionnaires with the pregnancy outcome due to missing or incorrectly typed merging variables. Additionally, many values were missing for two of the co-variates (maternal educational level and maternal diet) used in the multivariable logistic regression analyses. However, we did not perform multiple imputation due to the possible relation to unmeasured confounders. The exact type of pregnancy multivitamin tablets used by the women in the cohort remains unknown, and we do not know whether they continued taking multivitamins throughout their pregnancy. In addition, we do not have data on preconception multivitamin intake, and we were unable to control for micronutrient deficiency prior to pregnancy. The data on multivitamin intake were self-reported; thus, bias due to social desirability may be present. However, 7% of the included women originated outside Europe (Table 1), and generalisability may therefore be limited as our cohort consisted mainly of Caucasians from a high-income country.

Interpretation

In line with the national recommendation in Denmark, we found that 85% of the women in the Copenhagen Pregnancy Cohort had a daily multivitamin intake during their first trimester. This is an important improvement compared with a previous report on folic acid intake [20].

In line with a recent meta-analysis including eight studies from high-income countries showing no effect on preterm birth (relative risk = 0.84; 95% CI: 0.69-1.03) [7], we found no association between multivitamin intake during pregnancy and preterm birth. However, our results conflict with results from the Danish National Birth Cohort where regular periconceptional multivitamin intake in women with a pre-pregnancy BMI < 25 kg/m^2 was found to be associated with a reduced risk of preterm birth [17]. In contrast, our results indicated a tendency for BMI ≥ 25 kg/m^2 to be associated with a reduced risk of preterm birth. We speculate that this discrepancy may be due to less smoking and a lower alcohol consumption in the Copenhagen Pregnancy Cohort than in The Danish National Birth Cohort as the rate of preterm birth and the socio-economic status of the women was similar in these two Danish cohorts.

Our results conflict with results from Scholl et al. who found a decreased risk of both preterm birth and very preterm birth after peri- and postconceptional multivitamin intake [8]. The study population of Scholl et al. consisted of very young, mainly black women from a low-income area in the US, which is very unlike our study population. In addition, the rate of preterm birth was three times higher in the Scholl population than in the Copenhagen Pregnancy Cohort and the number of smokers was more than double in the Scholl population. Lifestyle factors may possibly be seen as a proxy for nutritional status; and hence the effect of multivitamin shown by Scholl et al. only applies to women with a poor nutritional status. Additionally, ART was not included as a possible confounder and the gestational age was not based solely on early ultrasound, which makes the diagnosis of preterm birth less accurate. In line with our results, in a study based on the Danish National Birth Cohort, Catov et al. found that periconceptional multivitamin intake among overweight women was not associated with a decreased risk of preterm birth [17]. Also, in line with our results, they did not find postconceptional multivitamin intake to be associated with a decreased risk of preterm birth in either lean or overweight women.

CONCLUSIONS

We found a high frequency of multivitamin intake. The risk of preterm birth remained unchanged despite multiple confounder control and regardless of the period of multivitamin intake studied. Future research should focus on the prospective evaluation of multivitamin intake in high-income countries, preferably before as well as during pregnancy.

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Accepted: 22 June 2020

Conflicts of interest: none. Disclosure forms provided by the authors are available with the full text of this article at Ugeskriftet.dk/dmj

LITERATURE

1. Simmons LE, Rubens CE, Darmstadt GL et al. Preventing preterm birth and neonatal mortality: exploring the epidemiology, causes, and interventions. Seminars Perinatol 2010;34:408-15.
2. Girsen AI, Mayo JA, Carmichael SL et al. Women’s prepregnancy underweight as a risk factor for preterm birth: a retrospective study. BJOG 2016;123:2001-7.
3. Baker PN, Wheeler SJ, Sanders TA et al. A prospective study of micronutrient status in adolescent pregnancy. Am J Clin Nutr 2009;89:1114-24.
4. Goletzke J, Buyken AE, Louie JCY et al. Dietary micronutrient intake during pregnancy is a function of carbohydrate quality. Am J Clin Nutr 2015;626-32.
5. Blumfield ML, Hure AJ, Macdonald-Wicks L et al. Systematic review and meta-analysis of energy and macronutrient intakes during pregnancy in developed countries. Nutr Rev 2012;70:322-36.
6. Danish Health Authority. Graviditet: spis folsyre, jern, D-vitamin og eventuelt kalk som kosttilskud. www.sst.dk/da/udgivelser/2015/anbefalinger-for-svangreomsorgen (20 Aug 2018).
7. Wolf HT, Hegaard HK, Huusom LD et al. Multivitamin use and adverse birth outcomes in high-income countries: a systematic review and meta-analysis. Am J Obstet Gynecol 2017;217:404.e1-404.e30.
8. Scholl TO, Hediger ML, Bendich A et al. Use of multivitamin/mineral prenatal supplements: influence on the outcome of pregnancy. Am J Epidemiol 1997;146:134-41.
9. Føtodatabasen: National årsrapport 2016. www.dfms.dk/images/foetodatabase/Arsrapport_FOTO_2016_final_anonymiseret.pdf (20 Aug 2018).
10. Knudsen LB, Olsen J. The Danish Medical Birth Registry. Dan Med Bull 1998;45(3):320-3.
11. Helmerhorst FM, Perquin DAM, Donker D et al. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. BMJ 2004;328:261.
12. Kazemier BM, Buijs PE, Mignini L et al. Impact of obstetric history on the risk of spontaneous preterm birth in singleton and multiple pregnancies: a systematic review. BJOG 2014;121:1197-208; discussion 1209.
13. Kim SS, Mendola P, Zhu Y et al. Spontaneous and indicated preterm delivery risk is increased among overweight and obese women without prepregnancy chronic disease. BJOG 2017;124:1708-16.
14. Lawlor DA, Mortensen L, Andersen A-MN. Mechanisms underlying the associations of maternal age with adverse perinatal outcomes: a sibling study of 264 695 Danish women and their firstborn offspring. Int J Epidemiol 2011;40:1205-14.
15. Masho SW, Bassyouni A, Cha S. Pre-pregnancy obesity and non-adherence to multivitamin use: findings from the National Pregnancy Risk Assessment Monitoring System (2009-2011). BMC Pregnancy Childbirth 2016;16:210.
16. Shah NR, Bracken MB. A systematic review and meta-analysis of prospective studies on the association between maternal

cigarette smoking and preterm delivery. Am J Obstet Gynecol 2000;182:465-72.

17. Catov JM, Bodnar LM, Olsen J et al. Periconceptional multivitamin use and risk of preterm or small-for-gestational-age births in the Danish National Birth Cohort. Am J Clin Nutr 2011;94:906-12.
18. Johnston EO, Sharma AJ, Abe K. Association between maternal multivitamin use and preterm birth in 24 states, pregnancy risk assessment monitoring system, 2009-2010. Matern Child Health J 2016;20:1825-34.
19. Sundhedsdatastyrelsen. Sundhedsregistre. http://end2019.esundhed.dk/sundhedsregistre/MFR/Sider/MFR06A.aspx (26 Nov 2019).
20. Friberg AK, Jørgensen FS. Few Danish pregnant women follow guidelines on periconceptional use of folic acid. Dan Med J 2015;62(3):A5019.