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Paternal preconception folate intake in relation to gestational age at delivery and birth weight of newborns conceived through assisted reproduction

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Abstract

Research question—Studies in rodents have shown that paternal folate intake prior to conception is associated with pregnancy and offspring outcomes. The aim of this study was to assess whether those associations may apply to humans as well

Design and settings—We prospectively analyzed data from 108 couples participating in a preconception cohort of couples undergoing infertility treatment using their own gametes between

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2007 and 2017, and whose treatment resulted in 113 pregnancies during the course of the study. Paternal and maternal pre-conception folate intake was assessed with a validated food frequency questionnaire. Linear mixed models were used to assess whether paternal preconception folate intake was associated with gestational age at delivery and gestational age-specific birth weight, while accounting for correlated data and potential confounders.

Results—In a multivariable-adjusted model, a 400 μg/day increase in preconception paternal folate intake was associated with a 2.6 day longer gestation (95% Confidence Interval: 0.8, 4.3) after adjusting for potential confounders, including maternal folate intake. Similar associations were found for folate from food and supplements. Maternal folate intake was not associated with gestational age at delivery. Neither paternal, nor maternal folate intake were associated to gestational age-specific birth weight.

Conclusion—Higher paternal preconception folate intake was associated with slightly longer gestation among live births achieved through assisted reproduction. Or results suggest that preconception exposures of the father may have an impact on the health of his offspring and therefore, that preconception care should shift from a woman-centric to a couple-based approach.

Keywords

maternal folate; paternal folate; offspring birth weight; gestational age

Introduction

Folates are a group of water-soluble vitamins that occur naturally in foods such as legumes and dark green leafy vegetables. In the United States, folic acid, a synthetic folate, is added to cereal foods, and included as part of most multivitamin supplements, and represents a major source of folates. Folates act as substrates and cofactors in multiple biological reactions including DNA and RNA synthesis, cell replication, cellular signaling and regulation of gene expression through methylation. During pregnancy, folate requirements increase because of rapid cell proliferation involved in fetal and placental growth. To cover this increased need and prevent the incidence of neural tube defects (Lm et al., 2015), the recommended dietary allowances (RDA) for folate are 400 μg dietary folate equivalents (DFE) per day (US Center for Disease Control and Prevention, n.d.). However, whether the reproductive benefits of folate intake, before or during pregnancy, extend to other outcomes is still unclear (De-Regil et al., 2015).

There is a growing interest in the effect of parental health and lifestyle before conception on the outcome of the pregnancy (Fleming et al., 2018; Stephenson et al., 2018). We have previously reported that maternal preconception dietary and serum folate are related to a higher probability of live birth among couples undergoing infertility treatment (Gaskins et al., 2014, 2015). Furthermore, a meta-analyses including 8 RCTs and a Cochrane review including 31 trials concluded that maternal folic acid intake was associated with higher birth weight (Fekete et al., 2012; Lassi et al., 2013), although it was not associated with preterm birth (Lassi et al., 2013) or gestational age at delivery (Fekete et al., 2012).

Little is known about the potential role of paternal diet in general and of paternal intake of folates on pregnancy and offspring outcomes in particular (Fleming et al., 2018). Nevertheless, increasing evidence suggests that paternal preconception exposures may be important for the fate of the pregnancy and resulting offspring (Kim, et al., 2013; McCowan et al., 2011; Shah et al., 2010; Sinclair et al., 2014). Some studies have identified paternal age and obesity as risk factors for low birth weight (McCowan et al., 2011; Shah et al., 2010). Before a recently published study of 511 singleton pregnancies (Hoek et al., 2019), all the evidence regarding the association of paternal folate status with offspring health was limited to animal models (Watkins et al., 2014; Watkins et al., 2017). Hoek et al. found both low and high levels of paternal periconceptional red blood cells folate were associated with reduced embryonic growth trajectories in 303 pregnancies conceived spontaneously, but not in 208 after in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). We aimed to extend the evidence in this area by assessing whether paternal preconception folate intake is associated with the duration of the gestation and offspring birth weight in pregnancies achieved by assisted reproduction techniques. To test this hypothesis, we used data from an ongoing prospective preconception cohort study of couples undergoing infertility treatment, where comprehensive data on maternal and paternal preconception diet is collected.

Subjects and Methods

Study Population

The Environment and Reproductive Health (EARTH) Study is an ongoing prospective cohort started in 2004 focused on identifying environmental and dietary factors associated with human fertility. Subfertile couples seeking evaluation and treatment at the Massachusetts General Hospital (MGH) Fertility Center were invited to participate, and an approximately 60% of women and 40% of men agreed to participate and were enrolled. At enrollment, trained study staff measured the height and weight of each subject, and completed a general health questionnaire covering lifestyle, demographics, and reproductive history. Body mass index (BMI) was calculated as weight (kg) divided by the height squared (m^2). Time spent in physical activities in the previous year was self-reported using a validated questionnaire. Diet was assessed with a previously validated food frequency questionnaire (FFQ). For this study, we considered couples who had completed a diet assessment before a treatment cycle (IVF, ICSI, or intrauterine insemination [IUI]), or up to 12 weeks after the day of peak E2 in the treatment cycle that resulted in pregnancy as of October 2017. Of the 367 treatment cycles resulting in a live birth, 254 (69%) were excluded due to missing or mistimed diet information during the preconception period on either the father (N= 169) or the mother (N= 72), and 13 were excluded due to missing data on delivery outcomes. Excluded fathers were, on average, less physically active, were less often smokers, less often white and had higher adherence to the Prudent dietary pattern than included fathers (Supplemental Table 1). Excluded mother we less physically active as well. The use of IUI and ICSI, as well as the frequency of multiple gestation and pre-term birth was more common in included couples. All other baseline characteristics did not differ between included and excluded couples. The final sample consisted of 113 pregnancies from 108 couples which resulted in the birth of 142 newborns (85 singletons, 54 twins and 3 triplets) with complete data on maternal and paternal preconception diet and pregnancy

related characteristics. Informed consent was obtained from all participants. This study was approved by the Human Subject Committees at the Harvard T.H. Chan School of Public Health and MGH.

Dietary Assessment

Participants were asked to complete a previously validated FFQ and report how often, on average they had consumed 131 foods and beverages during the past year (Yuan, et al., 2017; Yuan, et al., 2017). The FFQ had nine categories for intake frequency, from never, to two or more servings per day. Multivitamin and supplements users were asked to specify the brand of multivitamin or supplement, the dose, and frequency of use. The nutritional content of each food and the specified portion size were obtained from a database of the United States Department of Agriculture (Haytowitz D, et al., 2012) and supplemented with information from food and supplement manufacturers as needed. Nutrients intakes were estimated by summing the nutrient contribution of all food and supplement items. Total folate intake was calculated as DFE to account for differences in absorption between natural and synthetic folate (Bailey, 1998; Suitor et al., 2000). The intake of vitamin B6, vitamin B12, and methyl donors such as choline, betaine, and methionine, was also derived from the FFQ. To reduce extraneous variation in intake, all the micronutrients were adjusted for total energy intake using the nutrient residual method (Willett et al., 1986). Folate intake with this questionnaire has been validated against prospective collected diet records (r=0.71), red blood cell folate levels (r=0.51) (Giovannucci et al., 1998), and plasma folate levels (r=0.63) (Jacques et al., 1993). Two dietary patterns were identified using principal component analysis: the Prudent pattern and the Western pattern, as described elsewhere (Gaskins, et al., 2012). A summary score for each pattern was calculated to reflect how closely each participant adhered to them (Gaskins et al., 2012). Higher score indicates higher adherence to the respective pattern.

Assessment of Outcomes

Live birth was defined as the birth of a neonate on or after 24-week gestation. Information on treatment protocol and perinatal outcomes (gestational age at delivery and birth weight) was abstracted from electronic medical records by trained research nurses.

Statistical analyses

We categorized the men and women in two groups according to their intake of total folate. We used Wilcoxon tests and Pearson Chi-squared tests (or Fisher’s exact test when appropriate) to test for differences in baseline characteristics according to folate intake. We used linear mixed models to examine the association of maternal and paternal total folate intake with both gestational age at delivery and gestational age-specific birth weight calculated using the LMS method suggested by Fenton (Fenton et al., 2007). In the models for gestational age at delivery, one random effect was included to account for correlations in outcomes between siblings from pregnancies of the same couple. In the models for birth weight, an additional random effect was included to account for correlations in outcomes between multiples from the same pregnancy. Total folate intake was modeled as a continuous variable and scaled to estimate an increase of 400 μg/day in paternal or maternal total folate intake. We also identified those newborns who of reference (Fenton et al., 2013), and estimated the odds ratio for being small for gestational age according to paternal and

maternal folate intake, using generalized estimating equations and accounting for correlations in outcomes between multiples from the same pregnancy and between siblings from pregnancies of the same couple.

Confounding was evaluated in three progressively adjusted models. The first set of models adjusted for a participants' own covariates: age, intake of vitamin B6 and B12, methyl donors (choline, betaine and methionine), and total energy, and dietary pattern scores (Prudent and Western patterns). Models for maternal folate intake were additionally adjusted for maternal BMI and smoking status. The second set of models additionally adjusted for partners' covariates: age and intake of total folate, other methyl donors, and total energy. Models for paternal folate intake were additionally adjusted for his female partner's BMI and smoking status. The third set of models additionally adjusted for treatment and pregnancy related characteristics: primary infertility diagnosis (male, female or unexplained), type of infertility treatment (IUI, IVF or ICSI), and multiple pregnancy (singleton vs. multiple). Non-linearity was evaluated by comparing models where folate intake was modeled as a linear term to models that included a linear, quadratic and cubic term for folate intake using a likelihood ratio test. Interactions of paternal folate intake with paternal BMI (continuous), paternal age (continuous), primary infertility diagnosis (male cause, female cause or unknown) and pregnancy plurality (singleton or multiple) were evaluated introducing each of the interaction term in the fully adjusted model. To evaluate the robustness of our findings, we performed sensitivity analyses where we restricted the analysis to 1) participants whose folate intake was between the 5^{th} and 95^{th} percentile of the observed intake distribution and 2) participants whose dietary information had been received before the treatment cycle started. All analyses were conducted in SAS v9.3 (SAS Institute, Cary, NC).

Results

Fathers had a mean age of 36.5 years (standard deviation [SD] 4.8), and a mean BMI of 27.1 kg/m^2 (SD 3.7). Most men were Caucasian (93%) and had never smoked (41%). Mothers were a mean age of 34.4 years (SD 3.8) and had a mean BMI of 24.0 kg/m^2 (SD 4.7). Most women were also Caucasian (87%) and had never smoked (70%). Mean preconception folate intake, in DFE, was 989 μg/day (SD 537) among fathers, and 1797 μg/day (SD 670) among mothers. Most participants (56% of fathers, and 98% of mothers) were taking folic acid supplements. Male factor infertility was the most common primary infertility diagnosis among these couples (40%). The percentage of couples achieving pregnancy was 41% after ICSI, 40% after IVF, and 19% in IUI cycles. Most of the pregnancies were singleton (76%). There were 19 preterm births (18%), and the mean gestational age at delivery was 38.6 weeks (SD 2.3).

Men with higher folate intake also had higher intake of vitamins B6 and B12, lower total energy intake, and lower adherence to the Western dietary pattern (Table 1). Similar differences were found for their female partners. Maternal and paternal intakes of vitamin B6 (r=0.29), vitamin B12 (r=0.39), and adherence to both Prudent (r=0.40) and Western (r=0.46) dietary patterns' scores were positively correlated to each other. A smaller but still significant correlation was found for maternal and paternal folate intake (r=0.21). Paternal

folate intake was negatively related to his female partner's smoking status and her adherence to the Western dietary pattern, and positively related to his partner's intake of vitamin B6 and vitamin B12.

Paternal, but not maternal, folate intake was associated with a longer duration of pregnancy after accounting for correlations between multiples and adjusting for potential confounders (Table 2). Each 400 μg/d increase in paternal folate intake was related to a 1.7 day (95% CI: −0.1, 3.8) longer gestation in the crude model. This association became significant with additional adjustment for paternal characteristics and remained significant after progressive adjustment for maternal and pregnancy-related characteristics. In the fully adjusted model, a 400 μg/d increase in paternal folate intake was associated with 2.6 day (95% CI: 0.8, 4.3) longer gestation. Further adjustment for paternal race, BMI, and smoking status resulted in similar effect estimates (data not shown). In the fully adjusted model, the association between paternal folate intake and gestational age at delivery was similar for folate from food and from supplemental sources (data not shown). We found no evidence of non-linearity of this relationship. No significant independent association was observed for intakes of vitamin B6, vitamin B12, or methyl donors (choline, betaine and methionine). Maternal preconception folate intake was unrelated to duration of pregnancy in all analyses (Table 2). Moreover, neither paternal (OR 0.97 [IC 95% 0.68–1.40]), nor maternal (OR 0.59 [IC 95% 0.29–1.18]) preconception folate intake was significantly related to the risk of prematurity.

Neither paternal, nor maternal preconception folate intake was associated with gestational age-specific birth weight of the offspring (Table 3). Similarly, neither paternal (OR [95%CI]: 1.14 [0.79, 1.65]), nor maternal (OR [95%CI]: 1.83 [0.93, 3.59]) folate intake was associated with the risk of the offspring being small for gestational age after multivariable adjustment.

The association between paternal preconception folate intake and gestational age at delivery appeared to be stronger in multifetal pregnancies, couples with a primary diagnosis of male factor infertility, as well as for younger and leaner fathers (Figure 1). Statistically significant interactions, however, were only found for paternal BMI (p, interaction=0.046) but not for primary infertility diagnosis (p, interaction=0.12).

In sensitivity analyses, the association of paternal folate intake with gestational age at delivery remained significant when we excluded participants with extreme folate intakes (below the 5^{th} or above the 95^{th} percentiles), and when excluded participants whose diet was assessed after the treatment cycle leading to live birth had begun (Figure 2).

Discussion

We evaluated the relation between parental preconception folate intake and perinatal outcomes in a prospective cohort of subfertile couples undergoing infertility and treatment, and found that paternal, but not maternal, folate intake prior to conception was associated with longer duration of pregnancy (2.6 days for every 400 mcg/day increase in intake), after accounting for potential confounders, including maternal folate intake. Our findings parallel and refine emerging evidence that found that levels of paternal periconceptional red blood

cells folate levels were associated with embryonic growth trajectories (Hoek et al., 2019), because our results extend to couples undergoing a fertility treatment. Before that research, all the evidence in this area was reduced to studies in rodents, which reported that preconception folate status of males was related to placental development and offspring outcomes, independent of females' folate status (Kim et al., 2013; Lambrot et al., 2013). However, due to little previous evidence in human, the small size of the study, and the fact that all participants were undergoing infertility treatment, these findings should be interpreted with caution. It is therefore important that this question is addressed in other studies in order to determine whether it is generalizable to couples not undergoing medically assisted reproduction, and to fully characterize its nature and magnitude.

Previous studies in rodents demonstrated that males who were folate-deficient sired pregnancies with reduced placenta weights (Kim et al., 2011) and increased incidence of other abnormalities at the level of the placenta, such as fused placentas, that compromised fetal growth (Lambrot et al., 2013). It is thought that these effects are mediated through changes in the sperm epigenome (Kim et al., 2011), involving genes implicated in development and chronic disease (Lambrot et al., 2013). A recent study in mice reported that offspring fathered by a folate-deficient male showed differential expression of more than 300 genes in their placenta. Two of those genes, *Cav1*, a cell cycle regulator, and *Txndc16*,with function in cell homeostasis, were also differently methylated in male progenitor's sperm (Lambrot et al., 2013). Although DNA methylation is the most studied epigenetic modification, the underlying mechanism of epigenetic inheritance is still unknown (Vanhees et al., 2014). It is worth noting that studies in rodents have primarily focused on folate deficient vs. sufficient diets, whereas most of the men in our study met or exceeded the recommended folate intakes for general population. Hence, whether the underlying mechanisms suggested in experimental studies with rodents explain our findings needs to be determined.

In humans, the effect of folic acid on different crucial early stages of placental development is well documented (Timmermans et al., 2011; Williams, et al., 2011), but the evidence so far has largely focused on the effect of maternal, rather than paternal, folate intake. Our results are not in agreement with the meta-analysis (Fekete et al., 2012), and Cochrane review (Lassi et al., 2013) that found a positive association of maternal folate intake with offspring birth weight. Nevertheless, those studies did not account for paternal folate intake which, due to its correlation with maternal intake, could have resulted in confounding. Furthermore, one of the main outcomes in the meta-analysis (Fekete et al., 2012) was offspring birthweight instead of offspring gestational-age specific birthweight, which might have offered a more accurate approach to assess the specific effect of maternal folate intake independently of gestational age. Interestingly, a later meta-analysis (Hodgetts, et al., 2015) found that preconception, but not post-conception, maternal folate intake was associated with lower risk of small for gestational age. Since the potential effects of paternal exposures on pregnancy and offspring outcomes would be limited up to the conception, assessing whether these findings might be explained by confounding by paternal preconception folate status would be of high interest. The evidence regarding the effect of maternal folate intake on other outcomes, including the risk of preterm birth, is inconsistent (Mantovani, et al., 2014). Since preterm birth is an indirect measure of the length of a gestation with only two

categories (below or above 37 weeks of gestation), it would be important to assess whether the lack of significant results reported by several studies obscures an association that may be present when gestational age is modeled as a continuous variable.

An important limitation of this study was that 69% of the cycles that led to a live birth in the study were excluded from the analysis mainly due to non-participation by the male partner or missing paternal dietary data. For selection bias to occur in this study, selection into our analytical sample would have to be related to paternal folate intake and gestational age at delivery. Based on the 175 excluded men who had dietary information, there does not appear to be any differences in folate intake between included vs. excluded male participants. There does, however, appear to be a large difference in the incidence of preterm births between these two groups, although mean duration of gestation was similar. Thus, if there were any true differences in paternal folate intake (specifically, men with lower folate intake were less likely to be included in our study) and if there were any true differences in gestational length (specifically men who fathered longer pregnancies were less likely to be included in our study) - both of which are difficult to fully address given our available data - selection bias could be one potential explanation for our findings. This issue must be addressed by future studies. Diet assessment by FFQ is subject to measurement error. However, the FFQ we used relates well to biomarker levels (Giovannucci et al., 1998; Jacques et al., 1993; Yuan et al., 2017; Yuan et al., 2017). Moreover, associations previously identified with folate intake based on FFQ estimates have been subsequently replicated using biomarkers of intake in this population (Gaskins et al., 2014, 2015). Moreover, due to the prospective design of the study, measurement error would most likely be non-differential with respect to the outcomes, resulting in an attenuation of the observed associations. We acknowledge that the lack of information on individual's folate stores may represent another limitation. Because of the observational nature of the study, the possibility of residual confounding by lifestyle or other factors that were not measured, or poorly measured, must be considered. Thus, our findings need to be confirmed by a well-designed RCT before causality can be implied. We also acknowledge that small sample size may have affected the magnitude of the association, and the current study's findings may represent the upper bound of the true relation between paternal folate intake and gestation length. Since our study was restricted to couples undergoing infertility treatments, the results may not be generalizable to spontaneously conceived pregnancies. Still, these findings are interesting given the important contribution of infertility treatments to the frequency of preterm birth (Goldenberg et al., 2008; Jackson et al., 2004) and the growing utilization of these treatments in the US and Europe (Kamphuis et al., 2014). Strengths of this study include the prospective design, and the standardized assessment of lifestyle and dietary characteristics in both male and female participants, which increased the ability to adjust for confounders. More importantly, and despite the consequences for generalizability, conducting the study in a cohort of couples undergoing infertility treatment allowed precise timing of diet in relation to pregnancy initiation, and to obtain detailed information from the father; two design characteristics that are exceedingly uncommon in pregnancy cohorts.

In summary, we found that higher paternal folate intake prior to conception was associated with slightly longer gestation. On the other hand, we did not find that maternal folate intake was associated with gestational age at delivery. To our knowledge, this study represents the

first human evidence that paternal preconception folate status is associated with the length of the gestation, independently of maternal folate intake. However, given the limitations of the study, further investigations are needed to confirm and replicate these results in other populations. The implications of these findings are of great importance since, if confirmed, they suggest that preconception exposures of the father, including his diet and lifestyle choices, may have an impact on the health of his offspring and therefore, that preconception care should shift from a woman-centric to a couple-based approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key message

Higher paternal folate intake prior to conception was associated with slightly longer gestation. If confirmed, our results suggest that father's preconception exposures may impact on the health of his offspring.

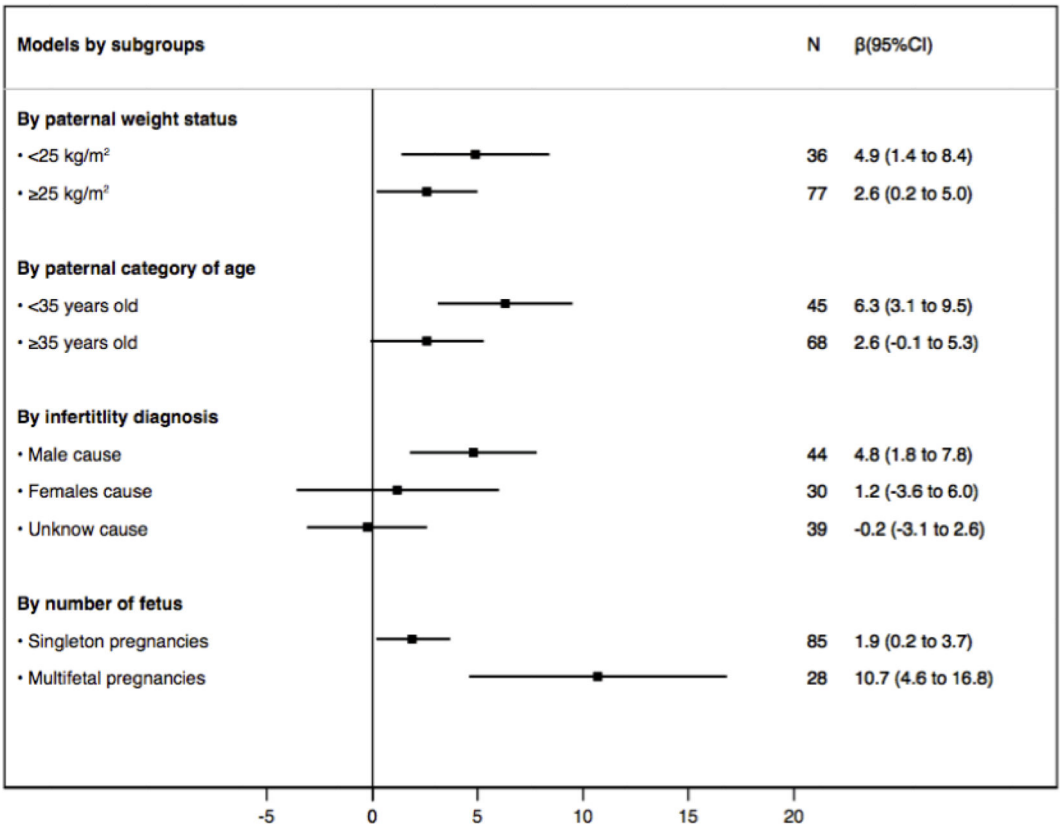

Figure 1. Adjusted difference (95% Confidence Interval) in gestational age at delivery (days) associated with a 400 µg/day increase in paternal folate intake (DFE)[a] by subgroups of paternal characteristics in the Environment and Reproductive Health (EARTH) Study (2007–2017). (N=113 pregnancies)[b].

Linear mixed models clustering for having rejoined the study (108 clusters; 5 participants had rejoined the study). All the models are adjusted for paternal characteristics: age (continuous), choline, betaine, methionine, vitamin b6, vitamin b12, and total energy intake (all continuous), and quality of the diet (2 dietary patterns identified in a factor analysis); maternal characteristics: age (continuous), folate, choline, betaine, methionine and total energy intake (all continuous), bmi (continuous), and smoking status (0= never smoke; 1= ever smoke); and infertility diagnosis (0=male; 1=female; 2=unknown), type of infertility treatment (0=IUI; 1= IVF; 2=ICSI), and multiple pregnancy (0=no; 1=yes).

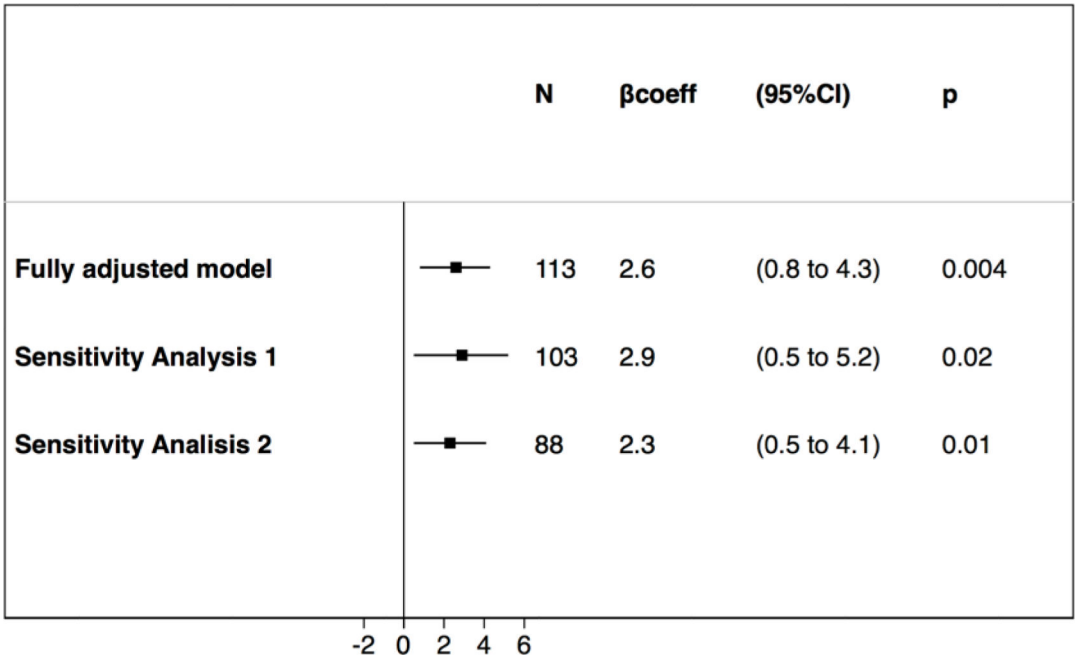

Figure 2. Sensitivity analyses for the difference (95% Confidence Interval) in gestational age at delivery (days) associated with a 400 μg/day increase in paternal folate intake (DFE) in the Environment and Reproductive Health (EARTH) Study (2007–2017).

Linear mixed models clustering for having rejoined the study (108 clusters; 5 participants had rejoined the study. All the models are adjusted for paternal characteristics: age (continuous), choline, betaine, methionine, vitamin b6, vitamin b12, and total energy intake (all continuous), and quality of the diet (2 dietary patterns identified in a factor analysis); maternal characteristics: age (continuous), folate, choline, betaine, methionine and total energy intake (all continuous), bmi (continuous), and smoking status (0= never smoke; 1= ever smoke); and infertility diagnosis (0=male; 1=female; 2=unknown), type of infertility treatment (0=IUI; 1= IVF; 2=ICSI), and multiple pregnancy (0=no; 1=yes).

Sensitivity Analysis 1: Restricted to participants within the 5^{th} and 95^{th} percentiles of folate intake.

Sensitivity Analys1s 2: Restricted to participants whose dietary information was collected before the cycle started.

Table 1.

Baseline characteristics[a] of the participants (108[b] men and 108[b] women) in the Environment and Reproductive Health (EARTH) Study (2007–2016) by paternal and maternal folate (DFE) intake (μg/day).

	Paternal folate intake (DFE)		
	< 900 μg/d (N=54)	**>= 900 μg/d (N=54)**	**p[c]**
Paternal characteristics:			
Age (years)	36.2 (3.9)	36.9 (5.6)	0.74
BMI (kg/m^2)	27.3 (3.9)	26.8 (3.4)	0.61
Physical Activity (MET h/week)	52.0 (61.8)	53.4 (72.6)	0.76
Smoking (ever smoker)	23 (42.6)	21 (39.9)	0.70
Race (white)	50 (92.6)	50 (92.6)	0.99
Folic Acid (DFE) (μg/d)	557 (140)	1421 (428)	<0.001
Choline (mg/d)	332 (65.2)	336.2 (51.6)	0.78
Betaine (mg/d)	97.8 (67.2)	113.1 (57.5)	0.50
Methionine (g/d)	1.8 (0.4)	1.8 (0.4)	0.91
Vitamin B12 (μg/d)	18.9 (95.5)	53.3 (131)	<0.001
Vitamin B6 (mg/d)	2.6 (3.3)	13.6 (33.4)	<0.001
Prudent dietary pattern	−0.3 (0.9)	−0.2 (0.9)	0.48
Western dietary pattern	0.3 (1.0)	−0.1 (1.0)	0.01
Energy (kcal/day)	2071 (555)	1863 (571)	0.03
Maternal characteristics:			
Age (years)	34.4 (3.3)	34.5 (4.2)	0.84
BMI (kg/m^2)	23.8 (5.4)	24.1 (3.9)	0.25
Physical Activity (MET-h/week)	45.9 (72.9)	48.4 (52.1)	0.56
Smoking (ever smoker)	20 (37.0)	12 (22.2)	0.09
Race (white)	48 (88.9)	46 (85.2)	0.57
Folic Acid (μg/d)	1654 (592)	1941 (717)	0.07
Choline (mg/d)	315 (70.0)	312 (68.6)	0.99
Betaine (mg/d)	90.3 (64.0)	91.5 (46.8)	0.99
Methionine (g/d)	1.7 (0.4)	1.7 (0.4)	0.96
Vitamin B12 (μg/d)	20.4 (67.5)	27.3 (81.7)	0.003
Vitamin B6 (mg/d)	7.7 (8.9)	12.9 (17.6)	0.02
Prudent dietary pattern	−0.1 (1.0)	−0.1 (1.0)	0.88
Western dietary pattern	0.1 (0.9)	−0.2 (0.8)	0.08
Energy (kcal/day)	1816 (507)	1697 (596)	0.21
Pregnancy related characteristics:			
Infertility diagnosis:			0.60
Male	20 (37.0)	23 (42.6)	
Female	13 (24.1)	15 (27.8)	
DOR	4 (7.4)	3 (5.6)	

	Paternal folate intake (DFE)		
	< 900 µg/d (N=54)	>= 900 µg/d (N=54)	p[c]
Endometriosis	0	1 (1.9)	
Ovulatory cause	7 (12.9)	7 (12.9)	
Tubal cause	2 (3.7)	3 (5.6)	
Uterine cause	0	1 (1.9)	
Unknown	21 (38.9)	16 (29.6)	
Infertility treatment:			0.15
IUI	13 (24.1)	7 (13.0)	
IVF	23 (42.6)	20 (37.0)	
ICSI	18 (33.3)	27 (50.0)	
Multiple pregnancy	15 (27.8)	11 (20.4)	0.37
Gestational age at delivery	38.3 (2.5)	38.8 (2.0)	0.33
Preterm births (<37 weeks)	10 (18.5)	9 (16.7)	0.80

[a] Values are presented as mean (standard deviation) or number (%) unless otherwise noted.

[b] 108 unique couples. 5 couples rejoined the study.

[c] From Wilcoxon test for continuous variables and chi-squared tests (or Fisher's exact test where appropriate) for categorical variables.

Abbreviations: DFE: Dietary folate equivalents; DOR: diminished ovarian reserve; IUI: intrauterine insemination; IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection.

Table 2.

Adjusted difference (95% Confidence Interval) in gestational age at delivery (days) associated with a 400 μg/day increase in paternal and maternal folate intake (DFE)[a] in the Environment and Reproductive Health (EARTH) Study (2007–2017).

	Paternal Folate intake (DFE) (N=113 pregnancies)[b]		Maternal Folate intake (DFE) (N=113 pregnancies)[b]	
	β (95% CI)	p	β (95% CI)	p
Crude	1.7 (−0.1, 3.8)	0.06	0.8 (−0.9, 2.5)	0.35
Multivariable model 1	2.2 (0.0, 4.4)	0.05	1.1 (−1.0, 3.2)	0.26
Multivariable model 2	2.2 (0.0, 4.4)	0.05	1.0 (−1.3, 3.3)	0.31
Multivariable model 3	2.6 (0.8, 4.3)	0.004	0.6 (−1.1, 2.3)	0.46

Abbreviations: DFE: Dietary folate equivalents.

[a]The β coefficient shows the increase in the length of the gestation (days) for every 400 μg/day increase in folate (DFE) intake.

[b]Linear mixed models clustering for having rejoined the study (108 clusters; 5 participants had rejoined the study).

Multivariable model 1 is adjusted for self characteristics: age (continuous), choline, betaine, methionine, vitamin b6, vitamin b12, and total energy intake (all continuous), and quality of the diet (2 dietary patterns identified in a factor analysis). Maternal model is additionally adjusted for maternal bmi (continuous), and smoking status (0= never smoke; 1= ever smoke).

Multivariable model 2 is additionally adjusted for partner's characteristics: age (continuous), folate, choline, betaine, methionine and total energy intake (all continuous). Paternal model additionally adjusted for maternal bmi (continuous), and smoking status (0= never smoke; 1= ever smoke).

Multivariable model 3 is additionally adjusted for the infertility diagnosis (0=male; 1=female; 2=unknown), type of infertility treatment (0=IUI; 1= IVF; 2=ICSI), and multiple pregnancy (0=no; 1=yes)

Table 3.

Adjusted difference (95% confidence interval) in z-score of gestational age-adjusted birthweight of the offspring associated with a 400 μg/day increase in paternal and maternal folate intake (DFE)[a] in the Environment and Reproductive Health (EARTH) Study (2007–2017).

	Paternal Folate intake (DFE) (N=142 children)[b]		Maternal Folate intake (DFE) (N=142 children)[b]	
	β (95% CI)	p	β (95% CI)	p
Crude	−8.4 (−25.2, 8.4)	0.32	1.29 (−12.2, 14.8)	0.85
Multivariable model 1	−12.66 (−31.0, 5.7)	0.17	0.86 (−16.6, 18.3)	0.92
Multivariable model 2	−8.5 (−27.0, 10.0)	0.36	−1.26 (−19.6, 17.1)	0.89
Multivariable model 3	−11.4 (−28.2, 5.4)	0.18	−4.80 (−21.4, 11.8)	0.57

Abbreviations: DFE: Dietary folate equivalents.

[a]The β coefficient shows the gestational age-specific z-score of birthweight for every 400 μg/day increase in folate (DFE) intake

[b]Linear mixed models clustering twins/triplets (113 clusters) and siblings from a previous pregnancy (108 clusters; 5 participants had rejoined the study).

Multivariable model 1 is adjusted for self characteristics: age (continuous), choline, betaine, methionine, vitamin b6, vitamin b12, and total energy intake (all continuous), and quality of the diet (2 dietary patterns identified in a factor analysis). Maternal model is additionally adjusted for maternal bmi (continuous), and smoking status (0= never smoke; 1= ever smoke).

Multivariable model 2 is additionally adjusted for partner's characteristics: age (continuous), folate, choline, betaine, methionine and total energy intake (all continuous). Paternal model additionally adjusted for maternal bmi (continuous), and smoking status (0= never smoke; 1= ever smoke).

Multivariable model 3 is additionally adjusted for the infertility diagnosis (0=male; 1=female; 2=unknown), type of infertility treatment (0=IUI; 1= IVF; 2=ICSI), and multiple pregnancy (0=no; 1=yes)