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ORIGINAL ARTICLE

Periconceptional folic acid prevents miscarriage in Irish families with neural tube defects

J. Byrne

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Abstract
Background Miscarriages occur to excess in sibships with neural tube defects (NTDs) and among maternal versus paternal relatives in NTD families. Folic acid prevents most NTDs. Its potential to prevent miscarriages has been controversial.
Aim We evaluated the relationship of maternal line and periconceptional folic acid with miscarriage.
Methods First cousins in Irish families with NTDs were interviewed about pregnancy outcomes and the health of their offspring.
Results Miscarriages were not more frequent among pregnancies of maternal versus paternal first cousins. Folic acid intake during early pregnancy significantly reduced the risk of miscarriage from 15.7 to 9.6%, for an adjusted odds ratio of 0.37 (95% confidence interval 0.19, 0.72, $p = 0.005$).
Conclusions Folic acid during pregnancy was associated with a reduction of approximately 60% in miscarriages. Miscarriages are common—one in every eight pregnancies in this study. If incorporated into pre-pregnancy counseling, these results could have significant public health impact.

Keywords Miscarriage · Neural tube defects · Folic acid · Family studies · Irish

J. Byrne (✉)
Boyne Research Institute, Duke House, Duke Street, Drogheda, Ireland
e-mail: jbyrne@boyneresearch.ie

Background

Risks of neural tube defects (NTDs), birth defects overall, adverse pregnancy outcomes and miscarriage are significantly greater in uncles and aunts, in first cousins (FCs) and in first cousins once removed (FCOR) among families with NTDs [1–4]. Periconceptional folic acid prevents NTDs, other birth defects and birth defects overall [4–6]. It may have other beneficial effects on development [7]. This report evaluates the risk of adverse pregnancy outcome, including miscarriage, to pregnancies of maternal compared to paternal first cousins and the protective effect of periconceptional folic acid.

Methods

This study reports results from Phase III of studies of Irish NTD families by the Boyne Research Institute. Phase I evaluated pregnancy histories and the health of siblings in the original nuclear families. Phase II subjects (uncles and aunts) were identified by their siblings during Phase I. Uncles and aunts were interviewed between 2000 and 2002 [1]. Phase III consisted of interviews with first cousins, the children of the uncles and aunts, between 2002 and 2009. Here, we report on the outcomes of pregnancies to first cousins and the protective effect of folic acid. A separate report describes the occurrence of birth defects in children of the first cousins—the FCOR [4]. The families with NTDs were identified through their membership in the Louth-Meath Branch of the Irish Association for Spina Bifida and Hydrocephalus, and the Ballymena branch of the (UK) Association for Spina Bifida and Hydrocephalus. Families were also recruited through word of mouth and through radio announcements in the Louth-Meath area. To

the data from the original study of first cousins (Phase III), we added pregnancies ascertained during a follow-up study of all individuals known to us who were in their reproductive years (carried out from 2007 to 2009). Place of residence was asked of respondents in the follow-up study; the majority of respondents were resident on the island of Ireland (77.7%), with the balance in Britain, Europe, Africa and Australia. The follow-up study identified a further 67 new pregnancies; these were added to the data for analysis. There was no difference in the proportion of pregnancies that miscarried between the follow-up study and original study (10.5 vs. 13.3%, respectively, $p = 0.5$). The original study included pregnancies to first cousins from 33 families; the follow-up study included pregnancies from 23 families, of which all except two families participated in the original study.

Adverse pregnancy outcomes were defined as preterm deliveries, stillbirths and miscarriages. Of these, we excluded current pregnancies, ectopic pregnancies, elective terminations and twins since they were more likely to end adversely. The Ethics Board of the Boyne Research Institute approved this study. Statistical analyses were carried out with SAS (Statistical Analysis System, Cary, NC). Simple comparisons were tested for statistical significance with Chi-square tests with alpha = 0.05, and two-tailed tests. Logistic regression models controlled for potential confounding. Effect modification was assessed by the Breslow-Day statistic.

Results

Of the 489 pregnancies, 63 (12.9%) ended in miscarriage. None of the following characteristics were associated with a statistically significant increase in the proportion of adverse pregnancy outcomes: the type of NTD of the proband, the gender of proband, uncle/aunt or first cousin, respondent (FC alone or with spouse), FC had birth defects versus not, birth order, year of birth of first cousin or partner, age of FC at birth of FCOR, medical conditions or special diet, exposures before or during pregnancy to smoking, drugs or alcohol, or supplemental folic acid before pregnancy. The proportion of pregnancies ending in miscarriage was greater under these circumstances: FCOR miscarriage occurred after 1997 ($p = 0.06$); second partner versus first ($p = 0.004$); iron tablets taken during pregnancy or not ($p = 0.05$); family size (1 or 2 vs. more, $p = 0.003$). Folic acid taken during the 3 months before pregnancy reduced the miscarriage rate from 13.8 to 10.7% ($p = 0.32$). Supplemental folic acid taken during the first 3 months of pregnancy was associated with a miscarriage rate of 9.6%, compared to 15.7% of non-supplemented pregnancies ($p = 0.05$) (Fig. 1). Folic acid tablets had been taken during early pregnancy by 61% of first cousins.

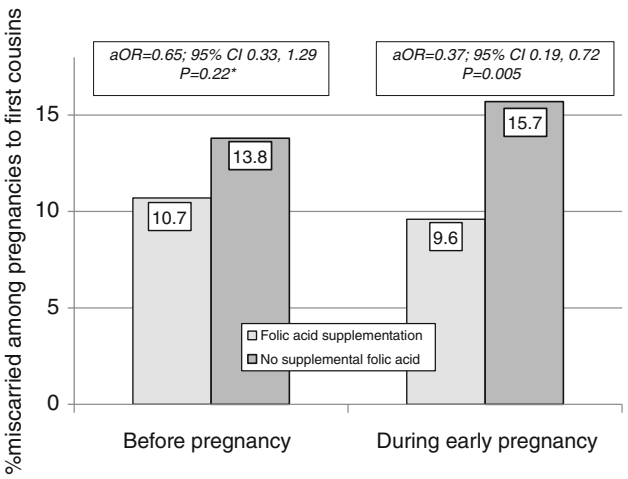

Fig. 1 Percent miscarried among pregnancies to first cousins in Irish families with neural tube defects by folic acid supplementation before or during early pregnancy. *aOR* adjusted odds ratio, adjusted for year of birth, number of partners, iron tablets and family size; *CI* confidence interval

There was no suggestion that maternal line contributed to an increase in the proportion of pregnancies ending in miscarriage: 15.1% of pregnancies to paternal first cousins miscarried compared to 10.8% to maternal first cousins ($p = 0.15$) (Table 1). This result did not change when the data were stratified by a number of other factors (type of NTD, gender of first cousin, or of uncle/aunt or of proband, or exposures before and during pregnancies).

The protective effect of supplemental folic acid during pregnancy on miscarriage was probed by a stratified analysis evaluating the potential confounding effect of FC year of birth, partner (1 vs. 2), iron tablets during pregnancy and family size. The odds ratio for the protective effect of folic acid against miscarriage remained statistically significant in all cases, with no evidence of effect modification. Logistic regression models confirmed this result. In a logistic regression model that included terms for FC year of birth, number of partners, iron tablets and family size, the odds ratio for the protective effect of folic acid taken during pregnancy against miscarriage was 0.37 (95% confidence interval 0.19, 0.72, $p = 0.005$). A similar analytic approach to the preventive effect of folic acid taken before pregnancy yielded a non-significant odds ratio of 0.65 ($p = 0.22$). The average gestation of miscarried pregnancies was 11.4 weeks if exposed to supplemental folic acid compared to 10.3 weeks for unexposed pregnancies ($p > 0.05$) (Table 1).

Discussion

Pregnancies to aunts and (partners of) uncles in this same study showed more adverse pregnancy outcomes among

Table 1 Adverse outcomes of pregnancies to first cousins by type of outcome and by line (paternal vs. maternal)

	Total		Paternal line		Maternal line	
	N	%	*N*	%	*N*	%
Full term liveborn child	411	84.1	195	81.9	216	86.0
Preterm pregnancy	13	2.7	5	2.1	8	3.2
Stillborn child	2	0.4	2	0.8	0	0
Miscarriage	63	12.9	36	15.1	27	10.8
Total	489	100.0	238	100.0	251	100.0

maternal first cousin pregnancies, with the difference largely explained by an excess of miscarriages to maternal uncles/aunts [1]. This matrilineal effect was not present among pregnancies to their children, the first cousins. However, a maternal preponderance of miscarriage was found in a North Carolina study of NTD families: both uncles/aunts and first cousins had more miscarriages in the maternal line than in the paternal line [8].

In this study, supplemental folic acid taken during early pregnancy was associated with a statistically significant reduction in the rate of miscarriage of about 60% (odds ratio 0.37, 95% CI 0.19, 0.72, $p = 0.005$), and a non-significant reduction of about 35% (odds ratio = 0.65) if folic acid was taken before pregnancy. The lack of statistical significance of the pre-pregnancy folic acid supplementation probably reflects the smaller number of women so exposed.

Recent studies provide support for our finding. A study of Austrian epileptic women on anti-epileptic medication found an odds ratio of 2.6 (inverse = 0.38) for the protective effect of supplemental folic acid taken during pregnancy but no significant effect for pre-conceptional folic acid. In addition, two doses of folic acid (0.3–0.5 and 5.0–5.4 mg) were associated with different effects: the lower dose conferred protection (0 miscarriages in 33 pregnancies), while the higher dose did not (9 miscarriages, 7.1%, in 127 women taking the higher dose) [9]. A large US study reported an odds ratio of 0.47, or a 50% reduction in miscarriage rate among participants exposed to vitamins during pregnancy [10].

However, not all studies agree on the protective effect of periconceptional folic acid on miscarriage. A large Chinese study found no protective effect of folic acid against miscarriage among women following a positive pregnancy test [11]. Of note, in the *Chinese* study, is the inclusion of women whose pregnancies may not have been clinically apparent, but detected biochemically only, the relatively low overall miscarriage rate (9.1%) and the unusual distribution by week of miscarriage, with a peak at 8 weeks instead of the usual 11–12 weeks [12]. In China, the dose of folic acid was 400 μg. The results of the two randomized clinical trials of periconceptional folic acid [6, 13] suggested that more miscarriages occurred in the supplemented group [14], though this possibility has proved controversial [15]. Both trials used higher folic acid doses (5 and 0.8 mg, respectively) than either the Irish or (the low dose) Austrian studies.

Our finding that miscarriage is prevented by supplemental folic acid during pregnancy is consistent with a growing literature on the influence of maternal micronutrient intake on the course and outcome of pregnancy. Reduction in the occurrence of other adverse pregnancy outcomes and in other birth defects (low birthweight, very low birthweight, preterm births and pre-eclampsia) has been associated with periconceptional multivitamin use [4, 16–20]. In addition, low plasma folate has been linked to increased rates of early miscarriage, especially of karyotypically abnormal conceptuses [21]. There is considerable biological justification for the potential of folic acid to prevent miscarriage. Dietary folate is a critical component of normal embryonic development, required for cell division because of its role in DNA synthesis [22], suggesting that supplemental folic acid could contribute to reductions in abnormal development and adverse birth outcomes.

These pregnancies of first cousins occurred between 1971 and 2009 (average 1997). An earlier report from this project of pregnancy outcomes to uncles/aunts did not find a significant protective effect of supplemental folic acid, despite increased folic acid intake by these families compared to the general Irish population [1, 23]. This may be because the uncle/aunt pregnancies occurred before knowledge and use of folic acid prophylaxis became widespread. There is evidence of recall bias in these data: more miscarriages were reported among pregnancies after 1997. It is unlikely that this bias explains the lack of matrilineal effect, since the protective effect of folic acid was strong despite bias.

Miscarriage is frequent, occurring in about one in every eight recognized pregnancies in this study. Pre-pregnancy counseling to incorporate supplemental folic acid before and during early pregnancy clearly has important public health consequences.

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