Prevention of Orofacial Clefts: Does Pregnancy Planning Have a Role?

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Objective: **To investigate the association between pregnancy planning and orofacial clefts in the United Kingdom.**

Design: **Case–control study.**

Setting: **Scotland and the Manchester and Merseyside regions of England.**

Participants: **One hundred and ninety-one children born with nonsyndromic orofacial cleft, 1997 to 2000, and 247 controls.**

Main outcome measure: **Cleft lip with and without cleft palate, and cleft palate.**

Results: **There was an inverse association between planning for pregnancy and orofacial cleft in the offspring (odds ratio [OR] = 0.51, 95% confidence interval [CI] = 0.33–0.79). An unplanned pregnancy together with smoking in the first trimester of pregnancy resulted in almost treble the risk of a child with an orofacial cleft when compared with those who planned their pregnancy and did not smoke (OR = 2.92, CI = 1.50–5.65).**

Conclusions: **Planned pregnancies were associated with a lower risk of orofacial clefts. Isolation of the elements of pregnancy planning implicated in these results is difficult. Current preconception advice needs to reach a wider audience; however, for maximum impact, efforts are needed to reduce the numbers of unplanned pregnancies.**

KEY WORDS: *case-control study, maternal smoking, orofacial clefts, planned pregnancy*

In the absence of a full understanding of the role of either genetics or the environment in the etiology of orofacial clefts (OFC), a variety of preventive strategies have been postulated and researched. The potential role of folic acid, and that of other vitamins, in the prevention of orofacial clefts has led to much research over the last 50 years (Czeizel, 2002). The beneficial effects of folic acid in the prevention of neural tube defects mean that supplementation is already advocated for all pregnancies in the U.K. (Department of Health, 2005). Many of the studies into the possible role of folic acid in relation to orofacial clefts have been either observational or nonrandomized intervention studies. Some have indicated a possible protective effect, but, as Czeizel (2002) points out, ''. . . starting vitamins before conception could just as easily be a marker for general health consciousness.'' In the study reported by Tolarova and Harris (1995), the taking of a micronutrient supplement (including 10 mg of folic acid) was but one feature of a 10-step protocol designed for the prevention of recurrence of cleft lip with or without cleft palate (CL/P), and undertaken by a self-selected group. This therefore was an example of pregnancy planning, and the authors acknowledged that the observed results may be due to factors other than the supplementation. A randomized clinical trial undertaken in Hungary from 1984 to 1992 did not show a reduction in the occurrence of nonsyndromic CL/P and CP (cleft palate only) (Czeizel, 2002), but this trial used doses of folic acid of 0.8 mg compared to larger doses used elsewhere, e.g., in the nonrandomized recurrence study reported by Tolarova and Harris (1995), and lacked statistical power to detect an effect.

Smoking during pregnancy has received much attention in public health research due to the known adverse effects including low birth weight and increased respiratory problems in childhood (Charlton, 1994). Recent work in the U.K. (Little et al., 2004a) has indicated that smoking in the first trimester of pregnancy is associated with an increased risk of OFC (odds ratio [OR] = 2.0; 95% confidence interval [CI] = 1.3–3.1), whilst a meta-analysis using data from 24 case–control and cohort studies from around the world showed consistent, moderate, and statistically significant associations between maternal smoking and oral clefts (relative risk 1.34 for CL/P and 1.22 for CP) (Little et al., 2004b).

The situation thus exists where general advice on pregnancy planning incorporates advice on folic acid supplementation

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(because of the known link with neural tube defects) and on smoking (to prevent low birth weight and respiratory problems etc.) whilst at the same time, the roles of these behaviors in the prevention of OFC are still being researched. Other behaviors postulated as potentially harmful regarding risk of OFC, including alcohol consumption and the use of certain drugs, are also already the subject of more general advice in pregnancy. Thus the challenge is to isolate the effect of these factors of interest, whilst also considering their combined effect, in order to be able to provide more detailed and/or stronger preconceptional advice for the prevention of OFC.

In investigating the role of pregnancy planning in the etiology of OFC, it is necessary to deal with the problems of definition that arise. The word ''planning'' carries various connotations including contraception use, timing of pregnancy, and actions taken (or not taken) in relation to a particular pregnancy. The focus in this paper is on the lifestyle/behavioral changes that may be undertaken prior to conception and/or in early pregnancy, aimed at achieving a favorable outcome from the pregnancy. However, use of the phrases ''preconception care'' or ''preconception counseling'' also raises problems, as some equate such phrases with preconception advice for those with specific problems such as diabetes or known genetic disorders. Barrett and Wellings (2002) discuss the challenges in eliciting information from respondents if people apply varying interpretations to the phraseology employed in questioning.

Worldwide, high proportions of births arise from unplanned or unintended pregnancies (World Health Organization, 1998). For example, in a recent study of women attending antenatal clinics in a district general hospital in Staffordshire (U.K.), 63% stated that their pregnancy was planned (Sen et al., 2001). Rosenberg et al. (2003) reported 40% of their sample, based on live births in Oregon, had ''unintended'' pregnancies (mistimed or unwanted). In 2001, an estimated 49% of pregnancies were unintended, with higher rates for younger age groups and in more disadvantaged groups (Finer and Henshaw, 2006).

The behavior of the mother-to-be may be influenced by the intendedness of the pregnancy. Kost et al. (1998) report that ''Both the intendedness of a pregnancy and the mother's social and demographic characteristics are important predictors of pregnancy-related behavior.'' Wallace and Hurwitz (1998) report that women who had never been pregnant and those who had not undertaken education beyond the age of 18 were significantly less well informed on preconception care. McGovern et al. (1997), in a Glasgow-based study, found that having an unplanned pregnancy (42% of their sample) and being in a younger age group were both factors associated with failure to take folic acid supplements, reflecting international patterns (Ray et al., 2004). Similarly, Delgado-Rodriguez et al. (1997) suggest that unplanned pregnancy is a major determinant of the inadequate use of prenatal care.

The role of professionals in the delivery of preconception care has received some attention in recent years (de Weerd et al., 2004; Heyes et al., 2004; Moos, 2004). The role of preconception counseling is recognized for families who already have a history of OFC but the more general role of preconception care in the prevention of OFC in the general population has received little attention. The results reported below come from a study designed both to investigate the role of intake of dietary and supplemental folate (to be published separately) and to investigate more generally other potential factors in the etiology of OFC. This paper reports on results relating to the importance of preparing for a pregnancy and the associated behavioral changes.

METHODS

A population-based case–control study was carried out between September 1, 1997, and January 31, 2000, and included 191 nonsyndromic OFC cases and 247 unaffected controls. Clinical records of cases were reviewed by experienced dysmorphologists in order to determine whether they were syndromic or nonsyndromic. Cases with isolated clefts or clefts associated with multiple anomalies that were not part of a recognized syndrome were included, including 12 infants with the Pierre Robin sequence.

Subjects were recruited from predetermined postcode sector regions, selected to represent urbanized areas of Scotland and Manchester/Merseyside and used as geographical recruitment boundaries. Areas included were as follows: Scotland: Grampian, Tayside, Fife, Lothian, Forth Valley, Greater Glasgow, Ayrshire and Arran, Lanarkshire and Borders; England: Manchester and Merseyside Health Board areas.

All infants born with clefts in these areas are referred to specialist centers for treatment. Cases were ascertained via the regional cleft teams who informed the study coordinator or local research interviewer of any affected child born within the predetermined geographical boundaries. Scottish cases were verified against the CLEFTSiS register (formerly the Scottish Cleft Lip and Palate Association Register), to which all clinicians in Scotland involved in the care of OFC patients contribute, and which supports the management of care. This register has been validated against the National Birth Register for Scotland and has been found to have a high level of completeness for live-born infants (Clark et al., 2003). English cases were verified against the Craniofacial Anomalies Network (CRANE) register.

In Scotland, potentially eligible controls were identified from the Community Health Index (CHI), a register of the general population which allows assessment of capitation payments for general medical practitioners. The CHI is also used for the provision of primary care services such as breast and cervical cancer screening and recall, and in the organization of child health surveillance and immunization. It has been shown to have a high level of completeness (Roworth and Jones, 1988; Garton, 1993; Ramsay et al., 1999). In England, potentially eligible controls were identified by contacting general medical practitioners in the same postcode sector region as the recruited case infant. Controls were matched with cases on sex, date of birth ($\pm$ 1 month), and region.

The initial approach, in which a study pack was either handed or posted to the subject's mother, was made by various

TABLE 1 Percentages Who Answered "Yes" to the Question "Was This a Planned Pregnancy?"

	All births (n = 438)			*Male child (n = 210)*		*Female child (n = 228)*	
	n	*% from Planned Pregnancy*	*p for χ^2 Test*	*% from Planned Pregnancy*	*p for χ^2 Test*	*% from Planned Pregnancy*	*p for χ^2 Test*
CL/P and CP	191	51.8	0.0003	49.5	0.0134	54.0	0.0078
- CL/P only	113	49.6	0.0004	44.8	0.0041	56.5	0.0709
- CP only	78	55.1	0.0265	62.5	0.7144	51.9	0.0127
Controls	247	68.8		66.4		71.1	

TABLE 2 Percentages Responding "Yes" to the Question: "Did You Make Any Conscious Changes in Your Lifestyle After You Became Aware That You Were Pregnant?"

	Cases (n = 191)		*Controls (n = 247)*	
	Planned Pregnancy	*Unplanned Pregnancy*	*Planned Pregnancy*	*Unplanned Pregnancy*
Prompts provided				
Socializing	45.9	56.5	54.7	54.6
Diet	53.1	51.1	64.1	58.4
Medication/supplements	68.4	65.2	65.9	59.2
Other	25.5	30.4	35.3	26.3

agencies, depending on the region. Completed consent forms were returned to the regional study interviewer, who was trained in interview techniques. The interviewer then telephoned to arrange a visit during which a structured interview was conducted. The interviews took place at a mean of 5.5 months after the birth for cases and 6.5 months after birth for controls.

Current habitual diet was assessed using a validated, semiquantitative food frequency questionnaire (Aberdeen FFQ, version 5.4 [Masson et al., 2003]). The questionnaire includes 150 food items and respondents were asked how often and how many ''measures'' they ate of each food item. Any changes to the usual diet during pregnancy were recorded. Sociodemographic information and use of supplemental nutrients were also recorded.

We assessed the relationship between CL/P, CP, and OFC of all types, and maternal response to the question ''Was this a planned pregnancy?''. Conditional and unconditional analyses produced similar odds ratios. Results of the unconditional analyses are reported as this allowed use of the full dataset, since not every case had a matched control, and increased the statistical power. We adjusted for the matching variables sex, season of birth, and region. We also considered potential confounding by maternal age, father's participation in the study, maternal education, maternal smoking, and use of illicit drugs, alcohol consumption, and folic acid supplementation. Results from this study regarding the association between smoking and orofacial clefts (Little et al., 2004a) have already been reported. These prior results led us to consider the effects of combinations of pregnancy planning and smoking.

The mothers were asked questions on lifestyle changes. However, the questions were worded to request information on changes undertaken after the awareness of the pregnancy and it was thus not possible to ascertain preconception lifestyle changes by those who planned their pregnancy.

Logistic regression was used to obtain a measure of the risk reduction that could be associated with pregnancy planning. Variables that might be expected to be confounders in this relationship were considered. The inclusion of known aspects of pregnancy planning might be expected to reduce the odds ratio, as part of any effect of pregnancy planning is likely to be explained by analysis of known components of such planning.

The study was approved by the local research ethics committees for each Health Board region within Scotland and by the corresponding committees for Manchester and Merseyside. Approval was also obtained from general medical practitioner subcommittees in Grampian.

RESULTS

An initial univariate analysis indicated the possible importance of pregnancy planning as a risk factor for orofacial clefts (chi-square test, $p = 0.0003$). The etiology of OFC may differ in males and females as suggested by the male predilection for CL/P and greater female tendency toward CP (Mossey and Little, 2002), and the authors therefore evaluated associations both by specific anomaly and by sex (Table 1).

Recorded lifestyle changes are listed in Table 2, and demographic data and responses to other questions of potential relevance to pregnancy planning are given in Table 3.

Maternal total folate intake (dietary and supplemental) in cases and controls was compared to check whether there was any possibility that folate played a role or helped explain the protective effect. There was no association between CL/P or CP and total folate intake (Table 4).

Table 5 shows the risk reduction associated with pregnancy planning, after adjustment for study design and covariates implicated in either OFC or pregnancy planning. The covariates used in the model were sex, center, season, mother's education and age group, father's participation, whether the mother smoked in the first trimester, folic acid supplementation, alcohol consumption during pregnancy, and use of illicit drugs. Overall, a planned pregnancy resulted in a substantial reduction in the risk of OFC in the offspring, halving the risk (OR = 0.51, CI = 0.33–0.79). Analysis by sex and type of cleft showed that the greatest reduction related to the risk of a male child with CL/P (OR = 0.32, CI = 0.15–0.67). It should be noted that some of the subgroups in Table 4 contain only a small number of subjects.

One known risk factor not included in the above analysis, due to small numbers leading to potentially unreliable results, was the reporting of first degree relatives with OFC. The inclusion of this risk factor in an initial analysis of the full sample led to the very small change in OR from 0.51 to 0.52.

As the risk from maternal smoking appeared to be relatively independent of the risk from an unplanned pregnancy, analyses

TABLE 3 Demographic Data Together With Responses That May Relate to Pregnancy Planning, Obtained From a Variety of Sources Within the Study

	Cases (n = 191)		*Controls (n = 247)*	
	Planned Pregnancy	*Unplanned Pregnancy*	*Planned Pregnancy*	*Unplanned Pregnancy*
Characteristic				
Age distribution of mothers, % under 25, 25 to 34, 35+	18, 64, 18	36, 45, 20	14, 71, 15	29, 57, 14
Fathers participating in study (%)	90.9	83.7	94.7	89.6
Mothers with postsecondary education (%)	40.4	46.7	55.3	55.8
From maternal questionnaire				
Smoking in first trimester (%)	40.4	44.6	18.8	33.8
Use of illicit drugs (%)	7.1	18.5	3.5	11.7
Reporting use of nutritional supplements periconceptionally (%)	83.8	72.8	88.2	74.0
With folic acid supplementation > 400 μg (%)	28.3	12.0	38.2	5.2
From food frequency questionnaire				
Reporting alcohol consumption (%)	61.6	57.6	65.9	79.2

were undertaken to consider the combined effect of these two risk factors (Table 6). The covariates included in this model were sex, center, season, mother's education and age group, father's participation, folic acid supplementation, alcohol consumption during pregnancy, and use of illicit drugs.

Each of these two behaviors—maternal smoking and an unplanned pregnancy—considered in isolation appears to double the risk compared with those adopting the alternative behavior. The risk associated with a mother who has an unplanned pregnancy and smokes in the first trimester is nearly three times the risk for a nonsmoking mother with a planned pregnancy (OR = 2.92, CI = 1.50–5.65).

DISCUSSION

Secondary Analysis

The results reported here on pregnancy planning were the result of secondary analysis of a study whose primary purpose was to investigate any link between folic acid supplementation and OFC (to be reported separately). It is acknowledged that this type of analysis, as opposed to the investigation of a predetermined hypothesis, runs the risk of unearthing spurious associations and this must be borne in mind in interpreting the results. A further problem related to the study design was that, although some questions related to various aspects of pregnancy planning, the study was not primarily designed to enable a detailed look at the different facets of behavior involved in such planning or their interaction. Related to this, there were difficulties in eliciting the exact timing of any changes made in the periconception period.

TABLE 4 Association Between Oral Clefts and Maternal Total Folate (Dietary and Supplemental) Intake

	Total Folate Intake			
*Quartile**	*Q1*	*Q2*	*Q3*	*Q4*
Median† (μg/d)	269	420	574	775
CL/P/controls	29/61	35/55	25/65	23/67
OR‡ (95% CI)	1.0 (Ref)	1.7 (0.83–3.44)	1.1 (0.50–2.21)	0.9 (0.44–2.03)
CP vs. controls				
CP/controls	22/60	20/61	18/64	18/63
OR‡ (95% CI)	1.0 (Ref)	1.2 (0.54–2.82)	1.1 (0.49–2.63)	1.0 (0.43–2.36)
OFC vs. controls				
OFC/controls	50/60	61/48	41/69	38/71
OR‡ (95%/ CI)	1.0 (Ref)	1.4 (0.76–2.55)	1.0 (0.57–1.94)	0.9 (0.50–1.75)

* Quartiles based on combined distribution of residuals of total folate intake on energy for each group of cases and controls (Hsieh et al., 1991).

† OFC and controls combined. Values are similar for CL/P and controls combined, and CP and controls combined.

‡ Odds ratio adjusted for sex and season of birth (matching variables), maternal education, the child's ethnic group, and total energy intake using the nutrient residuals technique (Willett et al., 1997).

Representativeness of the Sample

The rate for unplanned pregnancy among the controls (31.2%) is slightly lower than those reported by Sen et al. (2001) and McGovern et al. (1997). The possibility of selection bias cannot be ruled out, as those who had enjoyed a successful planned pregnancy may have been more likely to participate as controls in the study then those whose pregnancy was unplanned. One clear difference between planners and nonplanners in this study (Table 3) was in the age structures of the groups, with many nonplanners in the under-25 age group.

Timing of Lifestyle Changes (1)

The answers detailed in Table 2 were in response to a question on what changes were made after awareness of the pregnancy. There are two problems in interpreting these answers. If any changes had been made before awareness of the pregnancy (e.g., folic acid supplementation) how would the mothers have responded? Some may still have answered in the affirmative (if the changed behavior persisted after confirmation of the pregnancy) whereas others may have given a negative response to reflect that the timing of the change was not as detailed in the question. Additionally, it was evident that there was some overlap to the responses to this set of questions. For example, some respondents may have viewed a change in al-

TABLE 5 Association Between Pregnancy Planning and Oral Clefts in the Offspring: Planned (P) Versus Unplanned (Not P), After Adjustment for Study Design and Covariates

	All Births			*Males*			*Females*		
	P	*Not P*	*OR* P versus Not P (95% CI)*	*P*	*Not P*	*OR* P versus Not P (95% CI)*	*P*	*Not P*	*OR* P versus Not P (95% CI)*
OFC	99	92	0.51 (0.33–0.79)	45	46	0.37 (0.12–0.73)	54	46	0.57 (0.30–1.06)
- CL/P	56	57	0.46 (0.27–0.78)	30	37	0.32 (0.15–0.67)	26	20	0.58 (0.26–1.32)
- CP	43	35	0.62 (0.34–1.15)	15	9	0.39 (0.12–1.31)	28	26	0.53 (0.26–1.14)
Controls	170	77	1	79	40	1	91	37	1

* OR = odds ratio adjusted for sex and season of birth (matching variables), maternal education, the child's ethnic group and total energy intake using the nutrient residuals technique (Willett et al., 1997).

cohol consumption as a change in socializing, whilst others may have reported it as a change in diet or under ''other'' changes. This may explain why the more general question on ''planning'' shows a strong negative association with OFC but not these individual questions on lifestyle change. Furthermore, any one change on its own may not be sufficient for a protective effect, but the combination of a variety of behavioral changes (not necessarily the same ones for each person) may offer protection.

Timing of Lifestyle Changes (2)

The critical period for the formation of the lip and palate is from conception to 60 days (Sperber, 2001). Therefore it may be possible for some of the beneficial effects of certain behavioral changes to be achieved in some unplanned pregnancies, if the mother becomes aware of her pregnancy very early and takes action immediately. However, early recognition of the pregnancy is more likely in planned pregnancies, and some of the behavioral changes needed may require a more sustained period of change for the benefit to be realized, so behavioral changes undertaken by mothers after the confirmation of pregnancy (Table 2) may be of limited value with regard to OFC, although still of value with regard to other aspects of the health of both baby and mother.

Multivitamin Supplementation

The literature on the possibility of a nutritional contribution to orofacial clefts has, particularly among the B vitamins, had a significant focus on folic acid. The discovery that folic acid plays a primary role in the prevention of neural tube defects has undoubtedly contributed to this and an increasingly universal public health measure for prevention of neural tube defects is periconceptional supplementation using a minimum of 0.4 mg of folic acid. In the present state of knowledge there is no convincing evidence for the efficacy of folic acid in the prevention of nonsyndromic orofacial clefts. In most, if not all, of the studies that report an inverse association between folic acid supplementation and clefts, the maternal diet also contained other multivitamins. The nonrandomized recurrence trial in the Czech Republic reported by Tolarova and Harris (1995) commented on the apparent protective effect of multivitamin supplementation (containing 10 mg of folic acid) for CL/P prevention. However it must be remembered that, in their study, supplementation was part of a more extensive protocol adopted by those planning a pregnancy and therefore the full protocol may have been more important than any one element.

Smoking

It is known that high proportion of young mothers-to-be smoke (Information and Statistics Division, Scotland, 2005) and the advice against smoking in pregnancy is possibly one of the best-known public health messages. Furthermore, it has already been shown that smoking is associated with OFC (Little et al., 2004a, 2004b). Thus, it might have been expected that ''smoking'' would be a confounder in the relationship between planned pregnancies and OFC, and that the perceived effect would disappear or be substantially diminished once smoking was taken into account. This was not the case. It is possible that the addictive nature of nicotine makes smoking cessation one of the hardest pieces of advice for the mother-to-be to act on, and is therefore achieved by few. This means that any protective effect from ''planning'' would be dependent on the other changes that the mother-to-be is able to make.

TABLE 6 The Combined Effect of an Unplanned Pregnancy and Smoking on Odds Ratio for OFC and the Two Subgroups, After Adjustment for Study Design and Covariates

	Planned Pregnancy Nonsmoker			Planned Pregnancy Smoker			*Unplanned Pregnancy Nonsmoker*			*Unplanned Pregnancy Smoker*		
	n	*OR*	*95% CI*	*n*	*OR*	*95% CI*	*n*	*OR*	*95% CI*	*n*	*OR*	*95% CI*
OFC	59	1.0	reference	40	2.55	1.41–4.60	51	2.64	1.53–4.56	41	2.92	1.50–5.65
CL/P	35	1.0	reference	21	2.28	1.11–4.68	32	2.79	1.47–5.29	25	3.12	1.45–6.74
CP	24	1.0	reference	19	2.74	1.28–5.89	19	2.19	1.02–4.69	16	2.78	1.13–6.84
Controls	138			32			51			26		

Sex and Cleft Type

The sex ratio is known to differ between CL/P and CP, with a male predilection for CL/P and female tendency toward CP (Mossey and Little, 2002), indicating a different etiology. Hayes (2002), in reviewing environmental risk factors, suggests that CL/P has a stronger environmental component to its etiology. The risks associated with CL/P following an unplanned pregnancy were greater than for CP, in line with this hypothesis. A similar result was obtained by Krapels (2005) in a study conducted in the Netherlands, albeit with higher levels of pregnancy planning in both cases and controls. The risks associated with the different cleft types also show differences depending on the sex of the offspring (Table 5).

It is interesting to note that, amongst those with a male child with CL/P, 44.8% of mothers had planned their pregnancy whilst, amongst those with a female child with CL/P, 56.5% had planned their pregnancies. This is consistent with the multifactorial threshold hypothesis for non-syndromic orofacial clefts in that, with CL/P being more prevalent in male infants, a greater genetic liability towards CL/P is required if the child is a female. In theory, this also has implications for prevention as the multifactorial threshold model predicts that environmental manipulation would be more effective in protecting the more common type of cleft. Therefore pregnancy planning and avoidance of known risk factors would potentially prevent CL/P in a greater number of male fetuses.

Future Research

Prevention strategies assessed only in isolation, as is often the case in clinical trials, may provide no evidence of benefit even though such strategies may become important when part of a more detailed protocol. Additionally, there exists the consideration that different combinations of actions can be beneficial for different individuals. These possibilities provide complex challenges for researchers in designing future studies.

Conclusion

The overlap between advice currently available for mothers-to-be and factors, either proven or postulated as involved in the etiology of OFC, is substantial. Until future research is able to detail more precisely the protective actions necessary to minimize the risk of OFC, it would seem sensible to take steps to ensure that all mothers-to-be are aware of current preconception advice and its importance and are given appropriate help in implementing it. The set of actions undertaken by the mother-to-be will be dependent on the strength of the public health message put out, the access to that message and the feasibility of the actions outlined. The message is already reaching some more-privileged subgroups of the population. The challenge is to reach all mothers-to-be.

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