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Maternal Stressful Life Events and Risks of Birth Defects

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Abstract

Background—Several previous studies suggest that maternal stress may be associated with increased risk of certain birth defects. This study examined the association of maternal stressful life events with risks of several birth defects.

Methods—The data are from a recent, population-based case-control study. Telephone interviews were conducted with 1355 eligible case mothers and 700 control mothers. Maternal stress was measured by responses to 18 yes/no questions about life events that occurred from 2 months before through 2 months after conception.

Results—An increase in the stressful life events index (ie, number of "yes" responses to the 18 life-events questions) was associated with increased risk of cleft palate, cleft lip with or without cleft palate, d-transposition of the great arteries, and tetralogy of Fallot, after adjustment for maternal race-ethnicity, education, obesity, age, smoking, drinking, intake of folic acid-containing supplements, neighborhood crime, and food insecurity. For example, the odds ratio for a 3-unit change in the stress index was 1.45 (95% confidence interval = 1.03-2.06) for cleft palate. Increased stress was associated with an increased risk of spina bifida and anencephaly particularly among women who did not take folic acid supplements. A 3-unit change in stress was associated with a 2.35-fold increased risk of anencephaly among women who did not take supplements (CI =1.47-3.77) and a 1.42-fold increased risk among women who did (CI = 0.89-2.25).

Conclusion—The adverse health effects of stress may include increased risks of certain birth defects.

Several observational studies have examined the association of maternal stressful life events with risks of orofacial clefts among offspring.[1-9] All but 2 of these studies[5,9] reported increased risk of clefts among offspring born to women with higher stress. Only a few studies have examined birth defects other than orofacial clefts; they have reported increased risks of neural tube defects (NTDs)[7,10] and conotruncal heart defects[7,11] among women with higher stress. An important limitation of previous studies is that the measurement of stress has been nonstandardized or very limited in scope, for example collecting data on only 2 or 3 life events.

One mechanism by which maternal stressors may cause birth defects is through increased production of corticosteroids. Corticosteroids are teratogenic in animal models, for various organ systems.[1,12,13] Stressful life events have been shown to be associated with elevated maternal corticotrophin-releasing hormone and corticosteroid levels during pregnancy.[14,15] Further support for an association between stress and birth defects risks comes from the finding

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that infants born to women who took corticosteroid medications during the first trimester of pregnancy had an increased risk of oral clefts.[16-20] Another potential mechanism by which stress may cause birth defects is negative coping behaviors that lead to hazardous exposures such as smoking or alcohol intake or reduced nutrient intakes.

The evidence from animal models regarding corticosteroids, combined with limited but suggestive findings from human epidemiologic studies, establish the need to further examine the association between maternal stress and birth defects. This study examines the association of maternal stressful life events with risk of orofacial clefts, NTDs and conotruncal heart defects among offspring, using data from a recent, population-based case-control study.

METHODS

This case-control study included liveborn, stillborn (fetal deaths at ≥20 weeks gestation), and prenatally diagnosed, electively terminated cases that occurred to mothers residing in Los Angeles, San Francisco, and Santa Clara counties. The study included data on deliveries that had estimated due dates from July 1999 to June 2004. California Birth Defects Monitoring Program staff abstracted case information from medical records at hospitals and at genetic counseling centers serving the study population, to find cases diagnosed with birth defects before 1 year of age. This information was reviewed by a clinical geneticist (EJL). Infants diagnosed with single-gene disorders or chromosomal aneusomies were ineligible for this study. Each case was classified as isolated if there was no concurrent major malformation, or as nonisolated if there was at least 1 accompanying major malformation. Case groups included cleft palate, cleft lip with or without cleft palate, spina bifida, anencephaly, and the conotruncal heart defects (d-transposition of the great arteries and tetralogy of Fallot). Spina bifida included cases of lipomeningocele, meningomyelocele, and myelocystocele. For each conotruncal heart defect case, anatomic and physiologic features were confirmed by reviewing echocardiography, cardiac catheterization, surgery, or autopsy reports (EJL). Infants with d-transposition of the great arteries associated with an endocardial cushion defect or with double outlet right ventricle were excluded. Ascertainment of clefts and NTDs ended with the estimated due date of June 30, 2003; ascertainment of d-transposition of the great arteries and tetralogy of Fallot ended with the estimated due date of June 30, 2004. Nonmalformed, liveborn controls were selected randomly from birth hospitals, to represent the population from which the cases were derived. Ascertainment of controls ended with the estimated due date June 30, 2004.

Mothers were eligible for interview if 1) they were the biologic mother and carried the pregnancy of the selected study subject, 2) they were not incarcerated, and 3) their primary language was English or Spanish. Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, no earlier than 6 weeks after the infant's estimated due date. Numerous exposures were assessed, focusing on the periconceptional time period, which was defined as the 2 months before through the 2 months after conception.

In total, 80% of eligible case mothers (n = 1355) and 77% of control mothers (n = 700) were interviewed. Eleven percent of eligible case mothers and 12% of control mothers were not locatable, and the remainder of the mothers declined to participate. The median time between estimated due date and interview completion was 10 months for cases and 8 months for controls. We excluded from all analyses cases and controls with a family history of the selected defects in a parent or sibling, mothers who had type I or II diabetes, and mothers taking medications to prevent seizures (80 cases and 5 controls). Nonisolated cleft cases were also excluded, given that a different etiology is suspected for nonisolated clefts (86 cases). After these exclusions, we had available for analyses 695 controls (analyses of clefts and NTDs were

restricted to the 623 controls with estimated due date, through June 30, 2003) and 1189 cases —139 anencephaly, 186 spina bifida, 145 isolated cleft palate, 419 isolated cleft lip with or without cleft palate, 165 tetralogy of Fallot, and 136 d-transposition of the great arteries cases. (One case had 2 eligible diagnoses—anencephaly and tetralogy of Fallot).

Stressful Life Events

Mothers answered an 18-item inventory of stressful life events to assess the occurrence of specific events during the periconceptional period. The questions were taken from the Kaiser Permanente/California Department of Health Study of Pregnancy and Stress, and largely parallel many of the questions in existing, validated stressful life events assessment tools.[21-23] Questions included only potentially major events, and responses were yes/no, to maximize ability to recall the events objectively. Each woman was asked whether she or her husband (or partner) had started a new job or lost a job; whether she or anyone close to her had had a serious illness or injury, serious legal or financial problems, problems with drinking or drugs, or had problems with immigration; whether she or anyone close to her had been a victim of violence or crime; whether anyone close to her had died; whether she was separated or divorced or had had serious difficulties with her husband or partner; whether she had moved; and whether she had had serious problems or disagreements with relatives, neighbors, or in-laws. For legal reasons, mothers who were less than 18-year-old at the time of conception were not asked the questions about violence or crime. These young women (60 case mothers and 45 control mothers) were assigned as "No" for both of these questions so that they could be retained in the analyses. A stressful-life-events index was formed by summing the number of "yes" responses to these questions, giving equal weight to each. This assumes that the effects of the stressful life events are cumulative and additive across the various events.[24]

Covariates

Several known risk factors for the selected birth defects were included as covariates: maternal raceethnicity (US-born Hispanic, foreign-born Hispanic, non-Hispanic white, other); education (did not complete high school, high school graduate, some college, 4-year college degree or more); prepregnancy obesity (body mass index ≤29 versus >29 kg/m^2); age at delivery; the following exposures during the first 2 months after conception: cigarette smoking (any versus none), and alcohol intake (any versus none), and intake of folic acid-containing multivitamin/mineral supplement (any versus none) during the periconceptional period. Mothers also answered a series of 6 questions related to neighborhood crime[25] and 5 questions related to food insecurity[26] (ie, a lack of access to food to meet basic needs)[26] during the periconceptional period; these 2 factors served as measures of chronic stress in the living environment. Previous studies suggest that chronic stressors may exacerbate the effects of acute stressors[24] and may be important to reproductive outcomes.[24,25,27] A summary index was formed for each of these series of questions, by summing the number of "yes" responses to the questions.

Analyses

The unadjusted association of the sum of stressful life events with each outcome was evaluated using logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs). We specified the stress index as continuous for most analyses, but we also examined the index as categorical to ensure that a continuous specification seemed appropriate. Second, we evaluated whether the addition of a quadratic term improved the fit of the models, to determine whether the association of stress with the outcomes was nonlinear or suggested a threshold effect. Third, potential effect modification by covariates was assessed by including all 2-way interactions of stressful life events with each covariate in a single model for each outcome. The final

multivariable models contained all covariates, and any interaction terms that had a *P* value <0.10 in the model that included all 2-way interaction terms.

RESULTS

Most of the mothers of case and controls were Hispanic, many had less than a high school education, a majority took a folic acid-containing supplement during the periconceptional period, a majority did not report any positive responses to the questions about neighborhood crime, and most did not report any positive responses to the questions about food insecurity (Table 1). The percentage of mothers of controls reporting "yes" to each individual stressful life event question ranged from 1% to 21%. Correlations among the stressful life events questions ranged from 0.003 to 0.43, with most ranging from 0.1 to 0.2; results were similar for the mothers of cases (data not shown). A total of 56% of the mothers of controls and 64% of the mothers of cases reported at least 1 stressful life event (Table 2).

Table 2 shows the frequency distribution of the stressful life events index. When birth defects are examined as a single group, the ORs tend to increase with increasing stressful life events. A similar pattern of results was observed for each phenotype when analyzed separately (data not shown). We therefore specified the stressful life events index as a continuous variable in further analyses. Table 3 shows the unadjusted odds ratios reflecting the association of the continuous stressful life events index with each outcome. An increase in the stressful life events index was associated with increased risk of all types of birth defects, with the strongest association for isolated cleft lip with or without cleft palate and anencephaly. Addition of a quadratic term for the stressful life events index did not substantially improve models (*P*-values for the quadratic terms were all >0.05). We restricted the unadjusted analyses to women with no missing data on any covariates (1036 cases and 622 controls); results were similar when they included all women with data on stress (1174 cases and 688 controls) (data not shown).

Results adjusted for all covariates are also shown in Table 3. A 3-unit change in the stressful life events index was associated with an approximately 30-80% increased risk. The adjusted ORs tended to be slightly larger than the unadjusted ORs.

In the multivariable models that contained all 2-way interactions of the stress index with the covariates, there were 2 interaction terms with *P*-values <0.10: stress by folic acid supplement intake for anencephaly (*P* value 0.078) and stress by folic acid for spina bifida ($P = 0.098$). We simplified the models to explore these 2 interactions: these models included all covariates and the interaction terms for the stress index with folic acid intake but excluded the other 2-way interaction terms. The *P*-values for the folic acid interaction terms in these simplified models were 0.108 for anencephaly and 0.109 for spina bifida. The association of stressful life events with anencephaly and spina bifida was stronger among women who did not take folic acid supplements than among women who did take supplements (Table 4). For example, a 3-unit change in the stressful life events index was associated with a 2.4-fold increased risk of anencephaly among women who did not take folic acid supplements, and a 1.4-fold increased risk among women who did take supplements.

DISCUSSION

In this population-based case-control study, more stressful life events experienced by the mother around the time of conception were associated with increased risks of orofacial clefts, NTDs, and conotruncal heart defects among offspring. Increased risks were not explained by potential covariates—maternal race-ethnicity, education, obesity, age, smoking, drinking, intake of folic acid-containing supplements, neighborhood crime, and food insecurity.

Observations are consistent with previous studies,[1-4,6-8,10,11] with a much more detailed assessment of stress and a larger set of potential covariates than in previous studies.

As noted above, previous studies of these birth defects and stress also suggested increased risks. Whether this consistency of findings is due to a true association or pervasive bias across studies is uncertain, given the retrospective nature of most designs and the extremely limited exposure assessment by previous studies. Most studies of clefts included measures of stress that were vague or assigned by the interviewer rather than the woman.[2-6,9] Studies that included neural tube defects and conotruncal defects were limited to only a few events.[7,8,10,11]

Several lines of evidence support the plausibility of our findings. Stress results in increased catecholamine production, which in turn leads to decreased uterine blood flow and increased fetal hypoxia.[28] Animal studies indicate that hypoxia affects a variety of developmental processes (eg, cell death)[29] and organ systems, which could result in various types of birth defects.[12,30] Increased glucocorticoid levels are also associated with hyperinsulinemia and insulin resistance,[31] which in turn may be associated with increased risks of the studied birth defects.[11,32]

In an evaluation of effect modification by potential covariates, the association of anencephaly and spina bifida with maternal stressful life events was stronger among women who did not take folic acid-containing supplements. Experimental evidence suggests that vitamin B_6, which is a component of most folic acid-containing multivitamin/mineral supplements, may prevent glucocorticoid-mediated cleft palate.[33-35] A proposed mechanism for this observation is that increased vitamin B_6 results in reduced tissue responsiveness to glucocorticoids via suppression of glucocorticoid receptor activity.[36] Most experimental studies of the teratogenic effects of glucocorticoids have investigated orofacial clefting in the offspring; the explanation for our finding with NTDs, but not with clefts or conotruncal heart defects, is not apparent.

Strengths of this study include its comprehensive case ascertainment, detailed phenotypic review, population-based control selection, and satisfactory level of participation in maternal interviews. Given the relatively low frequency of the individual birth defects, we were limited to a retrospective study design, which does not allow measurement of potential physiologic correlates of stress during organogenesis. Even with improvements in the assessment of stress relative to previous studies of birth defects, our assessment of stress had limitations. The time-window of stressful events (2 months before through 2 months after conception) was somewhat broad. We cannot be sure whether we were truly studying the effects of chronic or of acute stress. Furthermore, the exposure window was not completely inclusive of development of all organs being studied (eg, closure of the palate may continue up to 12 weeks after conception). We limited the assessment of stress to the relatively objective report of whether certain events had occurred around the time of conception, because we felt women would be less able to objectively recall their perceived level of stress around the time of conception, after having delivered offspring with major malformations. However, recall bias still could have occurred, and the interpretation of the questions could have differed for mothers of cases and controls (eg, in how they defined “anyone close” to them). There is concern that mothers of malformed infants will overreport or more thoroughly report exposures than controls,[37-39] but several studies suggest that for many exposures recall bias is likely to be minimal[38-41]; however, none of these studies considered stress per se. We lacked information regarding whether the events occurred to the woman herself or the relatively subjective category of “anyone close” to her, and we gave equal weighting to all events. We also did not assess social support, which may be an important buffer of the stress response. One previous study observed that emotional support was associated with reduced risks of NTDs, but it did not modify or “buffer” their association with stressful life events.[10] Another study observed that social networks were

protective against NTDs.[42] We are unaware of other studies of social support and birth defects risks.

Increasing evidence suggests that stress during pregnancy is associated with adverse health effects among offspring.[43,44] The present study indicates that these adverse effects may include increased risks of certain birth defects.

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TABLE 1

Characteristics of Mothers of Cases (n = 1189) and Controls (n = 695)

	Cases*	Controls*
Race-ethnicity; no. (%)		
US-born Hispanic	194 (17)	153 (22)
Foreign-born Hispanic	501 (43)	263 (38)
Non-Hispanic White	273 (23)	142 (21)
Other	208 (18)	127 (18)
Education; no. (%)		
<High school graduation	381 (32)	200 (29)
High school graduation	240 (20)	166 (24)
1-3 yr of college	276 (24)	150 (22)
4 or more yr of college	277 (24)	166 (24)
Prepregnancy obesity		
BMI ≥29 kg/m^2	881 (82)	532 (82)
BMI >29 kg/m^2	197 (18)	118 (18)
Age at delivery (yrs); mean ± SD†	28.74 ± 6.36	28.31 ± 6.42
Smoking‡		
No	1108 (94)	633 (92)
Yes	72 (6)	54 (8)
Alcohol intake‡		
No	941 (80)	563 (82)
Yes	235 (20)	122 (18)
Intake of folic acid-containing supplements§		
No	515 (43)	270 (39)
Yes	672 (57)	423 (61)
Neighborhood crime¶		
None	640 (55)	374 (55)
Any	516 (45)	303 (45)
Food insecurity¶		
None	978 (83)	597 (87)
Any	201 (17)	91 (13)

*Numbers of cases and controls are less than the total due to missing data.

†Based on 1187 cases and 692 controls.

‡During the first 2 months after conception.

§During the 2 months before or 2 months after conception.

¶The percentage of women with any versus no “yes” responses to the series of questions, during the 2 months before through 2 months after conception.

TABLE 2

Frequency of Number of Stressful Life Events Reported by Mothers of Cases and Controls, From 2 Months Before Through 2 Months After Conception, and Association With Risk of Birth Defects

No. of Stressful Life Events	Cases (n = 1174)* No. (%)	Controls (n = 688)* No. (%)	OR (95% CI)
0†	424 (36)	300 (44)	1.0
1	248 (21)	146 (21)	1.20 (0.93-1.55)
2	195 (17)	100 (15)	1.38 (1.04-1.83)
3	111 (9)	56 (8)	1.40 (0.99-2.00)
4	86 (7)	38 (6)	1.60 (1.06-2.41)
5	41 (3)	19 (3)	1.53 (0.87-2.68)
6	39 (3)	11 (2)	2.51 (1.26-4.98)
7	9 (1)	8 (1)	1.18 (0.65-2.16)‡
8	9 (1)	5 (1)	—
9	8 (1)	5 (1)	—
10	2 (<1)	0	—
11	2 (<1)	0	—

*Numbers of cases and controls are less than the total due to missing data.

†Reference category.

‡Seven or more stressful life events were collapsed into a single category for estimation of the odds ratio.

TABLE 3

Unadjusted and Adjusted Association of a 3-Unit Change in the Stressful-Life-Events Index With Risk of Selected Birth Defects

	No. Cases	No. Controls	OR (95% Confidence Interval)*	
			Unadjusted OR (95% CI)	Adjusted† OR (95% CI)
Isolated cleft lip with or without cleft palate	364	556	1.40 (1.13-1.72)	1.34 (1.06-1.71)
Isolated cleft palate	122	556	1.26 (0.93-1.70)	1.45 (1.03-2.06)
Anencephaly	125	556	1.56 (1.18-2.07)	1.81 (1.28-2.56)
Spina Bifida	156	556	1.29 (0.98-1.70)	1.39 (1.00-1.94)
d-Transposition of the great arteries	124	622	1.15 (0.85-1.55)	1.27 (0.89-1.81)
Tetralogy of Fallot	145	622	1.26 (0.96-1.66)	1.38 (1.00-1.91)

*Reflects the OR for a 3-unit change in the stressful life events index; the OR for an n-unit change equals (OR for a 3-unit change)$^{n/3}$; eg the OR for a 6-unit change equals (OR for a 3-unit change)$^{6/3}$.

†Adjusted for maternal race-ethnicity, education, obesity, age, smoking, alcohol intake, folic acid supplement intake, neighborhood crime, and food insecurity.

TABLE 4

Association of a 3-Unit Change in the Stressful-Life-Events Index With Risk of Neural Tube Defects, Stratified by Folic Acid Supplement Intake During the First 2 Months After Conception

Folic Acid	No. Cases	No. Controls	OR (95% CI)
Anencephaly			
No	55	210	2.35 (1.47, 3.77)
Yes	70	346	1.42 (0.89, 2.25)
Spina Bifida			
No	70	210	1.79 (1.14, 2.81)
Yes	86	346	1.09 (0.69, 1.72)

*Reflects the OR for a 3-unit change in the stressful life events index; the OR for an n-unit change equals (OR for a 3-unit change)$^{n/3}$; eg the OR for a 6-unit change equals (OR for a 3-unit change)$^{6/3}$; ORs are adjusted for maternal race-ethnicity, education, obesity, age, smoking, alcohol intake, neighborhood crime and food insecurity.