Paediatr Perinat Epidemiol. Author manuscript; available in PMC 2015 July 01.

Published in final edited form as:

Paediatr Perinat Epidemiol. 2014 July ; 28(4): 338–344. doi:10.1111/ppe.12123.

Maternal stressors and social support as risks for delivering babies with structural birth defects

Suzan L. Carmichael[1,*], **Chen Ma**[1], **Sarah Tinker**[2], **Sonia A. Rasmussen**[2], **Gary M. Shaw**[1], and **the National Birth Defects Prevention Study**

[1]Department of Pediatrics, Stanford University, Stanford, CA, 94305

[2]Centers for Disease Control and Prevention, Atlanta, GA 30333

Abstract

Background—We examined the association of maternal stressful life events and social support with risks of birth defects using National Birth Defects Prevention Study data, a population-based case-control study.

Methods—We examined 7 stressful life events and 3 social support questions applicable to the periconceptional period, among mothers of 552 cases with neural tube defects (NTDs), 413 cleft palate (CP), 797 cleft lip +/− cleft palate (CLP), 189 d-transposition of the great arteries (dTGA), 311 tetralogy of Fallot (TOF), and 2,974 non-malformed controls. A stressful life events index equaled the sum of “yes” responses to the 7 questions. Social support questions were also summed to form an index. Data were analyzed using logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI), adjusted for maternal race-ethnicity, age, education, body mass index, smoking, drinking, and intake of vitamin supplements.

Results—Associations with the stress index tended to be higher with higher scores, but few 95% CIs excluded one. A 4-point increase in the index was moderately associated with NTDs (OR 1.5, 95% CI 1.1, 2.0) and CLP (OR 1.3, 95% CI 1.0–1.7). The social support index tended to be associated with reduced risk but most 95% CIs included one, with the exception of dTGA (OR for a score of three versus zero was 0.5, 95% CI 0.3–0.8).

Conclusions—Maternal periconceptional stressful life events, social support, and the two factors in combination were at most modestly, if at all, associated with risks of the studied birth defects.

Several observational studies have examined the association of maternal stressful life events with risks of orofacial clefts among offspring.[1–12] Most but not all[2,6] reported increased risk of clefts among offspring born to women who experienced higher stress during pregnancy. Few studies have examined this association with birth defects other than orofacial clefts; they have reported increased risks of neural tube defects (NTD)[1,10,13] and conotruncal heart

[*]Corresponding author: Suzan L. Carmichael, Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University, 1265 Welch Road, Rm. X109B, Stanford, CA 94305-5415, scarmichael@stanford.edu.

DISCLAIMER:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the California Department of Public Health or of the Centers for Disease Control and Prevention.

defects[1,10,14] among women with higher stress during pregnancy. Measurement of stress has tended to be very limited in scope, for example two or three stressful life events (e.g. death of a family member, divorce).

Biological plausibility for an association of stress during pregnancy with orofacial clefts has been demonstrated in animal models where administration of corticosteroids – a natural product of the stress response – can induce orofacial clefts.[15–17] In addition, increased risk of orofacial clefts has been reported among women taking corticosteroid medications in early pregnancy.[18,19]

Social support (i.e., the various forms of assistance received from one's social relationships) represents an important potential buffer against the negative impacts of the stress response. We are aware of two previous studies examining social support and birth defects. Both studies observed lower risk of NTDs among women with more social support.[13,20] In light of the potential buffering effects that increased social support may have on risk of birth defects, it is important to consider stress indicators and social support indicators not just as separate influences but also as combined influences on risk.

Maternal health-related behaviours and characteristics are also an important consideration. Negative health behaviours, such as cigarette smoking, may co-occur with stress as part of a coping mechanism and should therefore be investigated as confounders of associations between stress and birth defects. Other behaviours and characteristics may modify associations with stress; for example, intake of supplements could protect against its adverse effects,[15,16,21] and body mass index may impact the physiologic response to stress.[22]

The objective of the current study was to examine the association of maternal stressful life events and social support in early pregnancy with risks of orofacial clefts, NTDs and conotruncal heart defects among offspring. We used recent data from the National Birth Defects Prevention Study (NBDPS), a large, multi-center population-based case-control study that includes information on several potentially stressful life events, social support, and a variety of maternal characteristics and behaviours.

METHODS

These analyses included subjects with estimated dates of delivery (EDD) from January 2006 to December 2009 who participated in NBDPS; questions regarding stress and social support were not asked for earlier study years. Detailed study methods have been published.[23] In brief, eight states included liveborn, stillborn (fetal deaths ≥20 weeks gestation), and prenatally diagnosed and electively terminated cases (AR, CA, GA, IA, NC, NY, TX, UT) and one state included only liveborn and stillborn cases (MA).

Cases included infants or fetuses with neural tube defects (NTDs, including anencephaly, spina bifida, encephalocele and craniorachischisis); orofacial clefts (cleft lip with or without cleft palate, CLP, or cleft palate alone, CP); or the conotruncal heart defects tetralogy of Fallot (TOF) or d-transposition of the great arteries (dTGA), as confirmed by clinical, surgical, or autopsy reports. Conotruncal heart defects required verification by echocardiography, cardiac catheterization, surgical report, or autopsy. Cases resulting from known single gene or chromosomal abnormalities (syndromic cases) were ineligible, given their presumed genetic determinants. Infants whose clefts were believed to be secondary to another defect (e.g., holoprosencephaly) were ineligible for the study.

Each participating center randomly selected approximately 100 liveborn controls without birth defects per study year from birth certificates (AR, GA, IA, MA, NC, UT) or birth hospitals (CA, NY, TX) to represent the population from which cases were derived.

Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, no earlier than six weeks after the infant's EDD and no later than 24 months after the EDD. Interviews were conducted with mothers of 2532 cases (63% participation rate) and 3351 controls (60% participation rate) from the 2006–2009 cohort. Median time from actual date of delivery to interview was 10.5 months for cases (interquartile range from 6.9 to 15.0 months) and 7.8 months for controls (interquartile range 5.3 to 12.2 months).

Mothers were asked yes/no questions about whether they experienced five life events during the three months before or first three months of pregnancy (relationship difficulties; legal/financial problems; violence/crime; illness/injury; or a relative's death). In a separate section of the interview, they reported their employment and residence history during that time period; we considered a change in employment or residence as two additional stressful life events, bringing the total to seven. Women were asked three questions about social support (whether they could count on someone for emotional support, financial help, and help with daily tasks), all applicable to the same periconceptional time period as the stress questions. (Exact questions are in Supplementary Table 1.) Covariates were maternal race-ethnicity; age, education; prepregnancy body mass index; smoking or alcohol drinking in the month before or first trimester of pregnancy; and intake of folic acid-containing vitamin/mineral supplements. Complete data were available for 2974 controls and 2244 cases (552 NTDs, 413 CP, 797 CLP, 189 dTGA, 311 TOF; 18 cases had multiple phenotypes).

Stress and social support questions were examined individually and summed to create two indices. Multivariable logistic regression analyses were conducted to estimate odds ratios and 95 percent confidence intervals reflecting the association of each stressful life event and social support question, as well as the indices, with each birth defect. Results for anencephaly and spina bifida groups were similar so they are presented together. We examined the stress index in categorical and continuous (ordinal) form. We also examined stress and social support in combination, dichotomizing the stress index as 0–3 versus 4–7 and the social support index as 0–2 versus 3 to reflect 'high' or 'low' stress or social support. Analyses were adjusted for the covariates described above.

RESULTS

Most mothers of controls were non-Hispanic white (58%), between the ages of 25 and 34 years (55%), and had more than a high school education (63%); 21% were obese; and 17% smoked, 38% drank alcohol, and 89% took folic acid-containing supplements periconceptionally (Table 1). Each stressful life event was reported by 7–26% of control mothers, and 60% of all control mothers reported yes to at least one of the stressful life event questions. A 'yes' response was reported by 85–87% of control mothers for each of the social support questions, and 75% reported 'yes' to all three. Percentages were similar for case mothers.

Most of the adjusted odds ratios for individual life events and the specific birth defects under study were approximately 1.0, with only a few being elevated and having 95% confidence intervals that did not include 1.0 (relationship difficulties (NTDs), legal problems (CLP or ToF)) (Supplementary Table 1). Associations with the stress index tended to be higher with higher scores, although few 95% confidence intervals excluded one (Table 2). A 4-point increase in the index was moderately associated with NTDs (OR 1.5, 95% CI 1.1, 2.0) and CLP (OR 1.3, 95% CI 1.0–1.7). Associations with social support questions and the social support index tended to be associated with reduced risk but most 95% CIs included one, with the exception of dTGA (Table 2).

Analyses examining the association of stress and social support in combination indicated that the largest odds ratios were for women with high stress and low support (versus low stress and high support), for all of the studied phenotypes except TOF (Supplementary Table 3). However, even these odds ratios were modest and only the confidence interval for CLP excluded one (OR 1.6, 95% CI 1.01, 2.4).

COMMENT

In this study, maternal periconceptional stressful life events, social support, and the two factors in combination were at most modestly, if at all, associated with risks of NTDs, orofacial clefts or conotruncal heart defects. There was some suggestion of increased risk for NTDs and CLP for mothers who reported stressful life events. Social support was associated with reduced risks, most notably for dTGA.

Previous studies have suggested that increased stress during pregnancy is associated with increased risks of birth defects.[1–14] These assessments of stress has tended to be less comprehensive, however, including for example a few specific life events,[8,10,11,13,14] dichotomies of whether the mother was stressed or not (sometimes with uncertain methods of assessment),[2,4–7,9] or prevalence before versus after a natural disaster.[3,12] Most recently, a data linkage-based study from Denmark indicated higher risk of orofacial clefts among offspring born to women who experienced the death of a close relative during early pregnancy,[11] and another study indicated that the prevalence of clefts was higher after versus before Hurricane Katrina in the New Orleans area.[12] A previous study of California births, which included the same phenotypes as those included in the current study, included the most detailed assessment of stress to date, with data on 18 stressful life events. All of the studied phenotypes were associated with increased number of stressful life events.[1] For NTDs, these associations were particularly strong among women who did not take folic acid-containing supplements. The explanation for weaker associations in the current study is uncertain. One potential explanation is that the current study included fewer stressful life event questions than the previous California study (seven items versus 18). We did observe a tendency toward higher risks with higher number of stressful life events for most of the studied outcomes, but the results were imprecise.

We are aware of two other studies that examined social support and birth defects. One focused on social network size;[20] the other examined social networks and emotional support.[13] Both studies focused on NTDs and reported reduced risks. Associations in our study were in the same direction but only confidence intervals for dTGA excluded one.

When examining potential influences in combination, our results suggested that women with highest stress and lowest support had the largest risk estimates for most of the studied phenotypes, but again associations were modest and imprecise. Suarez et al. reported that social support did not modify the association with stress in their study of NTDs.[13] More detailed assessment of social support will be useful to confirm its potential role in birth defects etiology and in particular whether it can reduce the potential negative impact of stress.

Strengths of the current study include its population-based, multi-center design, careful case ascertainment, large size, examination of stress and social support in combination, and adjustment for several potential confounders. The general lack of association observed could be influenced by the relatively limited assessment of stress and social support. The assessment of stress included only seven questions, but this does represent more detail than most previous studies. In addition, the 6-month window of exposure does not allow separate investigation of acute versus chronic stressors. Responses to the questions about life events were limited to yes/no rather than having women rate the stressfulness of the events, in order to maximize ability to recall events objectively (job and address change were assessed via more detailed questions). Interviews were conducted with mothers of 63% of eligible cases and 60% of controls. We have no particular reason to believe that participation was related to periconceptional stress or social support, differentially for cases versus controls, but if it was, then selection bias may have affected our results. Similarly, we do not know whether mothers' recall of stress and social support was related to case or control status, but if it was, then recall bias could have affected our results. We adjusted for several potential covariates, but other potential confounders were not evaluated. For example, we did not adjust for medications that may be used to cope with stress (e.g., SSRIs, benzodiazapines); however, given that the associations with stress that we observed are modest at best, and use of these medications tends to be rare during pregnancy, it is unlikely that adjustment for use of these medications would make a substantive difference.

The negative impact of stress on risks of birth defects has been studied much less than other reproductive outcomes such as preterm birth.[24] It is important to continue to strive toward a better understanding of stress as a risk factor for birth defects, perhaps through a more in-depth assessment of stress and social support than is currently included in the NBDPS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the California Department of Public Health Maternal Child and Adolescent Health Division for providing data. This project was partially supported by NIH R03 DE020112 and CDC 6U01-DD-000489 and 1U01-DD-0006982.

References

1. Carmichael SL, Shaw GM, Yang W, Abrams B, Lammer EJ. Maternal stressful life events and risks of birth defects. Epidemiology. 2007; 18:356–361. [PubMed: 17435445]
2. Fraser FC, Warburton D. No association of emotional stress or vitamin supplement during pregnancy to cleft lip or palate in man. Plastic Reconstructive Surgery. 1964; 33:395–399. [PubMed: 14142137]
3. Montenegro MA, Palomino H, Palomino HM. The influence of earthquake-induced stress on human facial clefting and its simulation in mice. Archives of Oral Biology. 1995; 40:33–37. [PubMed: 7748110]
4. Czeizel A, Nagy E. A recent aetiological study on facial clefting in Hungary. Acta Paediatrica Hungarica. 1986; 27:145–166. [PubMed: 3756014]
5. Laumon B, Martin JL, Collet P, Bertucat I, Verney MP, Robert E. Exposure to organic solvents during pregnancy and oral clefts: a case-control study. Reproductive Toxicology. 1996; 10:15–19. [PubMed: 8998380]
6. Rajabian MH, Sherkat M. An epidemiologic study of oral clefts in Iran: analysis of 1,669 cases. Cleft Palate Craniofacial Journal. 2000; 37:191–196. [PubMed: 10749061]
7. Saxen I. Cleft lip and palate in Finland: parental histories, course of pregnancy and selected environmental factors. International Journal of Epidemiology. 1974; 3:263–270. [PubMed: 4412458]
8. Hansen D, Lou HC, Olsen J. Serious life events and congenital malformations: a national study with complete follow-up. Lancet. 2000; 356:875–880. [PubMed: 11036891]
9. Peer LA, Strean LP. Stress as an etiologic factor in the development of cleft palate. Plastic and Reconstructive Surgery. 1956; 18:1–8. [PubMed: 13359134]
10. Carmichael SL, Shaw GM. Maternal life event stress and congenital anomalies. Epidemiology. 2000; 11:30–35. [PubMed: 10615840]
11. Ingstrup KG, Liang H, Olsen J, Nohr EA, Bech BH, Wu CS, et al. Maternal bereavement in the antenatal period and oral cleft in the offspring. Human Reproduction. 2013; 28:1092–9. [PubMed: 23293222]
12. Goenjian HA, Chiu ES, Alexander ME, St Hilaire H, Moses M. Incidence of cleft pathology in greater new orleans before and after hurricane katrina. Cleft Palate Craniofacial Journal. 2011; 48:757–761. [PubMed: 21303264]
13. Suarez L, Cardarelli K, Hendricks K. Maternal stress, social support, and risk of neural tube defects among Mexican Americans. Epidemiology. 2003; 14:612–616. [PubMed: 14501277]
14. Adams MM, Mulinare J, Dooley K. Risk factors for conotruncal cardiac defects in Atlanta. Journal of the American College of Cardiology. 1989; 14:432–442. [PubMed: 2787814]
15. Peer LA, Bryan WH, Strean LP, Walker JC Jr, Bernhard WG, Peck GC. Induction of cleft palate in mice by cortisone and its reduction by vitamins. Journal of the International College of Surgeons. 1958; 30:249–254. [PubMed: 13575880]
16. Yoneda T, Pratt RM. Vitamin B6 reduces cortisone-induced cleft palate in the mouse. Teratology. 1982; 26:255–258. [PubMed: 7163974]
17. Salomon DS, Pratt RM. Involvement of glucocorticoids in the development of the secondary palate. Differentiation. 1979; 13:141–154. [PubMed: 232045]
18. Carmichael SL, Shaw GM, Ma C, Rasmussen SA, Lammer EJ. Maternal corticosteroid use and orofacial clefts. American Journal of Obstetrics and Gynecology. 2007; 197:585.e581–587. [PubMed: 18060943]

19. Pradat P, Robert-Gnansia E, Di Tanna GL, Rosano A, Lisi A, Mastroiacovo P. First trimester exposure to corticosteroids and oral clefts. Birth Defects Research Part A: Clinical and Molecular Teratology. 2003; 67:968–970.

20. Carmichael SL, Shaw GM, Neri E, Schaffer DM. Social networks and risk of neural tube defects. European Journal of Epidemiology. 2003; 18:129–133. [PubMed: 12733834]

21. Miller TJ. Cleft palate formation: a role for pyridoxine in the closure of the secondary palate in mice. Teratology. 1972; 6:351–356. [PubMed: 4643617]

22. Drapeau V, Therrien F, Richard D, Tremblay A. Is visceral obesity a physiological adaptation to stress? Panminerva Medica. 2003; 45:189–195. [PubMed: 14618117]

23. Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, et al. The National Birth Defect Prevention Study. Public Health Reports. 2001; 116:32–40. [PubMed: 11889273]

24. Wadhwa PD, Entringer S, Buss C, Lu MC. The contribution of maternal stress to preterm birth: issues and considerations. Clinics in Perinatology. 2011; 38:351–384. [PubMed: 21890014]

Table 1

Characteristics of mothers of control infants, National Birth Defects Prevention Study, 2006–2009.

		Percent of Controls[1] (n=2974)	Percent of All Cases[1] (n=2244)
Race-ethnicity	Non-Hispanic white	58	60
	Black	10	8
	Hispanic	22	22
	Other	10	10
Age (years)	<25	31	30
	25–34	55	55
	35 or older	14	15
Education	Less than high school	14	16
	Equal to high school	23	25
	Greater than high school	63	59
Body mass index (kg/m^2)	Underweight (<18.5)	5	4
	Normal weight (18.5–24.9)	50	48
	Overweight (25.0–29.9)	24	24
	Obesity (>=30.0)	21	24
Smoking[2]	None	83	80
	Any	17	20
Drinking[2]	None	63	64
	Some	25	23
	Binge drinking	13	13
Folic acid-containing vitamin/mineral supplement use	Began month before or first month of pregnancy	58	57
	Began second or third month of pregnancy	31	31
	Began later or none	11	12
Stressful life events[3]	Relationship difficulties	17	20
	Legal/financial problems	14	18
	Violence/crime	7	8
	Illness/injury	14	15
	Death of someone close	15	15
	Moved	18	18
	Changed jobs	26	26
Social support[3]	Emotional support	87	86
	Financial support	85	83
	Help with daily tasks	85	84

[1] Numbers may not add to 100% due to rounding.

[2] From one month before through three months after conception; binge drinking refers to having four or more drinks on at least one occasion

[3] From three months before through three months after conception

Table 2

Association of stressful life events and social support with risks of birth defects, National Birth Defects Prevention Study, 2006–2009.*

	Controls	NTD		CP		CLP		dTGA		TOF	
Stress index	No. Controls (total=2974)	No. Cases (total=552)	AOR (95% CI)	No. Cases (total=413)	AOR (95% CI)	No. Cases (total=797)	AOR (95% CI)	No. Cases (total=189)	AOR (95% CI)	No. Cases (total=311)	AOR (95% CI)
0	1199 (40%)	213	Reference	177	Reference	309	Reference	85	Reference	129	Reference
1	859 (29%)	142	0.9 (0.7–1.2)	109	0.9 (0.7–1.1)	219	1.0 (0.8–1.2)	49	0.8 (0.6–1.2)	82	0.9 (0.7–1.2)
2	508 (17%)	106	1.2 (0.9–1.5)	66	0.9 (0.7–1.2)	132	1.0 (0.8–1.2)	31	0.8 (0.5–1.3)	55	1.0 (0.7–1.4)
3	252 (8%)	53	1.2 (0.9–1.7)	31	0.9 (0.6–1.3)	74	1.1 (0.8–1.5)	10	**0.5 (0.3–1.0)**	30	1.1 (0.7–1.8)
4	102 (3%)	24	1.4 (0.9–2.4)	20	1.4 (0.8–2.3)	41	**1.5 (1.0–2.3)**	10	1.2 (0.6–2.4)	9	0.9 (0.4–1.8)
5	46 (2%)	10	1.5 (0.7–3.0)	8	1.2 (0.5–2.7)	15	1.2 (0.6–2.1)	2	n.c.	3	0.7 (0.2–2.2)
6–7	8 (<1%)	4	3.0 (0.9–10.1)	2	n.c.	7	**3.4 (1.2–9.6)**	2	n.c.	3	3.1 (0.8–12.2)
Continuous (4-unit change)			**1.5 (1.1–2.0)**		1.1 (0.7–1.5)		1.3 (1.0–1.7)		0.8 (0.5–1.3)		1.1 (0.7–1.6)
Social support question											
Emotional support	2601	464	0.8 (0.6–1.1)	347	0.8 (0.6–1.0)	681	0.9 (0.7–1.2)	167	0.9 (0.6–1.5)	275	1.0 (0.7–1.5)
Financial support	2527	446	0.8 (0.6–1.0)	336	0.8 (0.6–1.1)	669	1.0 (0.8–1.3)	157	0.8 (0.5–1.1)	263	0.9 (0.7–1.3)
Help with daily tasks	2531	456	0.9 (0.7–1.1)	343	0.9 (0.7–1.2)	672	1.0 (0.8–1.3)	154	0.7 (0.48–1.1)	261	0.9 (0.6–1.2)
Social support index											
0	150	37	Reference	32	Reference	52	Reference	17	Reference	20	Reference
1	223	54	1.0 (0.6–1.6)	32	0.7 (0.4–1.2)	52	0.7 (0.4–1.0)	10	**0.4 (0.2–0.8)**	20	0.7 (0.3–1.3)
2	367	71	0.8 (0.5–1.3)	53	0.7 (0.4–1.1)	109	0.9 (0.6–1.3)	18	**0.4 (0.2–0.8)**	34	0.7 (0.4–1.2)
3	2234	390	0.8 (0.5–1.1)	296	**0.7 (0.4–1.0)**	584	0.8 (0.6–1.2)	144	**0.5 (0.3–0.8)**	237	0.7 (0.5–1.2)

* Indices reflect number of questions that had a 'yes' response. Odds ratios were adjusted for maternal race-ethnicity, age, education, body mass index, smoking, drinking, and intake of vitamin supplements. Odds ratios are in **bold** if the CI excluded 1.0 before rounding

n.c. = not calculated