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Maternal Stressors and Social Support and Risks of Delivering Babies With Gastroschisis or Hypospadias

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Abstract

We examined the association of maternal stressful life events and social support with risks of gastroschisis and hypospadias, using data from the National Birth Defects Prevention Study, a population-based case-control study of US births taking place in 2006–2011. We examined maternal self-reports of 7 life events and 3 sources of social support during the periconceptional period among mothers of 593 gastroschisis cases, 1,142 male hypospadias cases, and 4,399 nonmalformed controls. Responses to the questions on stressful life events were summed to form an index (higher is worse), as were responses to questions on social support (higher is better). We used logistic regression to estimate adjusted odds ratios and 95% confidence intervals. The adjusted odds ratios for gastroschisis for a 4-point increase in the stress index were 3.5 (95% confidence interval (CI): 2.6, 4.8) among nonteenage mothers (age ≥20 years) and 1.0 (95% CI: 0.5, 1.7) among teenage mothers (age <20 years). The odds ratio for hypospadias (among all mothers) was 0.8 (95% CI: 0.7, 1.1). Adjusted odds ratios for a social support score of 3 (versus 0) in the 3 respective groups were 0.6 (95% CI: 0.4, 1.0), 1.0 (95% CI: 0.5, 2.3), and 0.6 (95% CI: 0.4, 0.9). Given the lack of prior research on these outcomes and stress, results should be interpreted with caution.

Keywords

birth defects; gastroschisis; hypospadias; pregnancy; stress

Maternal psychosocial stress is a suggested risk factor for various adverse pregnancy outcomes, but findings specific to structural birth defects, excepting orofacial clefts, is limited. Some previous studies suggest that maternal stress may also be associated with 2 other birth defects: gastroschisis, a congenital defect of the abdominal wall through which the intestines and other abdominal organs can protrude, and hypospadias, a congenital condition in males in which the urethral opening is displaced ventrally from the distal tip of the penis. In a recent study of 91 cases, Palmer et al. (1) reported that maternal stressful life

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events were associated with increased risk of gastroschisis, which they proposed could be attributable to the effects of stress on thrombotic, inflammatory, or endocrine pathways. Experimental studies have suggested that in utero administration of corticosteroids— which are a natural product of the stress response—results in increased risk of hypospadias (2). They have also suggested that exposure to corticosteroids, as well as maternal stress, is associated with reduced anogenital distance in male offspring (3,4). Reduced anogenital distance, like hypospadias, is thought to arise from impaired androgen function or signaling. Connections between the stress response and sex steroid production are well-known, albeit not particularly well understood during early gestation(5–7), which is when gastroschisis and hypospadias develop.

To extend these observational and investigational findings, we examined the association of maternal life events and social support (a potential buffer against the negative effects of stress) with risks of gastroschisis and hypospadias. We used data from the National Birth Defects Prevention Study (NBDPS), a large, multisite, population-based case-control study.

METHODS

Information on study methods has been published previously (8, 9). At 9 US sites, NBDPS investigators collected data on stress and social support from women with estimated dates of delivery between January 2006 and December 2011; these questions were not asked for earlier study years.

Cases included infants or fetuses with gastroschisis or hypospadias, as confirmed by clinical, surgical, or autopsy reports. Gastroschisis cases with a phenotype suggestive of limb-body wall complex or amniotic band sequence were excluded. Hypospadias cases were eligible if the urethral opening was proximal to the glans penis (also known as “moderate-to-severe” or “second or third degree” hypospadias). Cases resulting from known single-gene or chromosomal abnormalities (syndromic cases) were ineligible, given their presumed genetic determinants.

At each NBDPS site, researchers randomly selected approximately 100 liveborn controls without major birth defects per study year from birth certificates (Arkansas, Georgia, Iowa, Massachusetts, North Carolina, Utah) or birth hospitals (California, New York, Texas) to represent the population from which cases were derived. Analyses of hypospadias were restricted to male controls, since by definition only males had hypospadias.

Maternal interviews were conducted in English or Spanish, primarily by telephone, using a standardized, computer-based questionnaire 6 weeks–24 months after the estimated date of delivery. The participation rate was 65% for gastroschisis, 65% for hypospadias, and 64% for controls. Interview data from the 2006–2011 cohort on stress and social support were available for mothers of 697 gastroschisis cases, 1,241 hypospadias cases, and 4,972 controls. Median time from date of delivery to interview was 12 months for cases (interquartile range, 8–17 months) and 7 months for controls (interquartile range, 5–12 months).

Mothers were asked yes/no questions about whether they had experienced any of 5 stressful life events during the 3 months before pregnancy or the first 3 months of pregnancy (relationship difficulties, legal/financial problems, violence/ crime, illness/injury, or a relative's death). They also reported their history of employment and residence during that time period; we considered a change in employment or residence to be an additional stressful life event, bringing the total number of events to 7. Women were asked 3 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 time period as the stress questions. Specific questions are shown in the Appendix. Covariates, which were selected a priori, were maternal race/ethnicity; age; parity; education; prepregnancy body mass index (weight (kg)/height $(m)^2$); and smoking, alcohol use, and intake of folic acid-containing vitamin/mineral supplements during the month before pregnancy or the first trimester of pregnancy. Complete data were available for 593 cases with gastroschisis (85%), 1,142 cases with hypospadias (92%), and 4,399 controls (88%).

Responses to questions on stress and social support were examined individually (each item was scored as yes = 1, no = 0) and summed to create 2 indices. The assumption underlying this conventional approach is that the effects of stressful life events (or aspects of social support) are additive (10). Multivariable logistic regression analyses were conducted to estimate odds ratios and 95% confidence intervals reflecting the association of each stressful life event and social support question, as well each index, with each birth defect. We examined the stress index in both categorical and continuous (ordinal) form. We also examined stress and social support in combination, dichotomizing the stress index score as 0–3 versus 4–7 and the social support index score as 0–2 versus 3 to reflect "high" or "low" levels of stress and social support. Results of the analyses were adjusted for the covariates described above. Given the strong association of gastroschisis with young maternal age, we present results for this outcome separately for mothers who were under age 20 years (teenage mothers) and mothers who were aged 20 years or older (nonteenage mothers).

RESULTS

Relative to controls, mothers of gastroschisis cases were more likely to be Hispanic, younger, less educated, nulliparous, nonobese, smokers, binge drinkers, and nonusers of vitamin/ mineral supplements, whereas mothers of hypospadias cases were more likely to be non-Hispanic white, older, more educated, nulliparous, and users of supplements (Table 1). Among control mothers, the most frequently reported stressful life event was a job change (25%), and the least frequently reported was violence or crime (7%). A "yes" response was reported by 86%–88% of control mothers for each of the social support questions. Teenage control mothers were more likely than older control mothers to report most of the stressful life events (Table 2).

Among subjects born to nonteenage mothers, the adjusted odds ratios for gastroschisis and 5 of the 7 life events had confidence intervals that excluded 1.0 (the odds ratios ranged from 1.5 for changing jobs to 2.6 for relationship difficulties) (Table 2). In contrast, none of the 95% confidence intervals excluded 1 for gastroschisis among subjects born to teenage mothers or for hypospadias, and the range of odds ratios was narrower and closer to the null

(odds ratios were 0.7–1.4 for gastroschisis and 0.8–1.2 for hypospadias) (Tables 2 and 3). Among nonteenage mothers, a higher number of life events was associated with increasing risk of gastroschisis; for example, a score of 3–5 was associated with at least a 3-fold increased risk. When specified as a continuous variable, the odds ratio was 3.5 (95% confidence interval (CI): 2.6, 4.8) for a 4-unit change in the life events score. Odds ratios were closer to 1 for gastroschisis among teenage mothers and for hypospadias.

Among teenage mothers, social support was not associated with risk of gastroschisis. Social support was associated with lower risk of gastroschisis among nonteenage mothers and lower risk of hypospadias; for example, the odds ratio for a “yes” response to all 3 social support questions was 0.6 (95% CI: 0.4, 1.0) for gastroschisis and 0.6 (95% CI: 0.4, 0.9) for hypospadias (Tables 2 and 3).

Analyses examining the associations for stress and social support in combination did not show that high social support reduced the odds ratios observed with high stress.

DISCUSSION

In this study, maternal periconceptional stressful life events were associated with modestly increased risk of gastroschisis, but only among nonteenage mothers. They were not associated with risk of gastroschisis among teenage mothers or with risk of hypospadias. Social support was associated with reduced risk of gastroschisis among nonteenage mothers and reduced risk of hypospadias, but it was not associated with risk of gastroschisis among teenage mothers, nor did such support appear to modify the risk association with stressful life events.

We are aware of 1 previous study that examined the relationship between stressful life events and gastroschisis (1). In that study, Palmer et al. (1) reported higher risk among women with more stressful life events. They used the same 5 life event questions as the NBDPS and also included whether the woman had moved, but they did not include whether she had changed jobs. Several mechanisms were proposed, including thrombotic, inflammatory, or endocrine pathways. In our analysis, gastroschisis was associated with maternal stressful life events, but only among women who were at least 20 years of age. Babies born to teenage mothers are at severalfold higher risk of gastroschisis than those born to older mothers (11, 12), but the underlying mechanism for this higher risk is unknown. We examined results separately among younger mothers and older mothers to determine whether a higher prevalence of having experienced stressful life events during early pregnancy might contribute to the known increased risk among teenage mothers; it did not. One potential explanation for the difference in results by age is that the questions we used to characterize stressful events are less relevant among younger mothers and therefore potentially less valid. It is also possible that mechanisms contributing to risk of gastroschisis vary by age. We were unable to explore either of these explanations with the available data.

Hypospadias was not associated with maternal stressful life events. To our knowledge, this was the first study to examine this association. Corticosteroids, a natural product of the stress response, have been experimentally linked to hypospadias. In a previous analysis of

NBDPS data, we did not observe an association of hypospadias with use of corticosteroids (13). Fetal androgen production is critical to normal urethral closure. Prior studies suggest that activation of the maternal hypothalamic-pituitary-adrenal axis is associated with fetal androgen production (6, 7) and shorter anogenital distance and less masculinized behavior in offspring (3). However, the exact connections between maternal and fetal hypothalamic-pituitary-adrenal axis-related activity and sex steroid levels are somewhat uncertain, especially during early gestation, when hypospadias occurs. We also do not know whether these connections vary depending on whether stress is acute or chronic.

Our findings suggested that more social support (i.e., the various forms of assistance received from one's social relationships) was associated with reduced risks of gastroschisis among nonteenage mothers and hypospadias. However, we did not find evidence that higher risks associated with increased stress were dampened in the presence of greater social support.

Strengths of our study include its population-based, multicenter design, careful case ascertainment, large size, examination of stress and social support in combination, and adjustment for several potential confounders. Our examination of stress was more detailed than that in many prior studies of stress and birth defects but still limited, and we made no differentiation between chronic stress and acute stress. In addition, we did not weight the different life events, although some may have been more stress-inducing than others. Our inclusion of social support in our study was a strength, as social support may provide a buffer against the negative impact of stress, but few other studies of birth defects have considered it (14–16). Selection bias and recall bias are potential alternative explanations for our results. We do not have strong reasons to believe that nonparticipants would differ from participants (differentially by case/control status) with regard to the presence of stress during early pregnancy, or that recall for relatively objective questions about life events and social support would differ on the basis of case/control status; however, we did not have data with which to determine whether this was true. We purposefully chose to focus on questions related to concrete major life events rather than more subjective measures of stress, to help minimize recall bias.

In this study we observed an increased risk of gastroschisis, but only among nonteenage mothers, and no difference in risk of hypospadias, among mothers who reported more stressful life events during the periconceptional period. Social support was associated with reduced risks of both outcomes. The adverse impact of stress on risks of specific birth defects has been studied much less than the impact on risks of other reproductive outcomes, such as preterm birth (17). Minimal prior work has examined our study hypothesis in relation to gastroschisis and hypospadias, and as such our results should be interpreted with caution. It is important to continue to strive toward a better understanding of stress as a risk factor for birth defects, given that it is common and of concern to pregnant women.

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

Abbreviations

CI	confidence interval
NBDPS	National Birth Defects Prevention Study

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APPENDIX

Questions Related to Stressful Life Events and Social Support in the National Birth Defects Prevention Study

1. Did you experience any serious relationship difficulties with your husband or partner or become separated or divorced?
2. Did you or your husband or partner have any serious legal or financial problems?
3. Were you or someone close to you a victim of abuse, violence, or crime? Remember you just have to indicate yes or no.
4. Did you or someone close to you have a serious illness or injury?
5. Did someone close to you die?
6. Could you count on anyone to provide you with emotional support, such as talking over a problem or helping with a difficult decision, if you had needed it?
7. Could you count on anyone to provide you with help financially, such as paying bills or providing food or clothes, if you had needed it?
8. Could you count on anyone to provide you with help with daily tasks, such as grocery shopping, child care, or cooking, if you had needed it?

Note: A series of questions about occupational history and residential history were asked in separate sections of the questionnaire. From these questions, we determined whether mothers had moved or changed jobs during the periconceptional period.

Table 1

Characteristics (%[a]) of Mothers of Cases and Controls, National Birth Defects Prevention Study, 2006–2011

Characteristic	Gastroschisis		Hypospadias	
	Controls (*n* = 4,399)	Cases (*n* = 593)	Male Controls (*n*= 2,249)	Cases (*n* = 1,142)
Race/ethnicity				
Non-Hispanic white	59	49	59	75
Black	10	11	11	11
Hispanic	23	32	24	7
Other	8	9	7	7
Age, years				
<20	9	31	9	7
20–24	22	44	21	18
>25	70	25	70	75
Education				
Less than high school	14	22	14	6
High school completion	23	39	23	21
More than high school	64	40	63	73
Parity				
Nulliparous	40	65	41	54
Parous	60	35	59	46
Body mass index[b]				
Underweight (<18.5)	5	8	5	4
Normal weight (18.5–24.9)	51	64	51	54
Overweight (25.0–29.9)	23	20	23	20
Obese (≥30.0)	21	7	22	23
Smoking[c]				
None	83	65	82	85
Any	17	35	18	15
Alcohol[c]				
None	62	56	61	58
Some	25	20	26	29
Binge drinking[d]	13	24	13	13
Use of folic acid-containing vitamin/mineral supplements				
Began in month before pregnancy or during first month of pregnancy	60	41	58	68
Began in second or third month of pregnancy	30	43	30	26
Began later in pregnancy or none	11	16	12	6

[a] Numbers may not add to100% due to rounding.

[b] Weight (kg)/height (m)2.

[c] From 1 month before conception through 3 months after conception.

[d] Having 4 or more drinks on at least 1 occasion.

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Table 2

Association of Stressful Life Events and Social Support With Risk of Gastroschisis, National Birth Defects Prevention Study, 2006–2011[a]

Exposure	Teenage Mothers (Age <20 Years)						Nonteenage Mothers (Age ≥20 Years)						*P* for Interaction With Age
	Controls (*n* = 374)		Cases (*n* = 186)		AOR	95% CI	Controls (*n*= 4,025)		Cases (*n* = 407)		AOR	95% CI	
	No.	%	No.	%			No.	%	No.	%			
Stressful life events[b]													
Relationship difficulties	121	32	60	32	0.8	0.6, 1.3	626	16	162	40	2.6	2.0, 3.2	<0.05
Legal/financial problems	53	14	31	17	1.0	0.6, 1.7	553	14	114	28	2.2	1.7, 2.8	<0.05
Violence/crime	47	13	21	11	0.8	0.5, 1.5	261	7	58	14	1.6	1.2, 2.2	<0.05
Illness/injury	56	15	22	12	0.7	0.4, 1.2	563	14	67	17	1.2	0.9, 1.6	0.05
Death of someone close	72	19	35	19	1.0	0.6, 1.5	583	14	62	15	1.1	0.8, 1.4	0.81
Changed jobs	124	33	68	37	1.0	0.7, 1.5	970	24	158	39	1.5	1.2, 1.9	0.06
Moved	110	29	74	40	1.4	1.0, 2.1	633	16	122	30	1.7	1.4, 2.2	0.35
Stress index[c]													
0	93	25	42	23	1	Referent	1,707	42	79	19	1	Referent	<0.05
1	108	29	57	31	1.1	0.7, 1.8	1,194	30	116	29	1.9	1.4, 2.5	
2	89	24	37	20	0.8	0.5, 1.4	635	16	96	24	2.4	1.8, 3.4	
3	54	14	31	17	1.0	0.6, 1.9	307	8	60	15	3.1	2.1, 4.6	
4	16	4	11	6	1.3	0.5, 3.1	119	3	35	9	3.8	2.3, 6.1	
5	13	3	5	3	0.5	0.2, 1.6	51	1	13	3	3.4	1.7, 6.8	
6 or 7	1	<1	3	2		NC	12	<1	8	2	10.9	4.0, 30.3	
Continuous (per 4-unit change)					1.0	0.5, 1.7					3.5	2.6, 4.8	<0.05
Social support[b]													
Emotional support	299	80	149	80	1.0	0.6, 1.6	3,575	89	340	84	0.7	0.5, 0.9	0.06
Financial support	320	86	159	86	0.9	0.6, 1.6	3,447	86	325	80	0.7	0.5, 0.9	0.25
Help with daily tasks	321	86	162	87	1.2	0.7, 2.1	3,468	86	320	79	0.8	0.6, 1.0	0.09
Social support index[c]													
0	24	6	11	6	1	Referent	193	5	32	8	1	Referent	0.26
1	28	7	15	8	1.1	0.4, 2.8	271	7	45	11	1.0	0.6, 1.6	
2	54	14	25	13	0.9	0.4, 2.1	464	12	50	12	0.7	0.4, 1.1	

Exposure	Teenage Mothers (Age <20 Years)						Nonteenage Mothers (Age ≥20 Years)						*P* for Interaction With Age
	Controls (*n* = 374)		Cases (*n* = 186)		AOR	95% CI	Controls (*n*= 4,025)		Cases (*n* = 407)		AOR	95% CI	
	No.	%	No.	%			No.	%	No.	%			
3	268	72	135	73	1.0	0.5, 2.3	3,097	77	280	69	0.6	0.4, 1.0	
Stress and social support combined[d]													
Low stress, high support	253	68	122	66	1	Referent	2,994	74	247	61	1	Referent	0.04
High stress, high support	15	4	13	7	1.4	0.6, 3.2	103	3	33	8	2.8	1.8, 4.4	
Low stress, low support	91	24	45	24	1.0	0.6, 1.6	849	21	104	26	1.4	1.1, 1.8	
High stress, low support	15	4	6	3	0.7	0.2, 1.8	79	2	23	6	2.0	1.2, 3.4	

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; NC, not calculated.

[a]Odds ratios were adjusted for maternal race/ethnicity, age, education, parity, body mass index (weight (kg)/height (m)^2), smoking, alcohol use, and intake of vitamin supplements. Each row represents a separate regression model, except for the stress and social support indices and the "stress and social support combined" variable (1 model each).

[b]The reference group was women who responded "no" to each particular question; complete questions are provided in the Appendix.

[c]Indices reflect the number of questions that had a "yes" response.

[d]Women were designated as having low stress if the stressful life events index score was 0–3 and as having high stress if it was 4–7. Women were designated as having low social support if the social support index score was 0–2 and as having high support if it was 3.

Table 3

Association of Stressful Life Events and Social Support With Risk of Hypospadias, National Birth Defects Prevention Study, 2006–2011[a]

Exposure	Controls (*n* =2,249)		Cases (*n* = 1,142)		AOR	95% CI
	No.	%	No.	%		
Stressful life events[b]						
Relationship difficulties	382	17	188	16	1.2	1.0, 1.5
Legal/financial problems	323	14	148	13	1.0	0.8, 1.3
Violence/crime	165	7	58	5	0.9	0.6, 1.2
Illness/injury	316	14	159	14	1.0	0.8, 1.2
Death of someone close	354	16	152	13	0.8	0.7, 1.0
Changed jobs	563	25	243	21	0.8	0.7, 1.0
Moved	374	17	177	16	1.0	0.8, 1.2
Stress index[c]						
0	927	41	508	45	1	Referent
1	647	29	343	30	1.0	0.9, 1.2
2	368	16	171	15	0.9	0.7, 1.2
3	189	8	68	6	0.7	0.5, 1.0
4	71	3	31	3	0.9	0.6, 1.5
5	40	2	16	1	0.9	0.5, 1.6
6 or 7	7	<1	5	<1	1.4	0.4, 4.6
Continuous (per 4-unit change)					0.8	0.7, 1.1
Social support[b]						
Emotional support	1,984	88	1,031	90	0.8	0.6, 1.0
Financial support	1,914	85	1,003	88	0.9	0.7, 1.1
Help with daily tasks	1,950	87	1,006	88	0.8	0.7, 1.1
Social support index[c]						
0	107	5	57	5	1	Referent
1	160	7	53	5	0.6	0.4, 1.0
2	258	12	109	10	0.7	0.4, 1.0
3	1,724	77	923	81	0.6	0.4, 0.9

Exposure	Controls (*n* =2,249)		Cases (*n* = 1,142)		AOR	95% CI
	No.	%	No.	%		
Stress and social support combined[d]						
Low stress, high support	1,659	74	896	79	1	Referent
High stress, high support	65	3	27	2	0.9	0.5, 1.3
Low stress, low support	472	21	194	17	1.1	0.9, 1.4
High stress, low support	53	2	25	2	1.3	0.8, 2.2

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

[a]Odds ratios were adjusted for maternal race/ethnicity, age, education, parity, body mass index (weight (kg)/height (m)^2), smoking, alcohol use, and intake of vitamin supplements. Each row represents a separate regression model, except for the stress and social support indices and the "stress and social support combined" variable (1 model each).

[b]The reference group was women who responded "no" to each particular question; complete questions are provided in the Appendix.

[c]Indices reflect the number of questions that had a "yes" response.

[d]Women were designated as having low stress if the stressful life events index score was 0–3 and as having high stress if it was 4–7. Women were designated as having low social support if the social support index score was 0–2 and as having high support if it was 3.