

Maternal Stress During Pregnancy Predicts Cognitive Ability and Fearfulness in Infancy

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ABSTRACT

Objective: To examine the effects of prenatal stress on cognition and behavioral fearfulness in infants. **Method:** Mothers were recruited at amniocentesis at Queen Charlotte's and Chelsea Hospital, London, between 2001 and 2005, and recalled when their children were 14 to 19 months to assess cognitive development using the Bayley Scales and fearfulness using the Lab-TAB. Measures of prenatal and postnatal life events and current psychological state were collected at the postnatal visit. **Results:** Prenatal stress predicted both mental development ($r_s = -0.39$, $n = 123$, $p < .0001$) and observed fearfulness ($r_s = 0.33$, $n = 106$, $p < .001$); the magnitude of effect was essentially unchanged after covarying postnatal stressors, maternal education and psychological state, exposures to medications and substances during pregnancy, and birth outcomes. Prenatal stress accounted for 17% of the variance in cognitive ability and 10% of the variance in observed fearfulness. The correlation between mental development and fearfulness was minimal ($r = -0.06$, not significant). Prenatal partner relationship strain accounted for 73.5% and 75.0% of the prenatal stress related variance on infant cognitive and fearfulness scores, respectively. **Conclusions:** These findings strengthen previous research that suggests that fetal programming can be important for neurodevelopmental and psychiatric outcomes. They imply that the mechanisms by which mental development and fearfulness are affected are different and that prenatal stress due to relationship strain may warrant particular attention. *J. Am. Acad. Child Adolesc. Psychiatry*, 2007;46(11):1454-1463.

Key Words: stress, prenatal, fetus, programming, life events, infancy, cognitive development, fear.

Experimental animal investigations suggest that maternal stress during pregnancy can permanently modify neurodevelopmental systems in the offspring (Chapillon et al., 2002; Weinstock, 2005). There is robust evidence that prenatal stress results in shorter attention spans (Schneider et al., 1999), disruption in cognitive functioning (Chapillon et al., 2002), and anxiety

(Schneider et al., 2002). Prenatal stress can cause long-lasting alterations in the function of the hypothalamic-pituitary-adrenal (HPA) axis (Henry et al., 1994b; Weinstock et al., 1992) and in the number of dopamine receptors in the brain.

If parallel associations exist in humans, there would be substantial implications for public health, preventive interventions, and developmental theory. Several prospective studies show that maternal stress or anxiety during pregnancy is associated with adverse child developmental outcomes (Van den Bergh et al., 2005b), although some findings are mixed and questions remain about the mechanisms involved. Prenatal anxiety predicts lower mental development in several studies (Brouwers et al., 2001; Huizink et al., 2002), although one recent study found the opposite effect (DiPietro et al., 2006). Prenatal anxiety also predicts infant behavioral reactivity (Davis et al., 2004) and problem behavior in young children (Gutteling et al., 2005), with persisting effects at least into later

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childhood (O'Connor et al., 2003; Van den Bergh et al., 2005a). Several uncertainties remain about the nature of this association, however. For example, it is not always clear that the neurodevelopmental effects derived from prenatal anxiety/stress because several studies have not included postnatal confounds. Second, little is known about the nature of the risks in pregnancy that may have persisting effects on the child because studies have relied on general measures of distress or stress. Third, although human studies link prenatal anxiety or stress with several outcomes, it is not clear whether there is a singular underlying mechanism accounting for the effects so far reported.

The present study aims to address these questions. We sought to determine whether the effects of prenatal stress were independent of postnatal stress, whether there are particular forms of prenatal stress that are especially associated with adverse child outcomes, and whether the same or different children were at risk for adverse cognitive and behavioral outcomes. To do this, we examined a group of women and infants, obtained information about stressful life events experienced in pregnancy and the postnatal period, and examined aspects of the cognitive and behavioral development of the child. Delineating the patterns of associations across multiple outcomes is a step toward identifying the underlying mechanisms, from which appropriate intervention and treatment can be devised. Indicators of fearfulness/anxiety and cognitive delay were particularly chosen because they are clinically meaningful outcomes associated with developmental risk. That is, infants identified as fearful or highly reactive to novelty are more likely to develop symptoms of anxiety (Kagan, 2002; Schwartz et al., 2003). Also, although infant cognitive ability is only a modest predictor of long-term intellectual ability, it is the leading index of general neurodevelopment (Humphreys and Davey, 1988).

METHOD

Sample

Mothers and babies were recruited as part of a larger study on fetal hormone exposure and child development. Women were recruited sequentially from an amniocentesis clinic in a large urban maternity hospital, Queen Charlotte's and Chelsea Hospital, London, UK, between December 2001 and January 2005, and written informed consent was obtained. The majority were for karyotyping for Down syndrome. The study was approved by the institutional research ethics committee. All of the English-speaking mothers with full-term (≥ 37 weeks), healthy, and singleton infants,

whose birth outcomes were known, were invited to return to the pediatric clinic in the hospital when the child was between 14 and 19 months old (Fig. 1). They were excluded if the amniocentesis was for nonroutine amniocentesis, such as fetal structural anomalies and blood transfusion, or if there were incomplete data on the procedure. Two mothers were subsequently excluded because of insufficient fluency in English. Complete data on life events stress and cognitive outcomes were available for 123 children; data on the main temperament measure, fearfulness, were available for 106 children (for 17 children, it was not possible to complete the temperament assessment, which occurred later in the visit, primarily because of fatigue).

Mothers completed a 26-item Stressful Life Events Questionnaire, adapted from the Inventory of Ranked Life Events for Primiparous and Multiparous Women (Barnett et al., 1983), at the follow-up visit, and reported whether the event occurred and whether the event "affected me a little" or "affected me a lot."

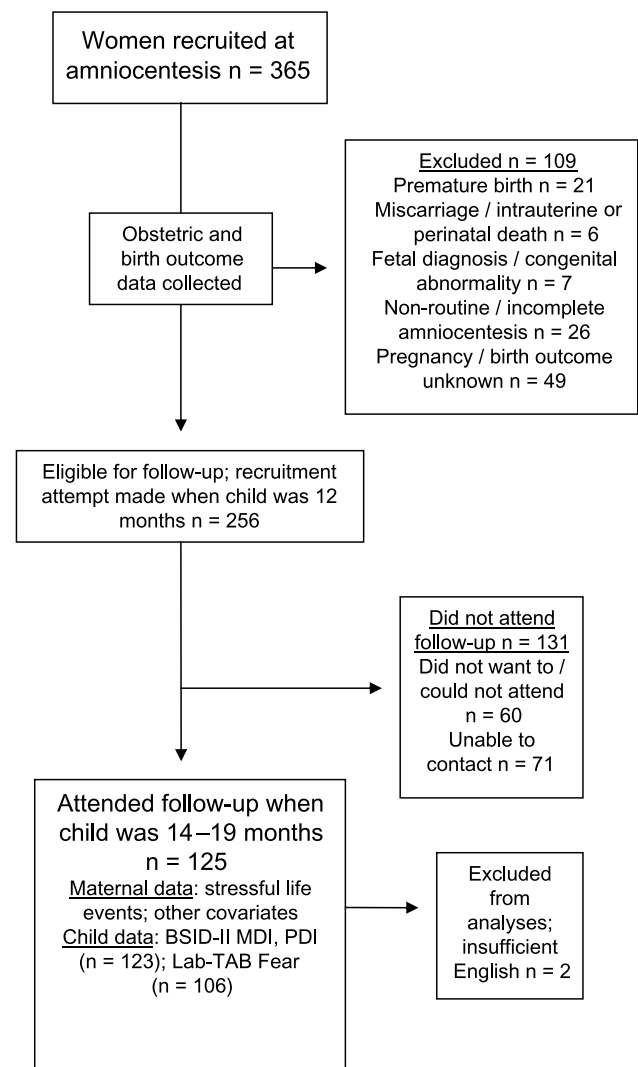


Fig. 1 Consort flowchart. BSID-II = Bayley Scales of Infant Development-2nd edition; MDI = Mental Development Index; PDI = Physical Development Index; Lab-TAB = Laboratory Temperament Assessment Battery.

Mothers also reported whether the event occurred prenatally or postnatally (birth to follow-up) or both. (All items from the Stressful Life Events Questionnaire are shown in Table 4.) The Stressful Life Events Questionnaire is similar in structure and focus to measures of stressful life events used in studies of nonpregnant adults. The scoring of the questionnaire resulted in two scores: the objective number and the perceived impact of the events experienced.

Child Outcomes

A trained developmental researcher who was blind to prenatal stress information administered the Bayley Scales of Infant Development-Second Edition (BSID-II; Bayley, 1993), a widely used standardized assessment of infant mental development (Mental Developmental Index [MDI]) and physical development (Physical Developmental Index). Interrater reliability was 90% for MDI and 97% for Physical Developmental Index.

Part of the Laboratory Temperament Assessment Battery (Lab-TAB)-Locomotor Version (Goldsmith and Rothbart, 1999) was used to assess infant temperament. The Lab-TAB is a leading observational measure of childhood temperament, with considerable support for its validity and clinical value (e.g., Askan and Kochanska, 2004). It consists of paradigms that are designed to elicit fear, anger/frustration, joy/pleasure, interest/persistence, and activity level. We used the unpredictable mechanical toy paradigm from the fear subscale and the puppet game paradigm from the joy/pleasure subscale.

During the unpredictable mechanical toy paradigm, the child sat at a table and a robotic dog was presented when the child was calm and alert. Each trial lasted about 20 seconds and consisted of the dog barking and walking toward the child as its eyes, mouth, and head moved. Three trials were presented unless the child became too distressed. When a trial was omitted, scores from the previous trial was assigned as per Lab-TAB coding instructions. The episode was videotaped and later rated by a researcher blind to maternal data using standard scoring procedures. In brief, for each trial, indicators of fear were assessed from facial expression, body posture, vocalizations, and escape behavior. Interrater reliability was calculated on 22 randomly selected tapes with a rater who was blind to all child and parent data. Pearson correlations were $r = 0.80$ for facial expression, $r = 0.75$ for body posture, $r = 0.92$ for vocalizations, and $r = 0.89$ for escape behavior (all $p < .001$); a composite score derived from the four indicators had an interrater reliability of $r = 0.94$; comparable levels of reliability were obtained for nonparametric (Spearman) correlations. The fear composite from the first trial is used in analyses.

The puppet game paradigm was used to assess joy/pleasure. It involved the presentation of a scripted puppet show lasting about 1 minute while the child was seated at a small table. The episode consisted of five trials. A composite score was determined based on intensity of smiling (0–3) and presence or absence of laughter, positive vocalizations, and positive motor activity (0–1) in all five trials. Interrater reliability on the previously noted random sample of tapes was $r = 0.93$ for laugh, $r = 0.82$ for positive movements, $r = 0.95$ for smile, and $r = 0.80$ for vocalizations; interrater reliability for the composite was $r = 0.93$; comparable levels of reliability were obtained for nonparametric (Spearman) correlations.

Psychosocial and Obstetric Covariates

Information on maternal age, parity, ethnicity (categorized according to UK National Health Service ethnic codes), smoking (cigarettes per day), alcohol (units per week), and prescription drug

use during pregnancy (prescription drug categories: selective serotonin reuptake inhibitor, antihypertensive, antiasthmatic, antiepileptic, steroid, and other) was collected at recruitment. Information regarding birth outcomes was collected from the child's hospital notes after delivery, including birth weight, gestational age at birth, method of delivery, and child sex. SD score of birth weight adjusted for gestational age and sex was calculated using software based on 1990 British Growth Reference data. At the follow-up appointment, we collected information on maternal education and child age at testing.

Maternal mental health and social support were assessed concurrent with the cognitive and behavioral assessments using maternal self-report questionnaire measures. The State-Trait Anxiety Inventory (Spielberger et al., 1983) was used to quantify levels of habitual (trait) anxiety and to control for the heritability of anxiety-like traits in the child. The State-Trait Anxiety Inventory is a widely used index of anxiety symptoms and has considerable validity, reliability, and clinical utility. The Edinburgh Postnatal Depression Scale (Cox et al., 1987) was used to determine maternal levels of depression, a factor known to be predictive of child developmental outcomes. The Edinburgh Postnatal Depression Scale is an established index of depressive symptoms in the perinatal period. The Social Support Questionnaire (Dragonas, 1992) was used to determine the quality of the mothers' social support network, also known to affect child developmental outcomes. A composite score is determined based on the size, accessibility, and self-perceived quality of the immediate social support network (including partner, extended family, friends, neighbors, and the state).

Statistical Analyses

A P-P plot was used to check the normality of distribution for all of the numerical data. Non-normally distributed variables (prenatal and postnatal stressful life events and smoking and alcohol intake during pregnancy) were log-transformed. Because some of the variables were still not normally distributed, both nonparametric (Spearman r_s) and parametric statistics were used to confirm the findings. Multiple regression analyses were used to test study hypotheses controlling for covariates. Based on evidence that maternal age, smoking and alcohol use in pregnancy, birth weight, and maternal education can affect the outcomes that we are measuring (e.g., Li and Poirier, 2003), they were included as covariates. We also included as covariates postnatal life events and postnatal maternal symptoms of anxiety and depression and social support to provide a strong test of the hypothesis that the effects of prenatal stress on child outcomes are not explained by concurrent maternal mental state.

RESULTS

Preliminary Analyses and Descriptive Statistics

Sample characteristics are provided in Table 1. There were no significant differences between the sample for whom fearfulness data were collected ($n = 106$) and the small group of individuals ($n = 17$) to whom this measure was not administered. In addition, analyses indicated that the results were substantively identical for the transformed and nontransformed life events data. We present results using the nontransformed variables

TABLE 1

Sample Characteristics for Mothers and Infants

	Cognitive Outcomes Group (<i>N</i> = 123) Mean ± SD; No. (%); Range	Behavioral Outcomes Group (<i>N</i> = 106) Mean ± SD; No. (%); Range
Maternal education		
No examination passed	4 (3.3)	4 (3.8)
GCSE or equivalent	14 (11.4)	11 (10.4)
A levels or equivalent	18 (14.6)	13 (12.3)
Diploma or equivalent	23 (18.7)	22 (20.8)
University degree	41 (33.3)	36 (34.0)
Postgraduate degree	23 (18.7)	20 (18.9)
Parity	0.89 ± 0.88	0.88 ± 0.88
Nulliparous	49 (39.8)	42 (39.6)
1 child	45 (36.6)	41 (38.7)
2 children	23 (18.7)	17 (16.0)
3 children	6 (4.9)	6 (5.7)
Racial background		
White	103 (83.7)	87 (82.1)
Asian-Indian/subcontinent	7 (5.7)	7 (6.6)
Black	10 (8.1)	10 (9.4)
Middle Eastern	3 (2.4)	2 (1.9)
Smoking during pregnancy, cigarettes/day	0.29 ± 1.84	0.31 ± 1.97
0	110 (89.4)	95 (89.6)
1–2	12 (8.8)	10 (9.4)
>2	1 (0.8)	1 (1.0)
Alcohol during pregnancy, units/wk	0.54 ± 1.54	0.60 ± 1.65
0	85 (69.1)	71 (67.0)
1–2	33 (26.8)	30 (28.3)
2	5 (4.1)	5 (4.7)
Prescription drugs in pregnancy		
None	106 (86.2)	94 (88.7)
SSRI	1 (0.8)	1 (0.9)
Antihypertensive	2 (1.6)	2 (1.9)
Antiasthmatic	8 (6.5)	7 (6.6)
Steroid	1 (0.8)	1 (0.9)
Other	3 (2.4)	1 (0.9)
Unknown	2 (1.6)	—
Maternal age, y	36.55 ± 4.12 25.00–45.00	36.89 ± 3.89 28.00–45.00
Maternal STAI (follow-up)	37.90 ± 10.15	37.57 ± 9.88
Postnatal depression (EPDS)	8.33 ± 4.61	8.23 ± 4.51
Social support (SSQ)	64.13 ± 8.61	63.82 ± 8.67
Method of delivery		
Normal vaginal delivery	62 (50.4)	57 (53.8)
Assisted vaginal delivery	18 (14.6)	12 (11.3)
Elective cesarean	19 (15.4)	14 (13.2)
Emergency cesarean	15 (12.2)	14 (13.2)
Unrecorded	9 (7.3)	9 (8.5)
Child age, mo	16.76 ± 1.41	16.74 ± 1.48

TABLE 1*Continued*

	Cognitive Outcomes Group (<i>N</i> = 123) Mean ± SD; No. (%); Range	Behavioral Outcomes Group (<i>N</i> = 106) Mean ± SD; No. (%); Range
Gestational age at birth, wk	39.47 ± 1.17	39.51 ± 1.12
Birth weight, g	3,490 ± 480	3,501 ± 477
Child sex		
Female	63 (51.2)	53 (50.0)
Male	60 (48.8)	53 (50.0)

Note: GCSE = general certificate of secondary education; SSRI = selective serotonin reuptake inhibitor; STAI = State-Trait Anxiety Inventory; EPDS = Edinburgh Postnatal Depression Scale; SSQ = Social Support Questionnaire.

because the results are more readily interpretable (i.e., the regression coefficients can be directly interpreted). It can be seen that, in general, this is a normal risk group indexed by such factors as levels of symptoms (the means were comparable to other normal risk samples); there was, however, the predictable range of risk (with the possible exception of smoking and alcohol intake, which were low). Maternal age was older than an average prenatal sample, but ranged fairly widely. The group was also well educated.

Maternal Prenatal Stress and Child Cognitive Outcomes

There was a significant negative correlation between the total number of stressful life events in the prenatal period and the child's MDI score ($r_s(123) = -0.39$, $p < .0001$); there was no evidence of a nonlinear effect. In contrast, the association between the total number of postnatal life events and MDI was not significant (NS) ($r_s(123) = -0.05$, NS). These findings were almost identical when mothers' perceived impact of events was analyzed instead of the number of events experienced for both prenatal and postnatal stressful life events ($r_s(123) = -0.38$, $p < .0001$ and $r_s(123) = -0.07$, NS, respectively). All of the analyses were therefore carried out using the number of life events experienced rather than perceived effect. The difference in magnitude of pre- and postnatal effects is noteworthy given the moderate stability of individual differences in number of life events reported in the prenatal and postnatal periods ($r_s(123) = 0.29$, $p = .001$).

The regression analysis is presented in Table 2. Prenatal stressful life events remained a significant

TABLE 2

Multiple Linear Regression Model for BSID-II MDI Scores

Predictor Variables	<i>B</i>	SE	β
Maternal education	1.37	0.63	.19*
Smoking during pregnancy	-2.84	2.21	-.12
Alcohol during pregnancy	0.23	0.55	.04
Child sex (female = 1, male = 2)	-2.67	1.65	-.13
Child age	-1.22	0.59	-.17*
Maternal age	-0.12	0.21	-.05
Trait anxiety at follow-up	-0.03	0.12	-.03
Depressive symptoms at follow-up	0.06	0.27	.03
Social support at follow-up	0.04	0.12	.03
Prenatal stressful life events, no.	-3.04	0.58	-.47**
Postnatal stressful life events, no.	0.65	0.47	.14

Note: $n = 123$; BSID-II = Bayley Scales of Infant Development-2nd Edition; MDI = Mental Developmental Index.

* $p < .05$; ** $p < .01$.

predictor of child BSID-II MDI and independently accounted for 17% of the observed variance in BSID-II MDI scores. Predictably, results also showed that children of better educated mothers scored higher. There was no evidence that the effects of prenatal stress on the MDI were moderated by postnatal depressive or anxious symptoms, social support, postnatal life events, child sex, maternal education, or prenatal smoking or alcohol intake (results not shown). Adding the obstetric covariates (see Method section) did not affect the results.

The physical development scale of the BSID-II was not significantly associated with prenatal or postnatal stressful life events ($r_s(123) = -0.11$, NS and $r_s(123) = -0.14$, NS; respectively).

Maternal Prenatal Stress and Child Fearfulness

There was a significant correlation between prenatal life events and the composite observed fearfulness score ($r_s(106) = 0.33$, $p < .001$). In contrast, the association between the total number of postnatal life events and composite Lab-TAB fearfulness scores was NS ($r_s(106) = -0.05$, NS). As we found with the Bayley analyses, these findings were almost identical when mothers' perceived impact of events was analyzed ($r_s(106) = 0.32$, $p < .001$, $p < .0001$ and $r_s(106) = -0.05$, NS, respectively).

Prenatal stressful life events significantly predicted child fearfulness scores independent of all other covariates (Table 3) and independently accounted for 10% of the observed variance in composite fearfulness scores; lower levels of concurrently reported social

support were also associated with higher observed fearfulness in the child. There was no evidence that the effects of prenatal stress on fearfulness were moderated by postnatal depressive or anxious symptoms, social support, postnatal life events, child sex, maternal education, or prenatal smoking or alcohol intake (results not shown). Adding obstetric covariates (see Method section) did not affect the results.

Correlation analyses revealed that neither prenatal nor postnatal stressful life events were associated with the composite observed Joy/Pleasure scale from the Lab-TAB ($r_s(85) = 0.10$, NS and $r_s(85) = 0.18$, NS, respectively).

Supplemental Analyses

The correlation between the BSID-II MDI and composite Lab-TAB fearfulness scores was minimal ($r_s(106) = -0.06$, NS). Follow-up partial correlation analyses indicated that the link between prenatal stress and MDI was unaffected by controlling for fearfulness; similarly, the prediction of fearfulness was unaffected when MDI was partialled. In addition, when the small group of subjects who were taking medication was omitted, the associations between prenatal stressful life events and child cognitive and fearfulness outcomes were essentially unchanged ($r_s(106) = -0.40$, $p < .001$ and $r_s(94) = 0.41$, $p < .01$, respectively).

Prediction From Specific Prenatal Stressful Life Events

Post hoc analyses were conducted to examine which stressful life events were particularly predictive and

TABLE 3

Multiple Linear Regression Model for Composite Lab-TAB Fearfulness Score

Predictor Variables	<i>B</i>	SE	β
Maternal education	0.04	0.22	.02
Smoking during pregnancy	-1.33	0.80	-.18
Alcohol during pregnancy	0.19	0.18	.10
Child sex (female = 1; male = 2)	-0.50	0.57	-.08
Child age	0.28	0.20	.13
Maternal age	-0.07	0.08	-.09
Trait anxiety at follow-up	-0.01	0.04	-.03
Depressive symptoms at follow-up	0.04	0.09	.05
Social support at follow-up	-0.09	0.04	-.25*
Prenatal stressful life events, no.	0.50	0.21	.27**
Postnatal stressful life events, no.	-0.10	0.16	-.07

Note: $n = 106$; Lab-TAB = Laboratory Temperament Assessment Battery.

* $p < .05$; ** $p < .01$.

TABLE 4

Correlation Coefficients (r_s) for Individual Items on the SLEQ (Prenatal) and Child BSID-II MDI and Composite Lab-TAB Fearfulness Scores

Questionnaire Item	MDI $r_s(n)$ ($n = 123$)	Lab-TAB $r_s(n)$ ($n = 106$)
1. You were admitted to the hospital	-0.11 (26)	0.08 (19)
2. You had a serious accident or illness	-0.09 (3)	-0.01 (2)
3. Your partner had a serious accident or illness	0.02 (5)	-0.01 (3)
4. A friend/family member had a serious accident/illness	-0.05 (13)	0.19* (13)
5. You were in trouble with the law	—	—
6. Your partner was in trouble with the law	—	—
7. You were separated/divorced	-0.19* (5)	0.28* (4)
8. Your partner lost his job	-0.08 (3)	0.04 (2)
9. You experienced a significant drop in income	-0.05 (13)	0.05 (13)
10. You had a major financial problem	-0.15 (9)	0.01 (8)
11. Your car or house was burgled	-0.07 (2)	0.09 (2)
12. You became homeless	-0.14 (3)	0.02 (2)
13. You found that your partner did not want your child	-0.11 (6)	0.14 (5)
14. You had a serious argument with your partner	-0.23* (39)	0.19* (36)
15. You had a serious argument with family or friends	-0.17 (10)	0.13 (9)
16. Your partner was physically cruel to you	—	—
17. Your partner was emotionally cruel to you	-0.38** (12)	0.20* (11)
18. You were physically cruel to your partner	0.08 (1)	0.01 (1)
19. You attempted suicide	—	—
20. A friend or relative attempted suicide	—	—
21. You suffered from mental illness	-0.20* (3)	0.03 (2)
22. A friend or relative suffered from mental illness	-0.19* (9)	0.07 (9)
23. Your partner died	—	—
24. A friend or relative died	-0.07 (15)	0.19* (15)
25. You had an extramarital sexual affair	-0.17 (2)	0.16 (2)
26. Your partner had an extramarital sexual affair	-0.09 (1)	0.03 (1)

Note: SLEQ = Stressful Life Events Questionnaire; BSID-II = Bayley Scales of Infant Development-2nd Edition; MDI = Mental Developmental Index; Lab-TAB = Laboratory Temperament Assessment Battery.

* $p < .05$; ** $p < .01$.

whether there was any pattern among these predictors. Table 4 demonstrates the correlations (Spearman r_s) between the number of individual prenatal stressful life events and both child outcome measures. There was consistent evidence that events pertaining to relationship strain were linked with both BSID-II MDI and fearfulness. Three events (“you were separated/divorced,” “you had a serious argument with your partner,” and “your partner was emotionally cruel to you”) were significantly related to the BSID-II MDI and composite Lab-TAB fearfulness in bivariate analyses. The three partner-related items listed above were the only items associated with both outcome measures and accounted for 73.5% and 75.0% of the total variance of prenatal stressful life events on infant BSID-II MDI and composite Lab-TAB fearfulness scores, respectively.

DISCUSSION

The main findings were that stressful life events in the prenatal period were negatively associated with mental developmental and positively associated with fearfulness in infancy, and the prediction of each outcome was essentially independent. These findings were independent of psychosocial and obstetric covariates as well as measures of concurrent symptoms and postnatal stress. The current findings build on previous studies showing that maternal stress during pregnancy predicts poorer cognitive outcome (Huizink et al., 2002; Laplante et al., 2004). An exception to this negative association has been reported (DiPietro et al., 2006). In the present study, we found no suggestion of a curvilinear relationship. It is not clear why our results differ, but it may be that their cohort was particularly financially and emotionally stable.

Our findings also offer an important extension to previous studies assessing behavioral outcomes, which have relied almost exclusively on parental report. We found that prenatal stress predicted an observational assessment of fearfulness independently rated from a structured laboratory assessment. The reliability of the prenatal effect is strengthened by the inclusion of multiple measures of postnatal maternal mood, including life events, symptoms, and social support. Nonetheless, other mediating mechanisms are possible, such as genetics. We are unable to rule out genetic explanations (i.e., we did not directly assess genes),

but several features of the results lead us to suggest that the effects observed are not explicable in terms of a simple genetic mediation. Most important, the effect of prenatal stress was specific to prenatal exposure, and the effect remained after controlling for both postnatal stress and maternal symptoms. If there were a simple genetic transmission, we would not observe an effect specific to the prenatal period or one that would persist after postnatal risks were statistically controlled. The same observation also makes other alternative explanations unlikely, notably maternal reporting bias. That is, there was minimal evidence that maternal mood or social adjustment concurrent with the infant assessment was associated with infant outcomes; more important, however, controlling for postnatal maternal mood and stress did not alter the prenatal prediction, which is incompatible with a maternal postnatal mood bias account of these findings. It is possible that there are more complex genetic mechanisms at work in which, for example, the specific genetic vulnerability of the child increases susceptibility to experience the adverse effects of prenatal stress. This would help to explain why all children are not affected by prenatal stress or are not affected in the same way. This needs testing, and the identification of likely genes or gene groups warrants further investigation (Wust et al., 2004). In general, then, the present findings strengthen previous research that suggests that the environment in utero can be important for neurodevelopment. Fetal programming may be as relevant for emotional and cognitive outcomes as it has been shown to be in many other areas of human health and development (Barker, 2002; Gluckman and Hanson, 2005).

It is of interest that there was not a significant correlation between the cognitive and fearfulness outcomes. This suggests that their associations with prenatal stress are mediated by different mechanisms. More research is needed to identify these mechanisms. There is a parallel need for further research to consider the role of developmental timing on the sensitivity to different brain regions that may be affected by prenatal stress.

Relationship strain with the partner emerged as the most predictive form of stress for both outcomes. This is of interest and extends findings from an early observational study (Stott, 1973). These results show that it is not only prenatal exposure to unusual and traumatic events (Laplante et al., 2004) that can affect

the cognitive development of the child. Moreover, although the present study did not assess domestic violence per se, the findings concerning relationship strain may be indicative of domestic abuse, which occurs during pregnancy at high rates and is now attracting widespread attention as a public health issue (Martin et al., 2001; Tan and Gregor, 2006). Our findings suggest that the adverse effects of domestic violence and strain may extend to the child. It remains to be seen whether interventions for domestic abuse, including improved detection, may confer positive side effects on the child. It is interesting to note that a marital preventive intervention carried out during pregnancy was associated with improved marital quality (Schulz et al., 2006). The present study suggests that there may also be beneficial effects for the child of a preventive intervention in pregnancy.

Thus, our study adds to the previous literature by having similar measures for prenatal stress and postnatal stress and showing that the former has an independent effect on child neurodevelopment; that different children are affected with respect to cognitive outcome and fear reactivity, suggesting that different underlying mechanisms must be explored; and providing evidence that stress due to relationship strain is particularly harmful.

Conceptually, it is of interest to consider why prenatal stress should affect child development. One possibility is a predictive adaptive response. This has been suggested as an adaptive mechanism whereby alterations to the intrauterine milieu result in changes to the developing offspring that help the child adapt to his or her future environment (Gluckman and Hanson, 2005). Increased fearfulness may be adaptive in a potentially harmful or threatening environment, indexed by maternal stress, although the application to lower cognitive abilities is less obviously consistent with a predictive adaptive response.

Limitations

This study has several limitations. The first is the retrospective measure of stressful life events, which may have biased the results. There are features of the present study that, according to research in this area (Henry et al., 1994a), may mollify concerns about bias, notably, the short timeframe and objective nature of events recalled; in addition, including postnatal mood as a covariate should address concerns about biased

recall. More practically, there are potential problems in assessing stressful events in pregnancy, including the possibility of missing events before parturition, and soon after birth may not be an optimal time for obtaining parental engagement. Another issue concerns our recruitment strategy. All of the women were recruited from an amniocentesis clinic because of the broader study focus on fetal hormone exposure. They were predominantly white, above average age, and well educated. These women are not representative of a typical antenatal or an especially high-risk population, although they may have experienced extra stress during their pregnancy due to the amniocentesis. Some potential biases of this recruitment strategy were addressed by including only children with normal outcomes and including maternal age and education as covariates. Also, although the state anxiety of these women was raised while awaiting the procedure, their trait anxiety was similar to that of a large control population attending the same hospital (Sarkar et al., 2006). However, <50% of those eligible for the follow-up actually participated, which reduces the generalizability from the initial cohort. Some of the numbers of subjects experiencing individual items are small (Table 4), and these results must be treated with caution. However, "you had a serious argument with your partner" was reported by 39 of those with an MDI result for the child, supporting the impact of relationship strain as important.

Finally, it is possible that the observational measures used may serve as an index of something other than what we were intending to measure. Performance on the BSID-II, as with any other assessment of young children, may be influenced by factors such as behavior or fatigue. The predictive value of the BSID-II for later IQ is not powerful, although it is the best developmental assessment of current cognitive ability for the age range of the present study and is predictive of reading and language abilities at age 8 (Siegel, 1989) and intellectual ability and development in later life (Humphreys and Davey, 1988). Although we partially controlled for inheritance of an anxious temperament by including maternal trait anxiety, we did not have a measure of parental IQ to control for parental cognitive ability. The design of comparing the effects of prenatal and postnatal stress does indicate that the effect of the prenatal environment is important independently of genetic factors. These limitations are offset by several strengths

of the study, most notably the use of independent assessments of the child from clinical assessment.

Clinical Implications

Several clinical implications may be derived from these findings. The first concerns the potential for prevention and especially the timing of prevention. Several studies show that anxiety or the roots of anxiety disorder are apparent at a young age. For instance, children found to be highly reactive in infancy are more likely to develop anxious symptoms later in childhood (Kagan et al., 1999), and adults identified as inhibited children at 2 years have heightened neurological responses to novelty (Schwartz et al., 2003). Furthermore, infants of mothers with a diagnosis of panic disorder (Warren et al., 2003) and depression (Halligan et al., 2004) have neurophysiological profiles indicative of greater arousal (i.e., elevated saliva cortisol concentrations), a profile that is also found in adolescents and adults experiencing the onset of a major depressive episode (Goodyer et al., 2000; Harris et al., 2000). Findings like these have prompted clinical research questions about early interventions for anxiety. There are now several evidence-based interventions for parents and infants (Boris and Zeanah, 2005; Lieberman et al., 2006), some of which have been shown to improve cognitive outcomes in the child (Cicchetti et al., 2000). Few of these studies, however, considered the possibility that an intervention in the prenatal period may be especially powerful. Treating anxiety or stress in pregnancy (for which there are many brief psychological therapies that do not have the potential negative side effects of pharmacological agents) may well have beneficial effects on the mother and would offer additional leverage to show a causal link between maternal distress in pregnancy and child well-being. Of course this requires direct study.

A second implication concerns public health. These findings are compatible with the literature on prenatal preventions, which suggest that an intensive intervention beginning in pregnancy may have beneficial effects on the child that persist into adulthood (Olds et al., 2004). The intervention delivered in the work of Olds and colleagues was not limited to the prenatal period and was broader than reducing prenatal anxiety or stress of the mother. Nonetheless, it may be that reducing prenatal distress is an important component to prenatal interventions with at-risk mothers.

Third, although we do not have data from directly testing a putative mechanism, such as the HPA axis, it is worth noting that the “programmability” of the HPA axis has been suggested by other findings in humans (Halligan et al., 2004; O'Connor et al., 2005) as well as in animals (Matthews, 2002; Schneider et al., 1999). If the HPA axis may be set by early stress exposure, then clinical research is needed to determine whether interventions—pharmacological or psychological—occurring later in life are effective by altering the HPA axis.

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Monitoring Health Related Quality of Life in Adolescents With Diabetes: A Review of Measures M. de Wit H.A., Delemarre-van de Waal, F. Pouwer, R.J.B.J. Gemke, F.J. Snoek

Particularly in chronic conditions, monitoring health related quality of life (HRQoL) of adolescents in clinical practice is increasingly advocated. We set out to identify and review the clinical utility of available generic and diabetes specific HRQoL questionnaires suitable for use in adolescents with type 1 diabetes. Four generic and five diabetes specific questionnaires were identified and evaluated. The responsiveness of most instruments warrants further research and standardisation of HRQoL measurement should be sought to facilitate comparisons across centres and countries. The PedsQL and the KINDL-R appear, at this time, to be the most suitable instruments. **Arch Dis Child** 2007;92:434–439.