Maternal Prenatal Cortisol and Infant Cognitive Development: Moderation by Infant–Mother Attachment

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Background: Experimental animal studies suggest that early glucocorticoid exposure may have lasting effects on the neurodevelopment of the offspring; animal studies also suggest that this effect may be eliminated by positive postnatal rearing. The relevance of these findings to humans is not known.

Methods: We prospectively followed 125 mothers and their normally developing children from pregnancy through 17 months postnatal. Amniotic fluid was obtained at, on average, 17.2 weeks gestation; infants were assessed at an average age of 17 months with the Bayley Scales of Infant Development, and ratings of infant–mother attachment classification were made from the standard Ainsworth Strange Situation assessment.

Results: Prenatal cortisol exposure, indexed by amniotic fluid levels, negatively predicted cognitive ability in the infant, independent of prenatal, obstetric, and socioeconomic factors. This association was moderated by child–mother attachment: in children with an insecure attachment, the correlation was [$r(54) = -.47$, $p < .001$]; in contrast, the association was nonexistent in children who had a secure attachment [$r(70) = -.05$, ns].

Conclusions: These findings mimic experimental animal findings and provide the first direct human evidence that increased cortisol in utero is associated with impaired cognitive development, and that its impact is dependent on the quality of the mother–infant relationship.

Key Words: Amniotic fluid, attachment, cognitive development, cortisol, prenatal stress, programming

The fetal programming hypothesis proposes that the environment in utero can alter the development of the fetus, with a permanent effect on the phenotype. This concept has been particularly developed by Barker and his colleagues, who have shown that the prenatal environment can have lasting effects on cardiovascular and metabolic functioning, with effects persisting into adulthood (1–2). Recent work has begun to examine the extent to which a programming model may also apply to behavioral, psychiatric, and neurodevelopmental outcomes in humans (3–5). Our study builds on this research by directly examining one proposed causal mechanism of a programming model, prenatal cortisol exposure, as a predictor of infant cognitive development, and it seeks to translate animal findings in this area by investigating the moderating impact of early child rearing.

The hypothesis that there may be developmental programming effects for human biobehavioral development derives from several sets of findings. The first is the accumulating evidence that prenatal anxiety or stress predicts cognitive, behavioral, and psychiatric outcomes in the child, independent of postnatal stress or anxiety (6–12). Child outcomes that are most consistently increased by prenatal stress or prenatal anxiety (both concepts have been used) are signs of distress/anxiety, symptoms of attention-deficit/hyperactivity disorder, and reduced cognitive ability. These findings are strikingly consistent with experimental animal work, which uses the prenatal stress model as a leading paradigm for showing programming effects on offspring outcomes (13–17). A further feature of the animal data are that they provide good evidence that exposure to glucocorticoids such as cortisol is one mechanism for these effects. For example, in nonhuman primates, prenatal stress effects can be mimicked by injecting adrenocorticotropic hormone, which stimulates the production of cortisol, to the pregnant mother (17). Animal studies also demonstrate long-term effects of prenatal administration of synthetic glucocorticoids, such as dexamethasone, on offspring brain development and behavior (18–19).

Whether a comparable glucocorticoid mechanism accounts for prenatal anxiety or stress effects on the child is not yet clear. There is, for example, human evidence that synthetic glucocorticoids that cross the placenta, including dexamethasone, can affect infant neurodevelopment when given in pregnancies threatened with preterm delivery (20). More broadly, the potentially widespread role for exposure to increased cortisol in human fetal brain development is indicated by a study showing, by microarray analysis, that increased cortisol exposure affects the expression of over a thousand genes in fetal brain cells (21). However, human studies have not yet shown that fetal cortisol exposure is directly associated with neurodevelopment in the child and is a mechanism accounting for the prenatal stress effect.

A separate line of investigation that provides indirect support for a human programming model involving early cortisol exposure is that which connects early stress with human psychological and psychiatric outcomes and hypothalamic-pituitary-adrenal (HPA) axis functioning (22–24). Although the impact of early cortisol exposure per se is unclear in these studies, the results suggest that the early rearing environment may alter HPA axis functioning and predict behavior and neurodevelopment. Other evidence (25–26) that links cortisol exposure and impaired cognitive functioning in adults underscores the need for further

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investigation of early glucocorticoid exposure on neurodevelopment.

Our study was designed to extend research on prenatal stress and anxiety and fetal programming in humans in two new directions. First, we tested the hypothesis that prenatal cortisol exposure, as indexed by amniotic fluid cortisol, predicts infant cognitive development. Collecting amniotic fluid provided us with particular leverage for assessing if prenatal cortisol exposure was directly linked with child outcome and mediated the association between prenatal maternal anxiety and stress and children's cognitive development. The second novel feature is the inclusion of the leading index of infant–parent relationship quality as a potential moderator of prenatal cortisol exposure. Animal data consistently show that the early rearing environment can reverse the adverse effects of prenatal stress (27–28), and there is a growing evidence in the animal literature showing that early rearing can alter biological risk, whether the risk derived from experimentally induced prenatal stress or from genetic risk (29). The application of these animal findings to humans is not known. Here we investigate, for the first time, the association between amniotic fluid cortisol, infant cognitive development, and any moderating influence of caregiving quality. We focus on child cognitive development, which has been reliably predicted from prenatal anxiety and stress (6–7); the availability of amniotic fluid cortisol allowed us to examine further a previously reported association between prenatal stress and cognitive development (6).

Methods and Materials

Participants

Mothers and babies were recruited as part of a prospective study on fetal hormone exposure and child development (30). Women were recruited sequentially from an amniocentesis clinic for karyotyping in a large urban maternity hospital between December 2001 and January 2005. Written informed consent was obtained from mothers; the study was approved by the institutional Research Ethics Committee at Imperial College London.

Of the 365 women who were recruited at amniocentesis, 109 were excluded because of clinical findings, prematurity, nonroutine amniocentesis, or unknown birth outcome. The remaining 256 English-speaking mothers with full-term (≥37 weeks), healthy, and singleton infants for whom prenatal biological samples were obtained were invited to return to the pediatric clinic when the child was between 14 and 19 months old. Of these, we were unable to locate 71, and a further 60 did not wish to participate or could not attend the clinic (because of moving away from the area), resulting in 125 children who were eligible and agreed to participate. The sample on which we obtained longitudinal follow-up data (n = 125) did not differ from those who were not followed up (n = 131) on key parameters listed in Table 1; however, mothers on whom we had follow-up data were slightly older than those on whom we did not (mean = 36.6 [SD = 4.1] years, compared with mean = 35.2 [SD = 5.4] years, respectively, p = .02).

Mean gestational age at the time of amniotic fluid sampling was 17.2 weeks (median was 16 weeks; range: 15–32, with 91% between 15 and 20 weeks). Gestational age was assessed to the nearest day by ultrasound-determined fetal biometry. Crown-rump-length was used at and before 13 weeks and biparietal diameter after 13 weeks to establish gestation using Hadlock's charts installed in the reporting software (31).

Table 1. Characteristics of the Study Sample (n = 125)

	Mean (SD)/Range or Number (%)
Maternal Age (years)	36.62 (4.12)/25–45
Gestational Age at Amniocentesis (weeks)	17.30 (3.24)/15–37
Time of Amniotic Fluid Collection (hours)	10.56 (1.09)/9.05–16.10
Maternal Education	
No qualifications	4 (3.2%)
GCSE or equivalent	14 (11.2%)
A-levels or equivalent	19 (15.2%)
Diploma or equivalent	24 (19.2%)
University degree	41 (32.8%)
Postgraduate degree	23 (18.4%)
Parity	
Nulliparous	51 (40.8%)
1 Previous child	45 (36%)
2 Or more previous children	29 (23.2%)
Racial Background	
White/Caucasian	103 (82.4%)
Asian-Indian subcontinent	7 (5.6%)
Afro-Caribbean	10 (8.0%)
Middle-eastern	3 (2.4%)
Fareastern	2 (1.6%)
Smoking During Pregnancy	.32 (1.86)
0 Cigarettes/day	111 (88.8%)
1–2 Cigarettes/day	12 (9.6%)
>2 Cigarettes/day	2 (1.6%)
Alcohol During Pregnancy	.53 (1.53)
0 U/week	87 (69.6%)
1–2 U/week	33 (26.4%)
>2 U/week	5 (4.0%)
State Anxiety: Prenatal	49.58 (13.47)/21–77
Gestational Age at Birth (weeks)	39.48 (1.17)/37–42
Birth Weight (g)	3489 (475)/2338–6000
Female Sex	65 (52%)
Child Age at Postnatal Visit (months)	16.73 (1.41)/14.4–20.0)
BSID Mental Development Index	97.33 (10.20)/70–122
BSID Physical Developmental Index	97.23 (10.24)/70–121
Amniotic Fluid Cortisol (nmol/L)	18.12 (8.98)/.66–50.25
Secure Attachment Classification	70 (57%)

GCSE is the approximate equivalent to high school diploma; A-level indicates that the individual passed college entrance examinations; diploma indicates a degree less than a university degree.

GCSE, General Certificate of Secondary Education; BSID, Bayley Scales of Infant Development.

Amniotic Fluid Cortisol Samples

During amniocentesis, an aliquot of up to 4 mL of amniotic fluid surplus to clinical requirement was drawn for the study and stored at −80°C until assay. Time of collection, to the nearest 15 min, was recorded. Total cortisol in amniotic fluid was assayed by radioimmunoassay (Coat-A-Count, DPC, Los Angeles, California), cortisol having been extracted by dichloromethane and reconstituted before assay. Intra- and interassay coefficients of variation for the amniotic fluid cortisol assay were 4.4% and 6.5%, respectively. There was some variation in the time of day of assessment and gestational age of amniotic fluid collection; these factors were considered covariates.

Maternal Plasma Cortisol

Maternal plasma was sampled at the same prenatal assessment; it is included for exploratory purposes. Maternal blood samples were collected immediately before the amniocentesis procedure

and centrifuged, and supernatant plasma was stored at −80°C until batch assay. Total cortisol was assayed by radioimmunoassay using Coat-a-Count (DPC). Intra- and interassay coefficients of variation for the cortisol assay were 5.4% and 4.1%, respectively.

Infant–Mother Attachment

Ainsworth's Strange Situation (32) is an extensively researched seven-episode laboratory assessment that capitalizes on the mild stress of the separation–reunion paradigm to assess the extent to which the child uses the parent as a secure base for exploration. Coding was made using established procedures for classifying dyads as insecure-avoidant, secure, insecure-ambivalent/resistant, and insecure-disorganized (32–33). The Strange Situation is arguably the most extensively studied and valid index of parent–child relationship quality in infancy. Securely attached children experience significantly more sensitive and responsive parenting than those rated as having an insecure pattern (34–35), and secure attachment predicts optimal behavioral and social development. Ratings from the Strange Situation index current relationship quality, but the relative stability in attachment (in)security (36) in infancy implies that it indexes the predominant pattern of caregiving quality in the child's early months of life. The primary coder received standard training at the Institute of Child Development, University of Minnesota, and achieved greater than 80% agreement on a reliability test of 35 cases. Strange Situation data could not be obtained on one child (n = 124).

Infant Cognitive and Physical Development

A developmental researcher who was blind to antenatal data administered the Bayley Scales of Infant Development—Second Edition (BSID-II) (37), a widely used standardized assessment of infant mental development that includes language and cognitive items (Mental Developmental Index, MDI) and physical development (Physical Developmental Index, PDI). The researcher underwent extensive training in administration and achieved an interrater reliability with an expert trainer of 90% for MDI and 97% for PDI. We report standardized scores that have a mean of 100 and SD of 15.

Psychosocial and Obstetric Covariates

Information on maternal age, parity, ethnicity (categorized according to UK National Health Service ethnic codes), smoking (cigarettes per day; because of a restricted range, this was recoded to no smoking vs. any smoking), alcohol (number of units per week), and prescription drug use during pregnancy (prescription drug categories: selective serotonin reuptake inhibitors, antihypertensive, antiasthmatic, antiepileptic, steroids, and other) was collected at recruitment. Information regarding birth outcomes and child sex was collected from the child's hospital notes. Standard deviation score of birth weight adjusted for gestational age and sex was calculated using software based upon 1990 British Growth Reference data.

Maternal Anxiety and Depressive Symptoms and Stress

Maternal mood and stress in the prenatal period were included as adjuncts to the prenatal cortisol exposure data. The Spielberger State–Trait Anxiety Inventory (STAI) (38) was completed at the prenatal and postnatal visits. The STAI is a widely used index of anxiety symptoms and has considerable validity, reliability, and clinical utility; we report state anxiety because of our interest in change from the pre- to postnatal periods. The Edinburgh Postnatal Depression Scale (39), a widely used index with considerable validity, was used to measure maternal depressive symptoms at the postnatal visit. Mothers also completed a 26-item Stressful Life Events Questionnaire, adapted from Barnett *et al.* (40), at the postnatal visit, and reported whether the event occurred and, if it did, whether the event "affected me a little" or "affected me a lot." Mothers reported if the event occurred antenatally or postnatally or both. We focus on the number of events because it is a more objective assessment of stress exposure (the findings are substantially identical for frequency and perceived impact of events).

Data Analysis

We first present sample characteristics and background correlations between amniotic fluid cortisol, attachment, maternal mood and stress, and Bayley scale scores. Second, we report bivariate associations between amniotic fluid cortisol and infant cognitive development, followed by a multivariate analysis in which we accounted for several sets of possible confounds. Prior analyses (30) indicated a small-to-moderate effect of gestational age and time of collection on amniotic fluid cortisol; these variables are therefore included in multivariate analyses. We also include, on an a priori basis, common obstetric and psychosocial covariates. Pre- and postnatal maternal mood and stress are also considered. Third, regression analyses are used to examine whether amniotic fluid cortisol mediated the previously reported association between prenatal stress and cognitive development and whether the link between amniotic fluid cortisol and cognitive development is moderated by attachment security; we distinguish between secure and insecure attachment but then also explore moderation in each of the subclassifications of insecure attachment. We followed the convention of transforming cortisol data using an ln transformation; this transformed variable is used for parametric analyses (in practice, the findings are substantively identical with transformed and nontransformed data). Also, although our primary focus is on cognitive development, we also report findings for physical development.

Results

Demographic data show that, as might be expected from a sample undergoing karyotyping, the sample included a sizable set of older pregnant women but ranged widely; there is also a comparatively high representation of individuals with a university degree. Both maternal age and education are included as covariates. In several other key areas, the sample was diverse and within normal range in terms of sociodemographic indicators, attachment classification, and child cognitive developmental scaled scores (Table 1).

Preliminary analyses indicated that amniotic fluid cortisol was not significantly correlated with maternal self-report measures of pre- or postnatal anxiety and depressive symptoms or life stress (all rs < .10); also, there was no association between amniotic fluid cortisol and quality of attachment, indexed by the secure (n = 70; 2.83 [.57]) versus insecure designation [n = 54; 2.79 (.59); $F(1,122)$ = .14; ln transformation values of amniotic fluid cortisol shown]. Attachment security was, however, associated with cognitive ability according to an analysis of variance (ANOVA): children with secure attachments scored higher (n = 70; 99.31 [9.28]) than children with an insecure attachment [n = 54; 94.94 (10.87), $F(1,123)$ = 5.82, p < .05]. ANOVA also indicated that Securely attached children also had mothers who reported lower levels of postnatal state anxiety compared with children with an insecure attachment [n = 69, 29.99 (7.35) and n = 53, 33.42 (11.39) for secure and insecure groups, respectively; $F(1,120)$ = 4.20, p < .05]. No other significant associations with attachment secured were found. Finally, the mental devel-

Table 2. Prediction of Cognitive Development from Prenatal, Obstetric, and Postnatal Data

	Model 1		Model 2	
Predictor	*B* (SE)	β	*B* (SE)	β
Intercept	111.62 (18.28)		125.12 (18.03)	
Maternal Age	.02 (.22)	.01	−.14 (.22)	−.06
Maternal Education	1.69 (.58)	.23[b]	1.87 (.57)	.26[b]
Child Age at Postnatal Visit	−.70 (.62)	−.10	−.68 (.59)	−.09
Child Sex (1 = F, 2 = M)	−2.69 (1.63)	−.13	−2.71 (1.56)	−.13
Collection Time of Amniotic Fluid	1.11 (.73)	.13	1.00 (.70)	.12
Gestational Age at Amniotic Clinic Visit	.18 (.27)	.06	.08 (.26)	.02
Birthweight/Gestational Age (ratio)	−1.50 (.78)	−.16	−1.52 (.75)	−.17[a]
Alcohol in Pregnancy	−.33 (.57)	−.05	−.17 (.55)	−.03
Smoking in Pregnancy	1.04 (1.51)	.06	1.51 (1.46)	.08
Amniotic Fluid Cortisol (ln)	−5.84 (1.55)	−.33[c]	−9.45 (2.15)	−.53[c]
State Anxiety: Prenatal	.00 (.06)	.01	.01 (.06)	−.02
State Anxiety: Postnatal	−.08 (.10)	−.07	−.04 (.09)	−.04
SLE: Prenatal	−2.88 (.57)	−.44[c]	−2.60 (.55)	−.40[c]
SLE: Postnatal	.48 (.43)	.10	.55 (.41)	.12
Secure Attachment			−15.26 (8.11)	−.75
Amniotic Fluid Cortisol × Secure Attachment			6.90 (2.85)	.99[a]

F, female; M, male; SLE, stressful life events (*n*).
[a] $p < .05$.
[b] $p < .01$.
[c] $p < .001$.

opment index of the Bayley scales was significantly associated with postnatal state anxiety [$r(123) = -.23$, $p < .05$]; postnatal state anxiety was therefore retained for regression analyses.

Prenatal Cortisol Exposure Predicts Infant Cognitive Development

Correlation analysis indicated a significant inverse association between amniotic fluid cortisol (ln transformed values) and standard scores from the Bayley Cognitive Development Scale [$r(125) = -.25$, $p < .01$]. We then undertook a multivariate regression analysis that included maternal education, maternal age, time of prenatal sample collection, gestational age at amniocentesis, child sex, alcohol and smoking in pregnancy, and birth weight for gestational age (Model 1 in Table 2); maternal anxiety and stress were also included. Results indicated that amniotic fluid cortisol remained an independent predictor of infant cognitive development; maternal education and prenatal stress were also significant predictors.

Further analyses indicated that prenatal stress and amniotic fluid cortisol were essentially separate predictors of child cognitive development. For example, the association between amniotic fluid cortisol and infant cognitive development was substantively unchanged when prenatal and postnatal maternal anxiety and stress measures were included [in a regression model the coefficient for amniotic fluid cortisol was $B = -6.21$ (1.74) and $B = -5.84$ (1.55), without and with anxiety and stress measures, respectively]. That, along with the lack of association between amniotic fluid cortisol and prenatal stress noted earlier, indicates that there was no evidence that the prenatal stress effect on cognitive development was mediated by amniotic fluid cortisol.

Amniotic fluid cortisol was significantly correlated with the physical development index from the Bayley Scales [$r(124) = -.25$, $p < .01$], but regression analyses showed that it did not significantly predict physical development independent of obstetric and psychosocial covariates.

Prenatal Cortisol Prediction Is Moderated by Infant–Parent Attachment

The moderating role of infant–parent attachment quality on the association between prenatal cortisol exposure and cognitive development is demonstrated in the regression (Model 2 in Table 2) and illustrated in Figure 1. The figure shows that prenatal cortisol exposure, indexed by amniotic fluid concentration, strongly predicted cognitive development in children with an insecure attachment history [$r(54) = -.47$, $p < .001$]; in contrast, the association among children with a secure attachment history was essentially zero [$r(70) = -.05$, ns]. Model 2 in Table 2 demonstrates that the significant prenatal cortisol exposure × infant–parent attachment interaction is independent of obstetric and psychosocial covariates as well as pre- and postnatal anxiety and stress. The association between prenatal cortisol and infant cognitive development was comparable (i.e., not significantly different) for the different subtypes of insecure attachment (avoidant, $r = -.27$; ambivalent, $r = -.50$; disorganized, $r = -.43$). We did not detect a significant amniotic fluid × attachment security interaction for the physical development index.

Supplementary Analyses

We conducted several sets of supplementary analyses to confirm the robust nature of the associations reported above and explore them further. First, although distribution of the amniotic fluid data did not suggest statistical outliers, we nonetheless examined whether the interaction findings were unduly influ-

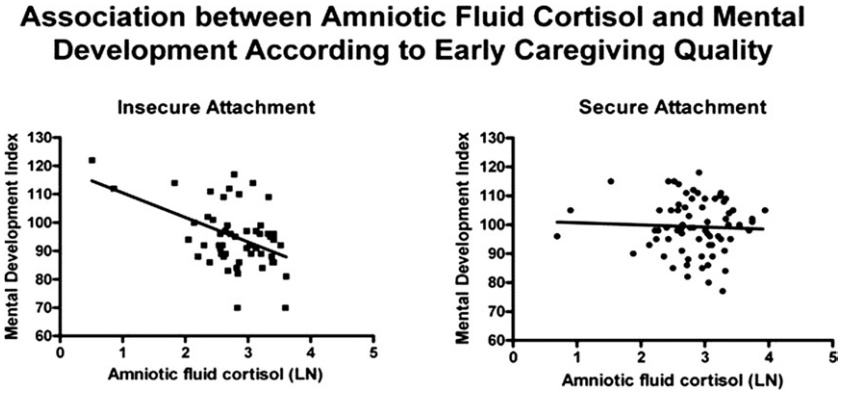

Figure 1. The association between amniotic fluid cortisol (ln transformation) and Mental Development Index of the Bayley Scale of Infant Development is significant and moderate in those children with insecure attachments [$r(54) = -.47$, $p < .001$] but negligible in children with secure attachments [$r(70) = -.05$, ns].

enced by comparatively extreme scores. We reanalyzed the data excluding those individuals with comparatively low scores on amniotic fluid cortisol (i.e., the four values <1 in the Figure 1). With these scores excluded, we still obtained a significant interaction between amniotic fluid cortisol and attachment security in predicting score on mental development index ($p < .05$), demonstrating the robust nature of the interaction. Second, the availability of maternal plasma cortisol allowed us to examine its role in the hypothesized cascade from prenatal anxiety and stress to child cognitive outcome. A key finding in this regard is that although maternal prenatal plasma cortisol was associated with amniotic fluid cortisol [in the subsample with child outcome data, $r(107) = .25$, $p < .01$], it was not significantly associated with infant cognitive development [$r(107) = -.13$, ns]. Third, the exploratory hypothesis that there may be developmental timing effects was tested in a regression analysis in which we added the interaction between gestational age at amniotic fluid assessment × amniotic fluid cortisol in predicting cognitive development after other main effects (Model 1 in Table 2). The regression coefficient (B 1.08, SE .57) has a significance value of $p = .06$ and may indicate that the association between amniotic fluid cortisol and child cognitive development was more negative earlier in gestation. Importantly, when the gestational age × amniotic fluid interaction was retained in the model, the amniotic fluid cortisol × infant–parent attachment interaction remained significant at $p < .05$.

Discussion

A sizable literature of experimental animal work on the programming effects of prenatal stress on the offspring is now being translated to human development. Among the findings so far reported, the association between prenatal anxiety or stress and child cognitive development is one of the most reliable and widely reported (6,41). An underlying hypothesis, based on experimental animal work, is that the effect of prenatal stress or anxiety on infant outcomes such as cognitive development derives from an HPA-mediated pathway. Specifically, elevated maternal prenatal stress or anxiety is thought to be related to an elevation in maternal prenatal cortisol, which crosses the placental barrier (notwithstanding the role of 11 beta-hydroxysteroid dehydrogenase two [11BHSD-2] in metabolizing maternal cortisol), to influence fetal brain development (42–43). There is limited support for this model in humans (44), but extensive animal work shows that prenatal exposure to raised glucocorticoids in rodents can damage the brain (45), and in monkeys, administration of dexamethasone in late gestation caused a reduction in hippocampal volume (46).

Our study provides the first direct human evidence that cortisol level in utero predicts infant cognitive development and that this effect is eliminated by a sensitive early rearing environment. However, although the prediction of infant cognitive development from prenatal cortisol exposure was significant and robust, it was essentially independent of multiple measures of maternal prenatal stress and anxiety. Accordingly, this research does not support cortisol as the mediating mechanism for the effects of prenatal stress on child cognitive development. Limitations of the study that may account for these nonfindings (as discussed later), but these results should encourage further investigation of alternative mediating mechanisms (e.g., cardiovascular system and catecholamines) to account for the link between prenatal stress and anxiety and child development.

The prediction of cognitive development from amniotic fluid cortisol may derive from several mechanisms. Understanding the mechanisms involved requires, in the first instance, a careful analysis of the causes of the variation in cortisol level in the amniotic fluid. Cortisol in the fetal circulation is a combination of that produced endogenously by the fetus and that derived from the mother and placenta. Cortisol in amniotic fluid reflects that excreted by the fetus—which may be genetically determined and a result of fetal stress—and includes transfer across fetal skin in early gestation and fetal urine and lung liquid production from midgestation. We were unable to distinguish whether amniotic fluid cortisol reflects fetal exposure (e.g., cortisol of maternal or placental origin predicts lower cognitive ability, as in the animal models) or production (e.g., fetuses producing higher levels of cortisol have lower cognitive ability). Human research is limited in differentiating between these alternatives because experimental leverage is limited for ethical reasons. Nonetheless, our novel observation that the amniotic fluid cortisol effect was moderated by quality of caregiving is more straightforward in its interpretation and in its implications for further research.

The prediction from amniotic fluid cortisol was stronger than that from maternal plasma cortisol, despite the moderate degree of overlap (30). It is well known that the barrier enzyme 11BHSD2 metabolizes cortisol to protect fetal development, although it is equally clear that there are individual differences in that process. Previous research on this sample showed, for example, that the association between maternal cortisol and amniotic fluid cortisol was increased in more anxious mothers (47). An important methodological implication is that amniotic fluid cortisol is a more direct index of fetal exposure than is cortisol (or corticotropin-releasing hormone or corticotropin) measured from the pregnant mother—although it is clearly more of a challenge to obtain.

The hypothesis that a sensitive or optimal early rearing environment has causal influence on biological processes in the young offspring is well established in animal work (29,48–49). Collectively, these and similar findings provide a basis for proposing that early life experiences—and caregiving is perhaps the most important type—have a lasting impact on the organism and may constitute a model for nongenetic intergenerational transmission (50). These models and the underlying mechanisms may apply to humans, but little evidence has been reported, and much available data derives from atypical samples and settings (51). Our finding in a normal risk sample that sensitive postnatal rearing, as indicated by secure infant–mother attachment, eliminates the effect of a biological risk exposure, indexed by amniotic fluid cortisol, is strikingly comparable to the animal work on prenatal stress and the broader animal literature on positive caregiving environment compensating for neurobiological vulnerability. These results provide a major translation and extension of the prenatal work in particular and of the research into the biological impact of early rearing more generally. Equally important, they raise a fundamental conceptual–methodological point that research into biological mechanisms of risk and disorder for neuropsychiatric outcomes needs to attend to how early caregiving experiences may alter the unfolding of these processes. The effects of caregiving in moderating prenatal influence may vary with the nature of the prenatal risk. We previously demonstrated, for fearfulness, that prenatal stress was exacerbated by an insecure/resistant attachment (52).

Limitations

One limitation is that amniotic fluid cortisol was assessed on a single occasion. That is an insurmountable limitation because repeat assessments of amniotic fluid for research purposes are

not possible; children of mothers who undergo multiple samplings are at very high risk for poor obstetric outcome. Although there was some diurnal influence on amniotic fluid cortisol (30), the effect is modest and, in any event, including time of data collection had no effect on the results; gestational age was also adjusted for. Also, the negative association between amniotic fluid cortisol and child cognitive development may not be causal. Additionally, we were not able to conduct postnatal visits on all eligible mothers on whom we had originally collected amniotic fluid data. It is also important to note that, of course, glucocorticoids have adaptive significance and should not be seen merely as an index of risk exposure. Further work is needed to identify the point at which cortisol levels are clinically elevated and may require clinical attention. Finally, we note that our ability to test a component of the model may have been impaired because we included total maternal cortisol (from plasma) rather than free cortisol (we did not have an index of cortisol binding globulin).

Clinical Application

These findings encourage further attention to the application of a programming model for public health and prevention of neuropsychiatric outcomes. Specifically, the findings suggest that early postnatal interventions may confer benefit to the child on both behavior and biology and that some prenatal effects may be modifiable by infant–parent attachment in the postnatal period. Early interventions using attachment models are now widespread and could be integrated with research on biological risk mechanisms. By contrast, it may be preliminary to judge the potential value of gathering amniotic fluid to infer potential risk for cognitive development; moreover, amniotic fluid alone would not be a reliable predictor of later cognitive development without a solid index of early caregiving quality.

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