Maternal Stress in Gestation: Birth Outcomes and Stress-Related Hormone Response of the Neonates

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Background: Relatively few studies have been made on neurobehavioral outcomes of prenatal maternal stress during the newborn period, and little research has focused on umbilical cord stress hormones including cortisol, adrenocorticotropic hormone (ACTH), norepinephrine, and epinephrine. Our objective was to investigate the effects of prenatal maternal life stressors on neonatal birth outcomes, neurobehavioral development, and stress-related hormones levels.

Methods: Participants were 142 mothers and their infants; 71 were selected as the prenatal life stressor exposed group and 71 as the control group matched on maternal age, gestational week, delivery type, socioeconomic and education status, and newborns’ sex. Maternal life stressors during pregnancy were determined using the Life Events Scale for Pregnant Women. Neonatal neurobehavioral development was assessed with the Neonatal Behavioral Neurological Assessment. Umbilical cord plasma stress-related hormones, including ACTH, cortisol, norepinephrine, and epinephrine were measured using an enzyme-linked immunosorbent assay.
1. Introduction

Findings indicate that the human fetus is exquisitely sensitive to physiological and psychological maternal stress, and prenatal stress can be measured with psychometric instruments. It has been proposed that prenatal maternal stress is linked to low birth weight (BW), lower BW, and smaller head circumference (HC). Studies also show that chronic prenatal maternal stress impairs fetal neurobehavioral development. Sandman et al. found that prenatal maternal stress disrupted cognitive performance during infancy and decreased brain volume in areas associated with learning and memory in 6- to 8-year-old children.

The hypothalamic–pituitary–adrenal (HPA) axis is one of the major systems involved in stress response and regulation. Data from a wide range of studies indicate that prenatal maternal stress is associated with elevated maternal cortisol levels during pregnancy, which can pass through the placenta in sufficient concentrations and increase fetal cortisol concentration. However, Nierop et al. concluded that pregnancy in women did not result in a restraint of the HPA axis to psychosocial stress. In addition, Entringer et al. retrospectively identified pregnant women who had been exposed to a severe life event and found the young adult offspring of the exposed group had a lower plasma cortisol but higher adrenocorticotropic hormone (ACTH) stress response. Therefore, cortisol response to stress events across studies is inconsistent.

The sympathetic–adrenal–medullary system (SAM), another neuroendocrine system, is known to be highly pliable and susceptible to the influence of environmental factors during development. Various studies report neonatal plasma norepinephrine (NE) and epinephrine (E) levels significantly increase with response to stress. A direct relationship between prenatal maternal stress and low birth weight, lower BW, and smaller HC may be related to the release of catecholamines, resulting in placental hypoperfusion and consequent restriction of oxygen and nutrients to the fetus, leading to fetal growth impairment.

Relatively few studies have been conducted into neurobehavioral outcomes of prenatal maternal stress during the newborn period, and little research has focused on umbilical cord stress hormones. Furthermore, due to interrelation between the HPA axis and the SAM, examination of both these systems has an increased possibility of providing valuable information about neuroendocrine changes.

In the present research, our objectives were to assess prenatal maternal stress on newborns’ BW and HC, neurobehavioral development, to analyze umbilical cord plasma ACTH, cortisol, NE, and E levels, and to explore whether prenatal maternal stress induce alterations of both hormones, birth outcomes, and neurobehavioral outcomes of newborns.

2. Methods

2.1. Study design and participants

In total, 327 neonates and their mothers were recruited from the Department of Gynecology and Obstetrics of the First Affiliated Hospital, Medical School of Xi’an Jiaotong University, Xi’an, China, from February to August 2010. The following inclusion criteria were applied: (1) mother aged 20–35 years; (2) first singleton pregnancy; (3) birth with no intrapartum complications; (4) gestation at birth 37–40 weeks and the baby developed normally; (5) Apgar score >7 at the 1st minute, 5th minute, and 10th minute after birth; (6) babies’ umbilical cord venous blood were collected; and (7) had a higher score (LESPW score >375) of Life Events Scale for Pregnant Woman (LESPW). Mothers and their neonates were excluded from the study if: (1) the mother used drugs or medication with risks for the fetus; (2) the mother was a smoker or drinker; (3) the mother developed any disease such as hypertension of pregnancy, gestational diabetes mellitus, hyperthyroidism, intrahepatic cholestasis of pregnancy, tumor, hysteromyoma, or abnormal pregnancy complications such as placental abruption or placenta previa; (4) the mother had abnormal gestation or birth history, such as habitual abortion or stillbirth; (5) the mother could not cooperate with us in the survey; or (6) neonates developed congenital malformation, congenital diseases, asphyxia, or birth trauma. Of the 327 mothers who had a higher score (LESPW score >375), 38 women accepted tocolytic therapy, 14 bore twins and five had stillbirths, six women had preterm delivery, and 159 were excluded because the cord blood was not collected. Of the remaining 105 cases, 27 who had pregnancy-induced hypertension and seven who had intrahepatic cholestasis...
were excluded from the study. The remaining 71 mother–infant dyads were selected as the prenatal life stressor exposed group (PS), including 31 women with vaginal delivery, and 40 with elective cesarean delivery, along with their newborns (38 boys and 33 girls).

Meanwhile, 71 neonates and their mothers in the department who had a lower LESPW score (<375) were matched to PS on maternal age, gestational week, delivery type, socioeconomic and education status, and newborns’ sex were selected as control group (CON).

This research was approved by the Xi’an Jiaotong University Ethics Committee and carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all enrolled mothers. To improve the accuracy of gestational age estimates, an ultrasound examination was used to confirm or correct the gestational age. The investigators would not collect the questionnaires until they had gone through the sheet twice in order to ensure the authenticity and integrity of the data with reference to the hospital medical record.

2.2. Data collection

We collected information regarding maternal age, reproductive history, pregnancy complications, gestational duration, babies’ birth process, type of delivery, Apgar score, BW, and HC from the medical records of the mothers and newborns. Maternal life stressors during pregnancy were determined by LESPW. Neonatal neurobehavioral development was assessed through the Neonatal Behavioral Neurological Assessment Scale, the first truly standardized, comprehensive assessment of newborn neurobehavior. Amiel-Tison et al subsequently developed the Neurologic and Adaptive Capacity Score via examining tone and reflexes. Based on the methods of Neonatal Behavioral Assessment Scale and Neurologic and Adaptive Capacity Score, Bao et al formulated NBNA. Subsequently repeated measurements in neonates showed that NBNA had distinct stability and reliability and was widely utilized by geographic location.

It consists of 20 items with scores of 0, 1, and 2 for each item. The items consist of five categories: behavioral assessment (6 items), passive muscle tension (4 items), active muscle tension (4 items), primitive reflexes (3 items), and general assessment (3 items). The maximum score is 40 with ≥37 regarded as normal. The assessment was carried out by a trained pediatrician within 10 min in a quiet, warm, and dimmed light room between two feeds.

2.3. LESPW

Maternal interview was administered to each mother when they hospitalized in the ward for delivery. After completing some brief questions on demographics, marital status, residence, education and job status, and household income (Table 1), mothers completed the questionnaire of LESPW, an established, well-validated, and used scale in China. The scale lists 53 potentially stressful life events during pregnancy covering family life, work, study, social relationships, and other aspects in life, consisting of subjective events (7 items) and objective events (46 items). Events are weighted according to different stressors. For example, divorce is weighted as 90, poor family finances is 56, moving to a new place is 31. The maximum possible score, if each of the 53 items applies, is 2955. In the scale, pregnant women whose total scores were ≥375 are assigned to gestational maternal life stressors exposed.

2.4. NBNA

When neonates were age 3 days, we used NBNA to measure neurobehavioral development of neonates in the study. Brazelton developed the Neonatal Behavioral Assessment Scale, the first truly standardized, comprehensive assessment of newborn neurobehavior. The Neurologic and Adaptive Capacity Score via examining tone and reflexes. Based on the methods of Neonatal Behavioral Assessment Scale and Neurologic and Adaptive Capacity Score, Bao et al formulated NBNA. Subsequently repeated measurements in neonates showed that NBNA had distinct stability and reliability and was widely utilized by geographic location.

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### Table 1: Characteristics of maternal demographic background.

<table>
<thead>
<tr>
<th>Variables*</th>
<th>PS (n = 71)</th>
<th>CON (n = 71)</th>
<th>Values</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y)</td>
<td>28.25 ± 2.85</td>
<td>28.17 ± 2.52</td>
<td>t = 0.187</td>
<td>0.852</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>38.97 ± 0.82</td>
<td>39.13 ± 0.72</td>
<td>t = 1.244</td>
<td>0.216</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural area</td>
<td>103 (72.5)</td>
<td>52 (73.2)</td>
<td>51 (71.8)</td>
<td></td>
</tr>
<tr>
<td>Urban area</td>
<td>38 (27.5)</td>
<td>19 (26.8)</td>
<td>20 (28.2)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle school</td>
<td>15 (10.6)</td>
<td>6 (8.5)</td>
<td>9 (12.7%)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>13 (9.2)</td>
<td>6 (8.5)</td>
<td>7 (9.9)</td>
<td></td>
</tr>
<tr>
<td>Bachelor degree</td>
<td>85 (59.9)</td>
<td>44 (62.0)</td>
<td>41 (57.7)</td>
<td></td>
</tr>
<tr>
<td>Higher than bachelor degree</td>
<td>29 (20.3)</td>
<td>15 (21.0)</td>
<td>14 (19.7)</td>
<td></td>
</tr>
<tr>
<td>Family income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2000 RMB/mo/person</td>
<td>19 (13.4)</td>
<td>9 (12.7)</td>
<td>10 (14.1)</td>
<td></td>
</tr>
<tr>
<td>2000–5000 RMB/mo/person</td>
<td>101 (71.1)</td>
<td>52 (73.2)</td>
<td>49 (69.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;5000 RMB/mo/person</td>
<td>22 (15.5)</td>
<td>10 (14.1)</td>
<td>12 (16.9)</td>
<td></td>
</tr>
</tbody>
</table>

CON = control group; PS = prenatal stress group.

* Data presented as mean ± standard deviation, or n (%).
The investigators have received strict professional training and were deemed to be capable of objective and substantive judgment on the findings.

2.5. Measurement of stress-related hormones in umbilical cord blood

Umbilical cord was double clamped immediately after neonatal delivery and we collected a total of 5 mL venous blood into anticoagulant coated tubes using Ethylene Diamine Tetraacetic Acid from the umbilical vein immediately after placental delivery. Umbilical cord blood samples were centrifuged at 3000 × g for 10 minutes at 4°C. Polycarbonate tubes filled with separated plasma were stored at −80°C until analysis for biochemical parameters. Each assay was performed after the thawing of plasma. Measurement of stress-related hormones was performed using specific enzyme-linked immunosorbent assay kits for ACTH, cortisol, NE, and E, respectively (Huaying Biotechnology Research Institute, Beijing, China).

2.6. Statistical analysis

The SPSS 13.0 software package (SPSS, Chicago, IL, USA) was used for data analysis. Normal distribution test was used for measurement data, and mean ± standard deviation was used to express data of normal distribution. Independent sample t test was used to test the difference in BW, HC, and NBNA score between PS and CON. Line × row Chi-square test was used to compare sociodemographic characteristics between PS and CON. Paired rank test was used since it showed that the levels of ACTH, cortisol, NE, and E in umbilical cord venous blood did not conform to the normal distribution. A difference was considered statistically significant at the p < 0.05 level.

3. Results

3.1. Maternal demographic characteristics

Maternal characteristic did not differ between PS and CON groups according to maternal age (Student t test; t = 0.187; p = 0.852), gestational age (Student t test; t = 1.244; p = 0.216), permanent residence (Chi-square test; χ² = 0.035; p = 0.851), level of education (Chi-square test; χ² = 0.817; p = 0.845), and family income (Chi-square test; χ² = 0.817; p = 0.851; Table 1).

3.2. Neonatal physical growth and neurobehavioral development in PS and CON groups

We compared BW, HC, and NBNA scores between PS and CON. In the CON group, 71 women had full-term newborns with BW of 3406.06 ± 368.46 g, HC 34.31 ± 0.97 cm, and NBNA score 37.54 ± 1.16. In the PS group, 71 women had full-term newborns with BW of 3250.14 ± 311.57 g, HC 33.83 ± 0.95 cm, and of NBNA score 34.72 ± 1.00. Newborns with maternal life stressors exposure had lower BW, smaller HC and significant lower score of NBNA (p < 0.01, and p < 0.001, respectively; Table 2).

3.3. Alterations of ACTH, cortisol, NE, and E levels in umbilical cord blood in PS and CON groups

To explore how maternal life stressors influence neonatal neuroendocrine function, we tested the umbilical cord venous plasma stress hormones. There was significant difference in umbilical cord plasma ACTH, cortisol, NE, and E levels between PS and CON (p < 0.001). Umbilical cord plasma cortisol levels in PS group (220.39 ± 20.22 ng/mL) was significantly lower (252.80 ± 22.86 ng/mL; p < 0.001), while ACTH (34.24 ± 10.85 pg/mL), NE (821.91 ± 253.79 pg/mL), and E (251.50 ± 83.83 pg/mL) were significantly higher in PS group (19.75 ± 7.15 pg/mL, 362.11 ± 114.72 pg/mL, and 121.20 ± 38.44 pg/mL, respectively; p < 0.001; Table 3).

4. Discussion

In this study, we found that newborns exposed to prenatal maternal life stressors had lower BW and smaller HC, which is consistent with a previous report. These findings provide further evidence that prenatal stress exposure is negatively associated with fetal physical development. Exposure to prenatal maternal cortisol appears to be an important factor linking gestational stress to lower BW and shorter height at birth. Elevated free circulating cortisol may pass through the placenta, prevent fetal growth rate, and reduce birth weight of prenatally stressed offspring. However, study also found that maternal life stress was associated with increased offspring BW and HC. One explanation for the inconsistent findings across studies may be that we used LESPW to assess maternal stressful social conditions before delivery, which covered potentially stressful life events during pregnancy.

We found that NBNA scores in PS group were significantly lower, implicating that gestational stress may negatively

| Table 2 | Comparison of birth outcomes and neurobehavioral development between prenatal stress (PS) and control (CON) groups. |
|---|---|---|---|---|
| Variables | PS (n = 71) | CON (n = 71) | t | p |
| BW (g) | 3250.14 ± 311.57 | 3406.06 ± 368.46 | 2.723 | 0.007* |
| HC (cm) | 33.83 ± 0.95 | 34.31 ± 0.97 | 2.954 | 0.004* |
| NBNA scores | 34.72 ± 1.00 | 37.54 ± 1.16 | 15.506 | <0.001* |

BW = birth weight; HC = head circumference; NBNA = Neonatal Behavioral Neurological Assessment.

* p < 0.01, PS versus CON.
affect fetal brain development. In this study, NBNA was used to estimate neurobehavioral development of the neonates at age 3 days, which assessed neonatal behavior, passive muscle tone, active muscle tone, primary reflex, and general assessment. Wadhwa22 examined the effects of stress-related psychoneuroendocrine processes in human pregnancy on fetal developmental and health outcomes. Their studies indicated that the maternal environment exerts a significant influence on the fetal neurodevelopmental processes related to recognition, memory, and habituation; chronic maternal psychological distress was significantly related to indices of fetal neurobehavioral maturation and reactivity.22 The developing fetal nervous system may be vulnerable to environmental perturbations because it has limited repair capabilities. The blood–brain barrier has not fully developed in utero and the sensitivity of neurotransmitter systems, which is set during critical developmental periods, affects the fetal response to all subsequent experience.23

The effects of maternal stress on fetal outcomes are mediated, at least in part, by the maternal HPA axis. Cortisol from mother can transport into the body of fetus through placenta and then trigger the dysfunction of fetus’ neuroendocrine system. It was reported previously that prenatal maternal stress entails activation of the HPA, which increases secretion of ACTH and cortisol.24 In the present research, our findings showed that newborns had higher ACTH, but lower cortisol levels, which suggested a discrepancy between ACTH and cortisol response. This hormonal profile of increased pituitary activity (high ACTH) and decreased adrenal activity (low cortisol) was consistent with adrenal hyporesponsivity, which occurs under conditions of chronic stress and downregulation of adrenal receptors.22 Yehuda et al23 observed lower cortisol levels in both mothers and their babies who developed post-traumatic stress disorder in response to the September 11 event. In fact, there is increasing evidence for a relatively decreased, rather than increased cortisol response in healthy individuals who have been exposed to severe acute or severe chronic stress.26 According to Heim et al,27 blunted cortisol responses to stressors describes what has been termed hypocortisolism.26 Another possibility for the reduced cortisol response may involve the diurnal rhythm in the adrenocortical response. Umbilical cord blood samples were collected over all daytime and nighttime hours, an unpredictable schedule without the dynamics of the normal circadian rhythm, producing a low pattern of cortisol levels. Future research is needed to extend our findings, such as collection of the blood samples considering of diurnal rhythm to further illustrate newborns’ hormone regulation.

The effects of prenatal stress on the fetus have also been mediated by heightened and/or abnormal activity of the maternal SAM with secretion of NE and E. Cord blood NE and E levels were found to be significantly higher in our experiment. It was demonstrated that elevations in prenatal NE were associated with lower BW.28 One of the possible explanations is stress-related changes occur on the vessels and result in decreased blood supply.1 Stress-induced increased level of NE provokes vasoconstriction and hypoperfusion of tissues, including placenta, which causes nutrient restriction in the fetus and contribute to fetal growth restriction.29

In spite of the revealing findings, the study has certain limitations. First, we collected umbilical cord blood and compared PS and CON by matching pregnant marital age, gestational age, marital status, education, household income, etc., but the number in some categories was small, resulting in some data missed, limited power of the results, and some systematic bias. Second, our design assessed prenatal maternal stress of the whole pregnancy before delivery, not at the different pregnant times. Thus, recall bias was inevitable. Additionally, women with delivery before 37 gestational weeks were excluded, which might result in under-evaluating the effect of life events stress in preterm. Finally, we solely screened prenatal stress by LESPW and neonatal neurobehavioral development by NBNA. It is not enough to assess the different severity of maternal stress on fetal birth outcomes although it can show part effects of self-reported life events stress on fetal growth.

The present study suggests that exposure to prenatal maternal stress results in increasing the risk of adverse birth outcomes and fetal neurobehavioral development. In addition, mothers who have experienced life stressors are accompanied by reduced umbilical cord plasma cortisol and elevated ACTH, NE and E levels.

Conflicts of interest

The authors declare no conflicts of interests with respect to the research, authorship, and/or publication of this article.

Acknowledgments

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Table 3 Comparisons of umbilical cord plasma adrenocorticotropic hormone (ACTH), cortisol, norepinephrine, and epinephrine levels between prenatal stress (PS) and control (CON) groups.

<table>
<thead>
<tr>
<th>Stress-related hormones</th>
<th>PS (n = 71)</th>
<th>CON (n = 71)</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH (pg/mL)</td>
<td>34.24 ± 10.85</td>
<td>19.75 ± 7.15</td>
<td>5.697</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Cortisol (ng/mL)</td>
<td>220.39 ± 20.22</td>
<td>252.80 ± 22.86</td>
<td>6.222</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Norepinephrine (pg/mL)</td>
<td>821.91 ± 253.79</td>
<td>362.11 ± 114.72</td>
<td>7.358</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Epinephrine (pg/mL)</td>
<td>251.50 ± 83.83</td>
<td>121.20 ± 38.44</td>
<td>6.883</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

** *p < 0.001 PS versus CON.*
References


