Prenatal Stress and Offspring Health Outcomes

Guizhen Du and Di Wu

Maternal psychosocial stress during pregnancy has been identified as a robust predictor of offspring health outcomes, especially in neurodevelopmental measures, including behavior and temperament. Thus it is now considered to be a risk factor for the development of childhood behavioral problems.

1 Maternal Stress Measures

Measures to quantify prenatal maternal stress vary widely at present. Unlike the detection of chemical exposures, most studies use questionnaires to assess stress, which have been designed to ascertain perceived stress, life events, depression, anxiety, occupational stress, and trauma. Different standardized questionnaires have been utilized to screen for common mental disorders and measure prenatal affective states, such as the General Health Questionnaire, Self-Reporting Questionnaire, Patient Health Questionnaire, Crisis in Family Systems, Exposure to Violence, Edinburgh Postnatal Depression Scale, Beck Depression Inventory, and State-Trait Anxiety Inventory. It must be emphasized that the results from questionnaires only generally reflect stress and psychosocial health. Great variability and lack of details and validation in some reports make it impossible to compare the stress measured among different studies.

Some researchers analyzed the level of maternal cortisol, which is a hormone whose production is increased when stressed. Usually, multiple measures have been applied to test maternal stress.

G. Du · D. Wu (✉)
State Key Laboratory of Reproductive Medicine, Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing, China
e-mail: diwu@njmu.edu.cn

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2 Prenatal Stress Exposure and Outcomes in Offspring

2.1 Birth-Related Outcomes in Offspring

Most studies analyzing infant outcomes observed gestational age, birth weight, and Apgar scores at birth. These measures are easily obtained and are usually thought to be basic thus most human studies have included these measure results. The difference in measuring these health indexes among different countries and cultures is small. Studies have shown significant associations between prenatal stress and birth weight, anthropometric measurements, Apgar scores, stillbirth or neonatal death rates, and methylation patterns in newborns (Table 1).

2.1.1 Gestational Age or Preterm Birth

2.1.1.1 Perceived Stress

Perceived stress is a measure of the degree to which situations in one's life are appraised as stressful. Usually, the perceived stress scale is used, which is carefully designed to psychologically determine the perception of stress. The association between perceived stress and gestational age is controversial. Some studies found a significant relationship between perceived stress and preterm birth [1], while others (small-sample-size and case-control studies) indicated that Perceived Stress Scale scores were not related to preterm birth [2]. The discrepancy may be due to the analytical limitations of a small sample size.

2.1.1.2 Life Events

Life events refer to family violence, conflicts among family members, and hospitalization/death of relatives, which can bring stress to the pregnant mothers. Most studies found that life events were significantly related to preterm birth [3]. Negative stressful life events can lead to anxiety or depression [4] and then indirectly relate to decreased gestational age.

2.1.1.3 Cortisol

Cortisol is thought to be a stress hormone. It is the only index which can be measured chemically and thus can be compared among different studies without culture correction. There is a significant relationship between elevated cortisol level, especially during the third trimester [5], and shorter gestational age [1]. In some studies [6], this relationship has been found only in male but not in female infants.

Table 1 Prenatal stress and offspring birth-related health summary

Country	Sample size of pregnant women	Prenatal stress measurement	Outcome measurement	Results (+/−)
Malawi [1]	1391	Perceived Stress Scale, salivary cortisol	Birth weight, birth length, head circumference, arm circumference, WAZ, LAZ, HCAZ	Salivary cortisol: +
				Perceived Stress Scale: –
Brazil [2]	865	Perceived Stress Scale, General Health Quest., State Trait Anxiety Inv.	LBW, preterm birth, intra-uterine growth restriction	LBW, preterm birth: +
				Intra-uterine growth restriction: –
China [3]	2782	Questionnaire: Life events	Preterm birth	+
Iran [4]	550	Depression Anxiety Stress Scales, Stressful Life Events Quest.	Preterm birth	–
Nepal [5]	737	Serum cortisol	Gestational age, LBW, preterm birth	Preterm birth: (OR = 1.04, CI = 1.00, 1.08)
				Birth weight/ LBW: –
Bangladesh [6]	1041	Salivary cortisol	Birth weight, birth length, head circumference, gestational age	+
Iran [7]	600	Spielberger State-Trait Anxiety Inv.	Preterm birth, LBW	Preterm birth, LBW: +
Ghana and Côte d'Ivoire [8]	719	Patient Health Quest., Generalized Anxiety Disorder Scale	Birth weight, LBW, head circumference, gestational age, preterm birth, Apgar score	Apgar: +
				Birth weight/ Gestational age/ Preterm birth: –
Mexico [9]	2623	Karasek's Job Content Quest.	Gestational age, preterm birth, birth weight, SGA	SGA: (OR = 4.93, CI = 2.09, 11.66)
South Africa [10]	544	Childhood Trauma Quest., Mini Int. Neuropsychiatric Interview to assess	WAZ, HCAZ, SGA, preterm birth	SGA, preterm birth, WAZ: –
				HCAZ: +
China [11]	2189	Revised Pregnancy Stress Rating Scale	Preterm birth	High pregnancy specific stress led to preterm birth: +
				Low and medium levels of pregnancy-specific stress: –

(continued)

Table 1 (continued)

Country	Sample size of pregnant women	Prenatal stress measurement	Outcome measurement	Results (+/−)
Romania [12]	474	Perceived Stress Scale	Birth weight, gestational age, SGA, preterm birth	Birth weight (CI = −213, −11)/preterm birth (OR = 2.81, CI = 1.17, 6.76)
Colombia [13]	46	Perceived Stress Scale	Preterm birth, LBW, preterm birth and LBW combined	–
Ethiopia [14]	1065	Self-Reporting Quest. of common mental disorders, List of Threatening Experiences Quest.	Birth weight, stillbirth, neonatal mortality, prolonged labor, time to initiation of breastfeeding	Birth weight, Self-Reporting Quest. stillbirth, or neonatal death: –
				Common mental disorders: low, RR = 1.4, CI = 1.0, 1.9; high, RR = 1.6, CI = 1.0, 2.6
				Delivery: RR = 1.5, CI = 1.0, 2.1
China [15]	1800	19-Item Prenatal Life Events Checklist	Preterm birth, birth weight	Birth weight in the first term: +
				Birth weight in the second and third term: –
Nicaragua [16]	147	Salivary cortisol, intimate partner violence, emotional distress, social resources	LBW, preterm birth, SGA	LBW, SGA: +
				Preterm birth: –
Bangladesh [17]	583	Edinburgh Postnatal Depressive Scale, State Trait Anxiety Inv.	LBW	LBW (OR = 2.24, CI = 1.37, 3.68)
				Anxiety (OR = 2.08, CI = 1.30, 3.25)
South Africa [18]	726	Beck Depression Inv., World Mental Health Life Events Quest.	Birth weight, head circumference, WAZ, HCAZ, SGA	Preterm birth: –
				WAZ (OR = 0.2, CI = 0.02, 0.4) and HCAZ (OR = 0.3, CI = 0.1, 0.6)
Sri Lanka [19]	835	General Health Quest.	SGA	+
China [20]	792	Perceived work stress: single questionnaire item	Birth weight	+

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Table 1 (continued)

Country	Sample size of pregnant women	Prenatal stress measurement	Outcome measurement	Results (+/−)
China [21]	463	Hospital Anxiety and Depression Scale	Obstetric outcomes	+
Iran [22]	29	Edinburgh Postnatal Depression Scale, Pregnancy-Related Anxiety Quest.	Apgar scores	+
Democratic Republic of Congo [23]	24	Semi-structured ethnographic interviews: Stressful events during pregnancy	Methylation of CRH, CRHBP, NR3C1, and FKBP5, from maternal venous blood, placenta, and umbilical cord blood	+
Democratic Republic of Congo [24]	25	Ethnographic interviews: deprivation, "mundane stressors," war stressors; Peritraumatic Distress Inv.	Methylation of NR3C1 promoter, birth weight	−

+/−:significant positive/negative relationships have been found
WAZ weight for age Z-score, *LAZ* length for age Z-score, *LBW* low birth weight, *PLBW* preterm low birth weight infant, *HCAZ* head circumference for age Z-score, *SGA* small for gestational age, *CRH* corticotropin-releasing hormone, *CRHBP* corticotropin-releasing hormone binding protein, *NR3C1* nuclear receptor subfamily 3 group C member 1, *FKBP5* FK506-binding protein 51, *OR* odds ratio, *CI* confidence interval, *RR* relative risk

2.1.1.4 Anxiety, Depression, and Other Mental Disorders

Researchers have demonstrated that scores from the Depression Anxiety Stress Scale [4] or State-Trait Anxiety Inventory [7] during pregnancy had a negative relationship with gestational age and prenatal maternal mental disorders could lead to preterm birth.

However, other studies [8] showed no significant relationships between anxiety and gestational age. The discrepancy may lie in the fact that these studies only sampled uncomplicated pregnancies. Pregnancy complications may play a key role in the relationship between prenatal maternal mental disorders with birth health outcomes. At the same time, limitations in sample size may also lead to an opposite result.

2.1.1.5 Other Stress Measures

Occupational stress [9], trauma [10], and pregnancy-related stress [11] had been analyzed by a couple of researchers, but the results require further study. They

showed that high stress [11], but not occupational stress [9] or trauma [10], had a significant relationship with preterm birth.

2.1.2 Birth Weight

2.1.2.1 Perceived Stress

Studies showed significant relationships between perceived stress and birth weight. High prenatal stress usually leads to reduction in birth weight [12]. Some studies failed [13] to detect this relationship due to small sample size.

2.1.2.2 Life Events

Maternal prenatal life events have not been found [14] to be significantly related to birth weight. However, studies that specified the timing of the life events showed that the occurrence of life events during the first trimester led to low birth weight [15].

2.1.2.3 Cortisol

Studies showed significant negative relationships between third trimester cortisol levels and birth weight in male but not female infants [6]. In fact, high perceived stress had been proved to be related to increased cortisol [16]. Cortisol may play an intermediate role in the relationship.

2.1.2.4 Anxiety, Depression, and Other Mental Disorders

Researchers [7] had demonstrated significant relationships between prenatal maternal common mental disorders (such as anxiety, depression) and low birth weight. Babies of women with high level of anxiety or depression (which could be assessed by the State-Trait Anxiety Inventory [17], Edinburgh Postnatal Depression Scale [18] and State-Trait Anxiety Inventory, Beck Depression Inventory [18], or General Health Questionnaire [2, 19]) tended to have lower birth weight.

2.1.2.5 Other Stress Measures

Occupational stress, trauma, and intimate partner violence had been assessed in some studies. Occupational stress was shown [19] to be significantly related to low birth weight. One study showed [20] that occupational chemical exposure and work stress had interactive decreasing effects on birth weight. Trauma [9, 10] and partner [16] violence had not been found to affect birth weight directly, though these two stress measures could lead to depression.

2.1.3 Anthropometric Measurements (Head Circumference and Birth Length)

Some studies indicated that prenatal depression (Beck Depression Inventory scores) [18] and lifetime trauma [10] had significant relationships with smaller head circumference and birth length, while others found that there was no difference in head circumference [8, 21] and birth length [21] between babies of mothers with or without anxiety and depression during pregnancy.

Interestingly, one study [6] found that there was a negative relationship between cortisol levels during the third trimester and birth length only in male but not in female babies, similar to the results found using gestational age.

2.1.4 Apgar Scores

One case-control study [22] found that women with anxiety or depression during pregnancy but receiving a stress management intervention finally had babies with higher Apgar scores compared to the group with anxiety or depression but without intervention. Apgar scores of offspring have been found [8] to be correlated with the scores from Patient Health Questionnaire and Generalized Anxiety Disorder Scale in pregnant women.

2.1.5 Stillbirth or Neonatal Death

Different from what people usually think, there was no relationship between stillbirth or neonatal death and prenatal maternal mental disorder and negative life events during pregnancy [12].

2.1.6 Methylation Patterns

The measure of methylation patterns is relatively new and has been analyzed only by a few studies with small sample sizes of fewer than 30 participants. Women with chronic stress and trauma during pregnancy showed [23] differences in methylation pattern of placental tissue, umbilical cord blood, and maternal venous blood. Four CpG sites (DNA regions containing cytosine nucleotide-phosphoric acid-guanine nucleotide) have been identified, which could further be linked to other birth measures such as weight. In another study [24], prenatal stress has been found to be related to cord blood methylation of the NR3C1 (Nuclear Receptor Subfamily 3 Group C Member 1) gene, whose function in offspring stress responses is worth researching.

2.2 *Later-Life Outcomes in Offspring*

Prenatal stress has also been related to later-life health problems such as anxiety, attentional deficits, social withdrawal, and helplessness in offspring. Because of follow-up limitations, only a few studies have focused on prenatal stress and later-life outcomes in offspring (Table 2).

2.2.1 Babyhood

Temperament: All the studies measuring temperament found significant results of prenatal maternal stress. Scores of adaptability and approach were higher in babies whose mothers experienced less distress during pregnancy. The scores from Edinburgh Postnatal Depression Scale at second trimester were found to be related to the socioemotional scores from Bayley Scales of Infant Development measured at age of 6 months [25]. Path analyses indicated that prenatal maternal mental disorders led to common postnatal mental disorders and then further affected socioemotional scores of babies. Prenatal maternal negative life events experience could lead to low baby mental development scores and high scores on attention, regularity, and persistence.

2.2.1.1 Motor Development

A study with a small sample size [26] indicated that there was no relationship between maternal negative life events experience and babies' motor development. Other studies [27] had not found a relationship between stress and neuromotor development right after birth, or at the age of 1 and 3 months.

2.2.1.2 Illness

A study among 954 women [28] found that persistent symptoms of common mental disorders during both pregnancy and postpartum (from Self-Reporting Questionnaire scores during third trimester and postpartum) had a relationship with infant diarrhea and illness (maternal-reported) at the age of 2 months. Results on relationships between prenatal stress and other illnesses were inconsistent.

2.2.2 Childhood

2.2.2.1 Behavioral Outcomes

Research has often noted children's behavior as an issue of great concern, but due to the length of time required for a longitudinal study of this nature, there are few

Table 2 Prenatal stress and offspring later-life health summary

Country	Sample size of pregnancy women	Prenatal stress measurement	Outcome measurement	Results (+/−)
Vietnam [25]	378	Edinburgh Postnatal Depression Scale to assess common mental disorder	Bayley Scales of Infant and Toddler Development Social-Emotional Questionnaire	–
China [26]	152	19-Item Prenatal Life Events Checklist	Bayley Mental & Psychomotor Dev. Index, Toddler Temperament Scale	1stT life events: +
				Life events: –
South Africa [27]	101	Feelings about pregnancy, life events, family relationships	Neuromotor development 3, 32, and 93 days after delivery	Motor scores <3:42.5% in the high-stress group and 15.4% in the low-stress group
Ethiopia [28]	954	Self-Reporting Quest. of common mental disorders	Infant illness episodes since birth	Diarrhea: +
				Persistent common mental disorders and acute respiratory infection: +
				In multivariate analyses: –
Brazil [30]	370 (children)	Questionnaire: Mothers were asked "whether the pregnancy was a peaceful time or marked by discord and arguments"	Teacher report form of ADHD symptoms	ADHD: +
South Africa [31]	953	Interviews: Marital, family, economic, and societal stress and violence	Richman Behavior Screening Questionnaire at ages 2 and 4	+
China [33]	216	Hamilton Anxiety Scale, Hamilton Rating Scale for Depression	Resting blood pressure and heart rate at age 7–9 years	+
Brazil [34]	409	Perceived Stress Scale, General Health Quest., State Trait Anxiety Inv.	Body mass index Z-scores at ages 5–8 years	+

(continued)

Table 2 (continued)

Country	Sample size of pregnancy women	Prenatal stress measurement	Outcome measurement	Results (+/−)
Mexico [35]	417	Crisis in Family Systems Revised survey of negative life events	Asthma, wheeze	+

+/−:significant positive/negative relationships have been found
ADHD attention deficit hyperactivity disorder

reports relating prenatal stress with childhood behavior. However, most studies on the matter showed significant relationships between prenatal maternal stress and alterations in child behaviors. One study [29] analyzed second to third trimester maternal salivary cortisol level and scores from Self-Reporting Questionnaire and these pregnant women's children's behavior (Child Behavior Checklist) and cortisol at age of 9. Maternal salivary cortisol level, but not Self-Reporting Questionnaire scores, had a significant relationship with Child Behavior Checklist scores, but not cortisol in children. In another study [30], researchers evaluated the distress of pregnant women using one single retrospective interview question and screened their children (6–13 years old) according to attention deficit hyperactivity disorder (ADHD) symptoms, which had been defined by Teacher Report and the Child Behavior Checklist. Discord during pregnancy was significantly related to reported ADHD. This result was consistent with another study that evaluated prenatal maternal emotional distress using a single retrospective question and compared behavior results in offspring (6–12 years) with and without ADHD. It showed that prenatal maternal stress had a significant relationship with childhood ADHD. One study [31] assessed third trimester stress in pregnant women and their children's behavioral problems using the Behavior Screening Questionnaire when they reached 2–4 years. There was a significant relationship between prenatal maternal stress and children (4 years old) behavioral problems. One study [32] that interviewed women shortly after delivery used a single questionnaire to evaluate mood. Psychological disorders were estimated in their children (6 years old) using the Development and Well-Being Assessment. It showed that maternal mood was significantly related to psychological disorders among children.

2.2.2.2 Other Health Outcomes

Some researchers collected heart rate [33], physical growth [34], and asthma [35] as health outcomes in children after prenatal maternal stress. One study [33] evaluated prenatal maternal depression and anxiety state and these women's children's

(7–9 years old) heart rate and blood pressure before, during, and after a video game (which was thought to bring stress). Children with prenatal anxious mother had high heart rate and blood pressure following the video game stress. Prenatal maternal anxiety had been found to be significantly related to children heart rate and blood pressure. However, another study [33] examined prenatal maternal stress three times during pregnancy according to the data collected from General Health Questionnaire, Perceived Stress Scale, and State-Trait Anxiety Inventory. They also analyzed body mass index Z-scores in their children (5–8 years old). Results indicated that scores from second trimester General Health Questionnaire were significantly related to children's body mass index Z-scores. Further analysis also found that prenatal negative life events were related to wheezing among children.

3 Conclusions

Studies show significant relationships between prenatal maternal stress and health outcomes in offspring at birth, during babyhood, and childhood. It is extremely important to utilize appropriate and well-accepted methods across different studies in order to summarize the discoveries in prenatal stress and offspring health outcomes. Because of the variability in definitions of stress, measures of maternal stress need to be normalized not only by maternal education, age, and household income, etc. but also by the cultures with which both participants and researchers identify. This normalization requires careful collection and analysis of covariates, especially those that might have interactive effects with prenatal maternal stress. Long-term follow-up studies are encouraged since there are only a few at present. One of the main research directions in the near future is the development and validation of brief, simple, well-understood survey measures that can allow fast evaluation of prenatal maternal stress and be integrated into expansive studies on maternal and child health.

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