CHAPTER 11

Stress in Pregnancy

Impacts on Mother and Child

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Research conducted over the past 30 years has demonstrated that maternal emotional stress in pregnancy is associated with somatic diseases for children in later life (Painter et al. 2012; Tamashiro and Moran 2010). Although less studied than risks related to physical health, convincing evidence exists regarding detrimental effects of prenatal stress on child neurodevelopment, behavior, and mental health (Glover 2011; Graignic-Philippe et al. 2014; Van den Bergh et al. 2017). Such effects have been found not only for maternal distress related to a psychiatric disorder but also for various types of stress that do not fall within any definable category of mental illness. More specifically, there is a distinction between prenatal stress and distress, whereby *prenatal stress* includes daily hassles, perceived stress, pregnancy-related worries, and major life events, and *prenatal distress* includes psychological symptoms and disorders such as anxiety and depression, both of which have been associated with adverse fetal and child outcomes.

The effects of prenatal stress have usually been studied under the fetal programming hypothesis, which postulates that environmental risk factors to which a fetus is exposed in utero (e.g., malnutrition) alter fetal development, exerting sustained effects on child health (Barker 1995a, 1995b). This hypothesis, also known as the Barker hypothesis or the developmental origins of health and disease (DOHaD) model (Fleming et al. 2015), suggests that the fetus adapts in reaction to environmental cues on physiological, neuroendocrine, and metabolic levels by programming or reprogramming its biological systems while they are still immature and therefore extremely malleable. Gestation is a particularly vulnerable period for brain development, and even subtle alterations in brain structure and function resulting from environmental conditions can have long-

term consequences. Most studies report negative effects of prenatal exposure to maternal stress on brain–behavior development, indicating greater child susceptibility to mental health problems and disorders later in life.

Surprisingly, some studies report positive effects of prenatal stress (DiPietro et al. 2006, 2010; Kantonen et al. 2015; Lin et al. 2014; Rothenberger et al. 2011) and elevated maternal cortisol in pregnancy (Glynn and Sandman 2012) on child outcomes, suggesting that prenatal stress is not necessarily pathogenic. Several hypotheses have been proposed to explain such findings, diverging from the traditional diathesis–stress model (Zuckerman 1999) that links stress with increased vulnerability to disease. According to some authors, prenatal stress may provide more stimulation for the fetus, enhancing fetal sensitivity (and physiological and behavioral reactivity) to environmental cues and, thereby, postnatal developmental plasticity. This may be a risk factor but also an opportunity, depending on the child's postnatal environment (Hartman et al. 2018, 2019). More sensitive and reactive children may be at a higher risk of mental health problems if exposed to postnatal adversity (e.g., low parenting quality); conversely, they may benefit more from postnatal supportive environments compared with children without prenatal stress exposure (Hartman et al. 2018). Another explanation may be that the exposure to prenatal stress leads to fetal adaptations or "programmed" changes (e.g., heightened vigilance, alertness, aggressiveness, or impulsivity) that may improve children's chance for survival, preparing them for the demands of the extrauterine world. As some authors put it (Sandman et al. 2012b), it is not the stress, per se, but rather the incongruity between the pre- and postnatal environments that leads to less favorable outcomes in children who are exposed prenatally to conditions that differ from those into which they are born.

What seems to be of pivotal importance is the magnitude of prenatal stress. While reporting positive effects for moderate levels of stress, DiPietro et al. (2006) and Laplante et al. (2008) also found detrimental outcomes for high levels of stress. In addition, Hartman et al. (2020) observed that children who were exposed to the least prenatal stress were the most affected by maternal postnatal stress. It seems, therefore, that both too little and too much stress may be pathogenic, whereas moderate levels of stress might be beneficial (DiPietro 2004, 2012). Yet these results must be interpreted with caution because they may apply to specific samples only. The studies showing positive effects of prenatal stress are mostly based on data from families of higher socioeconomic and educational status (DiPietro 2012; Laplante et al. 2008). Although there may be a positive association between moderate prenatal stress and specific child outcomes, little is known about the factors modulating such association (e.g., timing and type of stress) or the direction of the effects in different developmental domains (e.g., such that better performance in one domain is accompanied by worse performance in another domain).

Despite some inconsistencies, the bulk of existing research shows a higher risk of detrimental neurodevelopmental outcomes and mental health disorders following exposure to stress in utero. As such, maternal stress in pregnancy may function as a "third pathway" of familial transmission of risk for psychiatric disorder, apart from shared genes and quality of parental care. It should, however, be emphasized that most children exposed to prenatal stress remain unaffected, and as such, the nature of this association consists in *increasing the risk* rather than causing inevitable mental health problems and disorders. Figure 11–1 summarizes the relationships between maternal stress and child outcomes.

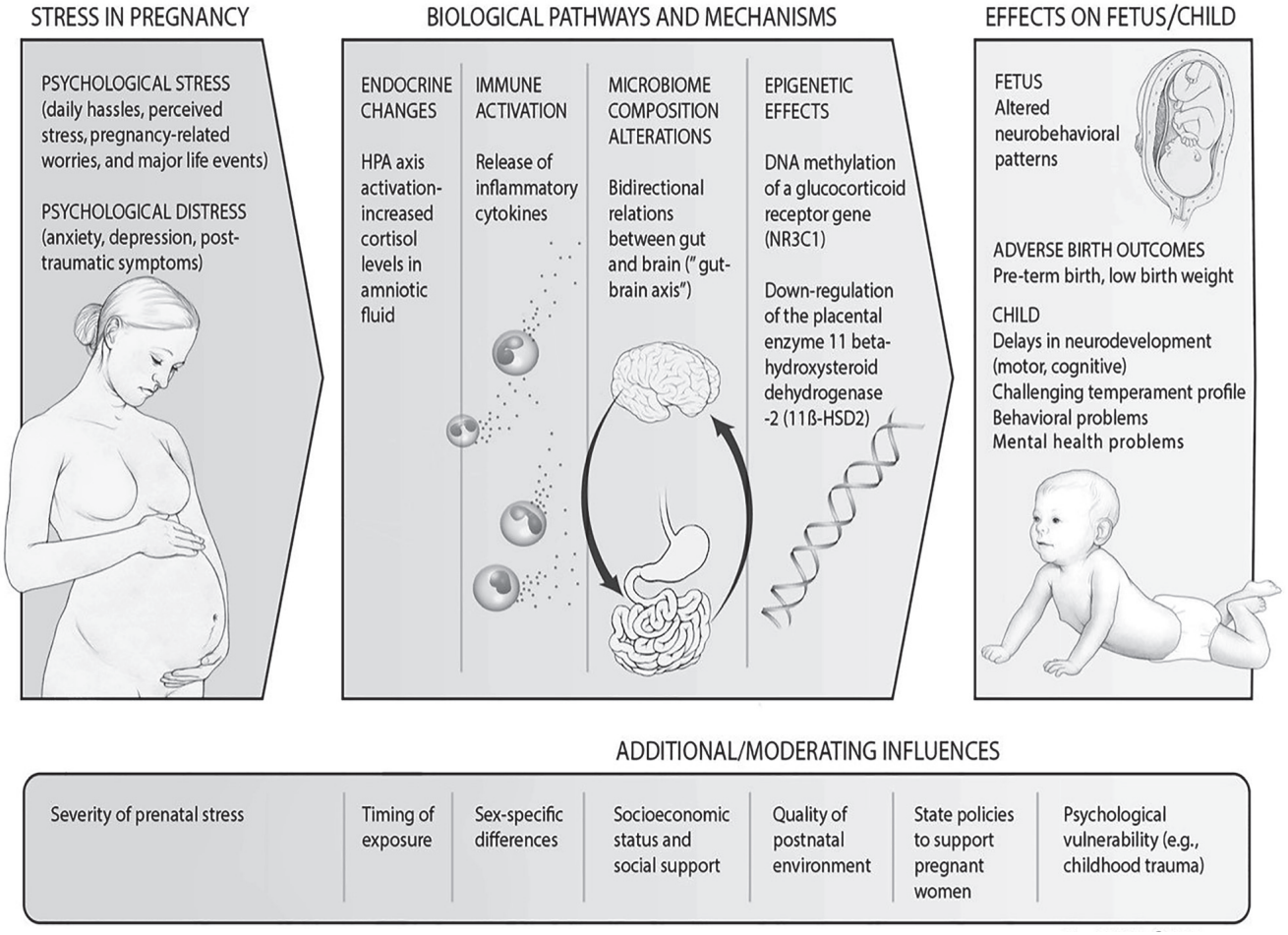

FIGURE 11–1. The effects of stress in pregnancy on child outcomes: biological mechanisms and moderating factors.
Source. Image by David Rini.

Types of Prenatal Stress and Distress

The term *prenatal stress* refers to a wide range of different types of stress that can occur during pregnancy. These include daily hassles, such as job strain; perceived stress, such as feeling overwhelmed or out of control; pregnancy-related anxieties, such as worrying about the baby's health or fear of giving birth; and major life events, such as the death of a loved one (Class et al. 2011) or natural and manmade disasters. *Prenatal distress*, on the other hand, includes a range of psychological symptoms and disorders, such as depression and anxiety, which can be either preexisting to the pregnancy or onset during pregnancy (Table 11–1). These stresses and distresses can occur in the form of a single event, a series of events, or on a daily chronic basis in women with or without definable psychiatric illnesses (Mulder et al. 2002). Although we can make distinctions among different types of prenatal stress and distress, it remains unclear whether these distinctions coincide with differential effects on fetal and child outcomes (Monk et al. 2018). Nevertheless, they provide meaningful insights for treatment, and potential differences in outcomes continue to be investigated.

Distinctions among different types of prenatal stress and distress can be made based on prevalence, because their estimated prevalence varies depending on the type of stress or distress being considered (Monk et al. 2019b; Van den Bergh et al. 2017; Ward et al. 2017). During pregnancy, 8%–12% of women are estimated to meet diagnostic criteria for major depressive disorder (Melville et al. 2010), a rate that doubles in low-income and socioeconomically disadvantaged samples (Fisher et al. 2012). Similarly, 13% of pregnant women are estimated to meet criteria for an anxiety disorder (Vesga-López et al. 2008). These estimates increase when symptoms are self-reported. For instance, Loomans et al. (2013) found that 30% of women self-report high levels of concurrent depression and state anxiety during pregnancy. Loomans et al. (2013) additionally found that up to 52% of pregnant women experience daily stress, such as job strain, during pregnancy and 9% experience pregnancy-related anxiety, although neither of these identified groups report high levels of depression or state anxiety. Depression and anxiety are the most common mental health disorders during pregnancy, and other common nonpsychotic disorders include PTSD and personality disorders, with estimated prevalence rates of 6%–8% and 6%, respectively (Howard et al. 2014).

Although distinct, the different types of stress and distress are often correlated. For example, depression and anxiety are often comorbid during the prenatal period, and women who are depressed during pregnancy are more likely to meet criteria for an anxiety disorder than those who are not (Dindo et al. 2017). Additionally, women who have experienced a trauma prior to being pregnant are nearly five times more likely to be depressed in pregnancy than women without a trauma history (Seng et al. 2010). Even trauma that occurs as far back as childhood is associated with increased symptoms of both depression and anxiety during pregnancy (Letourneau et al. 2019). Comorbid prenatal stresses can thus be considered not only in terms of additive but also interactive effects, whereby one type of preexisting stress can enhance the likelihood of risk for another type of stress. The proper identification of different prenatal stresses and their comorbidities has the potential to lead toward more precise treatment, as opposed to treatment that fails to recognize comorbidities and thus alleviates distress only partially (Dindo et al. 2017).

TABLE 11–1. Types of prenatal stress and distress and their estimated prevalence

Prenatal stress (estimated prevalence)	Prenatal distress (estimated prevalence)
Stressful life events (63%)	Prenatal anxiety (13%)
Daily hassles (52%)	Prenatal depression (8%–12%)
Pregnancy-related anxieties (9%)	PTSD (6%–8%)
Perceived stress (8%–11%)	Personality disorders (6%)
Severe life events (1%)	

Fetal and Child Outcomes

Prenatal Stress and Fetal Neurobehavior

Research focusing on the effects of prenatal stress on fetal neurobehavior most frequently examines two indicators of fetal response to stress: motor activity and heart rate/heart rate variability (HRV) or reactivity. In general, studies investigate either the effects of maternal chronic stress (sometimes depression or anxiety) or the effects of stress that was induced experimentally.

Maternal chronic stress in pregnancy has been linked to a higher fetal activity and heart rate. For example, DiPietro et al. (2002) found that the fetuses of stressed mothers were more active across gestation compared with those whose mothers showed more positive emotionality. In line with this finding, Dieter et al. (2001) reported increased fetal activity in depressed mothers. In another study, DiPietro et al. (2010) observed no association between maternal trait anxiety and fetal motor activity or heart rate, but they did find a link between higher maternal pregnancy-specific stress and marginally higher motor activity, increased coupling of fetal motor activity and heart rate, and higher fetal HRV. Higher HRV is typically considered a mark of better emotion regulation (Sloan et al. 2017) and may be regarded as an index of more advanced CNS maturation. A recent study (Walsh et al. 2019) reported lower coupling of fetal motor activity and heart rate in physically stressed pregnant women (i.e., women with physical indicators of stress, such as higher average blood pressure), but not in those with psychological stress. However, Monk et al. (2016) found an indirect effect of high perceived stress in pregnancy on lower fetal coupling through placental DNA methylation.

Because the literature on fetal responses to maternal stress is variable, researchers have focused on the effects of experimentally induced stress to measure these effects more directly. Using the Stroop color-word task in a series of studies, Monk et al. (2000, 2003, 2004, 2011) found significant increases in fetal heart rate in response to the stressor in a group of mothers with psychological vulnerability (anxiety and depression) but not in those without such vulnerability. DiPietro et al. (2003) reported no changes in fetal heart rate using the same method to induce mild stress in pregnant women, but their results were based on a general sample of mothers regardless of psychological vulnerability. Other studies employed direct stimulation of the fetus. For example, Makino et al. (2009) observed that fetuses showed a different heart rate pattern in response to vibroacoustic stimulation depending on maternal trait anxiety scores. Fetuses of mothers from a high trait anxiety scores group displayed a biphasic response

pattern characterized by acceleration followed by deceleration, whereas the response of fetuses from mothers with low trait anxiety scores consisted of a single long period of acceleration, one acceleration lasting >1 minute, or at least two accelerations lasting >15 seconds. Maternal psychological status thus seems to be of crucial importance, modulating fetal reactivity to stress possibly as a consequence of shaping fetal development over gestation. Moreover, different types of psychological vulnerability may elicit differential fetal response. Reissland et al. (2018) reported that anxiety was associated with an increased fetal response (eye-blink reactions), whereas depression was associated with a decreased fetal response to sound and light stimulation.

Taken together, maternal psychological status—chronic mood or distress—in pregnancy affects fetal neurobehavior and reactivity to stressful stimuli. Both chronic and acute stress elicit fetal response characterized mostly by higher intensity of motor activity and heart rate. Some authors suggest that this is not necessarily a developmental disadvantage; higher fetal motor activity has been linked with more optimal motor maturation and development (DiPietro et al. 2010). It is, however, too early to draw final conclusions in this regard because the results of previous studies are ambiguous—prenatal stress has also been associated with delayed fetal maturation (Sandman et al. 2012a).

Prenatal Stress and Birth Outcomes

According to the fetal programming hypothesis, the prenatal environment is of crucial importance to health throughout the lifespan (Barker 1995b). Originally, birth weight was considered a proxy for the quality of environment in utero (Barker 1990). Indeed, low birth weight and other unfavorable birth outcomes, such as preterm birth, have been linked with various prenatal factors, including maternal stress, as exemplified in several studies (Copper et al. 1996; Lima et al. 2018; Wadhwa et al. 1993).

However, the assertion that prenatal stress results in unfavorable birth outcomes is not without controversy. In his seminal work, Istvan (1986) suggested that although there is sound evidence of the negative effects of stress on birth outcomes in animal research, the results for humans remain inconsistent and unconvincing due to methodological study limitations. Those limitations include retrospective assessment of stress in pregnancy or failure to account for important confounders, such as biomedical factors that increase obstetrical risks (e.g., hypertension in pregnancy, preeclampsia). A later meta-analysis supported this line of reasoning by concluding that there is no evidence for the association between general or pregnancy-specific anxiety and detrimental birth outcomes and that the significant associations that have been found were primarily in studies with lower-quality methodology (Littleton et al. 2007). A meta-analysis conducted by the same research team several years later reported that the association between prenatal psychosocial stress and low birth weight was in fact significant but very small (Littleton et al. 2010). Finally, a meta-analysis that was limited to prospective studies published from 1970 to 2012 (Bussières et al. 2015) substantiated the association between prenatal stress and low birth weight and preterm birth, with findings specific to different types of stress: pregnancy-related anxiety and stress yielded a stronger association than general stress, life events, or natural disasters. Nevertheless, the results of the studies remain conflicting. For example, a recent study distinguishing different prenatal stress phenotypes (i.e., mental health or mood symptoms and physical indicators of stress) found that women showing physical but

not psychological indicators of stress had increased risk of preterm birth compared with the healthy group (Walsh et al. 2019).

Prenatal Stress and Child Neurodevelopment and Psychopathology

State Regulation, Stress Reactivity, and Temperament

Several studies have shown that infants of mothers who had depressive symptoms in pregnancy have poorer regulation of behavioral states, autonomic stability, and neurobehavioral maturity in the first days of the postpartum period (Figueiredo et al. 2017; Gerardin et al. 2011; Pacheco and Figueiredo 2012). The child's stress reactivity is another frequently studied outcome in the context of prenatal stress, exposure to which has been linked with altered child's hypothalamic-pituitary-adrenal (HPA) axis functioning. However, the direction of this effect is inconsistent and has been shown to vary depending on the type of stress, with different types eliciting blunted or increased HPA axis reactivity. For example, Romero-Gonzalez et al. (2018) found that maternal perceived stress in pregnancy predicted lower cortisol but that pregnancy-specific stress predicted higher cortisol in neonates. Measuring cortisol and cortisone in the first morning urine of 45-month-old children, Send et al. (2019) found a lower nocturnal rate of cortisol and cortisone in children who had been exposed to prenatal stress. In a similar study, children age 6 years had higher hair cortisone, but not cortisol, levels detected in association with prenatal stress (Molenaar et al. 2019). Cortisone is a metabolite of cortisol, with the enzyme 11β hydroxysteroid dehydrogenase type 2 (11β-HSD2) converting cortisol to cortisone in the peripheral tissues. Measuring cortisone in addition to cortisol may thus provide a more complete picture of the cumulative amount of active and inactive corticosteroids (Molenaar et al. 2019).

Prenatal stress has been linked with more difficult child temperament and negative emotionality, but this association appears to be modulated by child sex and by the type and timing of stress. For example, Simcock et al. (2017a) found that higher levels of objective hardship related to a flood disaster (Queensland Flood in 2011) during pregnancy were associated with more irritable temperament in boys but not in girls at age 6 months; moreover, the mothers with higher emotional response to the flood reported more active-reactive infants. Laplante et al. (2016), too, assessed the effects of disaster-related prenatal stress on infant temperament 6 months postpartum and observed poorer temperament in children exposed to higher maternal stress in utero.

Examining the differential effects of various types of prenatal stress on infant temperament at 3 months of age, Chong et al. (2016) demonstrated evidence for the effects of anxiety (both state and trait) on infants' negative emotionality and poor attention regulation but found no effects of prenatal depression. Similarly, Nolvi et al. (2016) attempted to disentangle the effects of prenatal depression, anxiety, and pregnancy-specific anxiety on infant emotional reactivity at 6 months postpartum and concluded that only pregnancy-specific anxiety predicted infant reactivity (more specifically, overall negative emotional reactivity and its aspects fearfulness and falling reactivity). In a study by Austin et al. (2005b), only trait anxiety—not depression or perceived stress in pregnancy—predicted "difficult" infant temperament.

Overall, it appears that maternal anxiety is a much stronger predictor of infants' traits associated with temperament than is maternal depression, although depressive

symptoms in pregnancy were found to be associated with higher activity/impulsivity and sleep problems in young children (Gerardin et al. 2011). Nevertheless, most studies on the effects of prenatal distress on child temperament used parent-report questionnaires, which makes it impossible to disentangle child behavior from maternal perceptions of it that may be biased by maternal psychological status. As for the timing of stress, Sandman et al. (2012a) observed the strongest association between stress and impaired emotion regulation in infants if the stress occurred early in gestation, but research to date is insufficient to draw final conclusions about the effects of timing of prenatal stress on child reactivity and regulation.

Motor Development

Studies about the effects of prenatal stress focus frequently on motor development in infancy because it is strongly predictive of later outcomes across different developmental domains. Substantial evidence shows that prenatal stress, such as depressive symptoms or stressful life events, predicts poorer motor skills and delayed motor development in young children (Cao et al. 2014; Gerardin et al. 2011; Lin et al. 2017; Moss et al. 2017) despite several positive or null findings. For example, Simcock et al. (2016) found better motor development outcomes in 2-month-old infants whose mothers were exposed to a flood during pregnancy, but this effect changed with increasing child age, such that prenatal exposure to a flood predicted delayed motor development in the children at 6 and 16 months of age. Sandman et al. (2012b) found positive effects of prenatal depressive symptoms on motor development in the first postpartum year, but only in infants whose mothers had experienced congruent levels of depressive symptoms in pregnancy and postpartum. This was true even for children of mothers with relatively high levels of pre- and postpartum depression. Nevertheless, Koutra et al. (2013) found no association between prenatal stress and motor development in young children.

The effect of prenatal stress on motor development appears to be stronger if the exposure occurs in late pregnancy (Cao et al. 2014; Grace et al. 2016; Moss et al. 2017; Simcock et al. 2016). Additionally, differential effects according to the type of stress have also been found. For example, Simcock et al. (2016) observed that delayed motor development was associated with exposure to a flood in utero but not with maternal traumatic stress symptoms related to the flood. In contrast, Moss et al. (2017) found a negative effect of disaster-related stress on motor development in 16-month-old children, but only for negative maternal appraisal of the overall flood consequences and not due to the flood exposure per se. Effects on motor development are documented beyond the period of early childhood. Grace et al. (2016), following children until adolescence, evidenced suboptimal neuromuscular development at ages 10, 14, and 17 years in children whose mothers experienced a higher number of stressful life events in late pregnancy. However, stressful events occurring earlier in pregnancy were not associated with child's later motor outcomes in this study.

Cognitive Development

Prenatal maternal stress is also associated with adverse outcomes in cognitive development domains, including word comprehension, nonverbal cognitive tasks (Henrichs et al. 2011), language development (King et al. 2012), problem solving (Simcock et al. 2017b), IQ, working memory (Evans et al. 2012), and performance in math tasks (Pearson et al. 2016). A meta-analysis by Tarabulsy et al. (2014) detected a significant

association, albeit with a small effect size, between prenatal stress and cognitive development, with a larger effect documented in studies assessing prenatal stress retrospectively. Moreover, they found that studies with objective indicators of prenatal stress (e.g., objective severity of a natural disaster or a number of stressful events) reported greater effect sizes as compared with those examining subjective indicators (e.g., perceived stress, pregnancy-related stress or anxiety). This conclusion is also supported by other research groups (Moss et al. 2017; Simcock et al. 2017b).

Differential effects were found for depressive symptoms, anxiety, and pregnancy-related anxiety. For example, Koutra et al. (2013) found detrimental effects of depressive symptoms, but not of anxiety, on child cognitive performance. Depression was associated with lower IQ score in children 8 years of age (Evans et al. 2012), whereas anxiety was associated with impaired working memory in children of the same age in another study (Pearson et al. 2016). Buss et al. (2011) observed that lower visuospatial working memory in children ages 6–9 years was related to pregnancy-related anxiety; neither state anxiety nor depression explained any additional variance.

The effects of prenatal stress on child cognition appear to be more severe for girls than for boys. Investigating the association between perceived stress during pregnancy and infant cognition at the age of 4.5 months, Merced-Nieves et al. (2020) observed that maternal stress is associated with delayed development of physical reasoning, but this effect was only true for girls and not for boys. Li et al. (2013) also observed sex-specific effects at 10 years of age in association with maternal life stress events (e.g., job loss, residential move) in pregnancy, finding that prenatal exposure to stress was associated with lower reading scores in girls but with higher reading and math scores in boys. Simcock et al. (2017b) reported that at high levels of maternal subjective flood-related stress in pregnancy, girls had lower scores on the problem-solving domain than boys at 6 months of age. In addition, Buss et al. (2011) found that pregnancy-specific anxiety was associated with lower inhibitory control in girls only at ages 6–9 years. However, King et al. (2012) found adverse effects of a natural disaster (Quebec Ice Storm of 1998) during pregnancy on boys but not girls in terms of their IQ scores at 11 years of age.

Similar to the motor development domain, the timing of the stress exposure may be decisive for the severity of outcomes in the cognitive domain. However, although late pregnancy has been found to be a critical period for motor development, the effects on cognitive performance appear to be stronger if stress occurs early in gestation (Sandman et al. 2012a). Moreover, the intensity of prenatal stress appears to alter cognitive outcomes. Laplante et al. (2008) found a curvilinear and not a linear relation between prenatal stress and cognitive and language abilities in preschoolers, indicating that high levels of prenatal stress are related to less optimal performance in children, whereas moderate levels of stress may enhance it.

Although evidence links prenatal stress with less optimal cognitive development, study results have been mixed, with some authors reporting no association (Karam et al. 2016) and others reporting positive effects (Li et al. 2013). Importantly, studies that accounted for maternal IQ observed that the significant association between prenatal stress and child cognitive outcomes does not persist after taking this additional factor into consideration (Van den Bergh et al. 2017). Thus, despite evidence for this association, further research is needed to draw firm conclusions. Table 11–2 summarizes the relationship between stress and several neurodevelopmental outcomes.

TABLE 11–2. Effects of prenatal stress on fetal and child behavior and neurodevelopment

Domain	Specific outcomes	Type of distress and timing
Fetal neurobehavior	↑ Motor activity	Chronic stress, depression
	↑ Heart rate reactivity	Experimentally induced stress in psychologically vulnerable women
	↑ Heart rate variability	Pregnancy-specific stress
	↑ ↓ Coupling of fetal motor activity and heart rate	Pregnancy-specific stress, perceived stress
Child temperament	↑ Negative emotionality	Maternal anxiety appears to have greater effect than depression
	↓ Emotion/attention regulation	No conclusive evidence regarding timing
	↑ Emotional reactivity	
	↑ Temperamental "difficulty"	
Child neurodevelopment	↓ Motor development	Exerts stronger effects if occurs in late pregnancy
		Findings about effects of different types are conflicting
	↓ Cognitive development	Objective indicators (e.g., objective severity of a natural disaster) have greater effect than subjective indicators
		Stronger effects if occurs in early pregnancy

Mental Health

Accumulating evidence shows an association between maternal distress in pregnancy and offspring mental health problems (Table 11–3), particularly internalizing (emotional) and externalizing (behavioral) symptoms (Cents et al. 2013; Hentges et al. 2019; Lahti et al. 2017; Leis et al. 2014; Loomans et al. 2011; O'Donnell et al. 2014; Pickles et al. 2017; Robinson et al. 2008, 2011; Tearne et al. 2015). Internalizing and externalizing behaviors have been found to be predicted by different types of stressful events, both those beyond mother's control (e.g., death of a relative) and those at least partly within her control (e.g., marital problems) (Robinson et al. 2011) and have been linked to prenatal depressive symptoms, anxiety (Cents et al. 2013; Lahti et al. 2017; Leis et al. 2014; Loomans et al. 2011; O'Donnell et al. 2014), and pregnancy-specific anxiety (Pickles et al. 2017).

There are, however, some discrepancies in the current research on the effects of maternal prenatal distress on externalizing and internalizing behaviors in offspring. For example, Korhonen et al. (2014) observed that prenatal depression was associated with externalizing but not internalizing problems in adolescents, whereas Betts et al. (2014) found the opposite. In addition, a study assessing the effects of natural disaster–related stress found that internalizing problems in young children were linked to maternal objective flood-related hardship (e.g., financial loss related to the disaster) rather than to stress experienced in response to the flood (McLean et al. 2019). How-

TABLE 11–3. Effects of prenatal stress on offspring mental health

Mental health domain	Types of maternal prenatal distress associated with offspring mental health outcomes
ADHD	Stressful life events; major life events (bereavement); anxiety
Anxiety	Perceived stress, depressive symptoms, anxiety, pregnancy-related anxiety, exposure to a natural disaster
Autism	Stressful life events; major life events (bereavement)
Borderline personality disorder	Anxiety, depression
Conduct disorder	Anxiety; stressful life events
Depressive symptoms	Perceived stress, stressful life events, depression, anxiety
Eating disorders	Exposure to a natural disaster
Internalizing and externalizing problems	Stressful events, depression, anxiety, pregnancy-specific anxiety, exposure to a natural disaster
Schizophrenia	Daily life stress, but results of studies are mixed

ever, in a similar study, maternal subjective distress in response to the storm exposure, rather than the exposure itself, predicted both internalizing and externalizing problems in children (King et al. 2012). Nevertheless, it can be difficult to distinguish prenatal from postnatal effects; Velders et al. (2011) found that parental postnatal psychological functioning, rather than prenatal depressive symptoms, was associated with child emotional and behavioral problems.

Interestingly, no differences in the effects of prenatal stress with respect to the time of exposure were observed in the study by Robinson et al. (2011); effects on child behavioral problems due to exposure to stressful life events in the first 18 weeks of pregnancy were similar to those of exposure at 34 weeks of gestation. Similarly, Lahti et al. (2017) found no effect of timing of maternal depression across pregnancy on child behavioral problems. However, they did find an effect of depression severity, whereby the most detrimental outcomes were detected in children whose mothers had shown clinically significant levels of depressive symptoms during pregnancy.

The effects of prenatal stress on emotional and behavioral problems may persist from infancy to adolescence and into adulthood. These childhood outcomes have been reported in children ages 3–5 years (Cents et al. 2013; King et al. 2012; Loomans et al. 2011; O'Donnell et al. 2014; Pickles et al. 2017), 6–9 years (King et al. 2012; O'Donnell et al. 2014), 10–11 years (King et al. 2012; Leis et al. 2014; O'Donnell et al. 2014), 12–13 years (O'Donnell et al. 2014), 14 years (Betts et al. 2014), 16 years (Korhonen et al. 2014), and 21 years (Betts et al. 2014).

Prenatal stress has also been linked with childhood anxiety. In one study, prenatal depression was associated with higher scores on a generalized anxiety scale in 1-year-old infants (Gerardin et al. 2011). Similar results were found in another study where maternal exposure to flood in pregnancy predicted anxiety in 4-year-old children; however, objective flood-related hardship, rather than subjective distress, predicted childhood anxiety (McLean et al. 2019). Evidence suggests that the effects of prenatal distress (e.g., perceived stress, depressive symptoms, anxiety, pregnancy-related anxiety) on anxiety symptoms in offspring may extend to preadolescence (Davis and Sandman 2012) and even into adulthood (Capron et al. 2015).

Children exposed to prenatal stress also appear to be at an increased risk for symptoms of depression, which were observed at different ages throughout childhood. For example, prenatal stress has been associated with depressive symptoms at 12 years of age (Davis et al. 2020), and stressful life events in early pregnancy have been linked with high levels of depressive symptoms in children 10–19 years of age (Kingsbury et al. 2016). Maternal prenatal anxiety and depression have been found to be associated with an increased risk of depression in the offspring up to 18 years of age (Capron et al. 2015; Pearson et al. 2013).

Evidence also suggests that prenatal stress might play a role in the development of autism (Class et al. 2014; Rijlaarsdam et al. 2017; Ronald et al. 2011), particularly in boys. For instance, Ronald et al. (2011) found that stressful events in pregnancy, such as divorce or a residential move, predicted autistic traits in boys but not girls at the age of 2 years. The timing of prenatal stress may modulate the effects on autism, as evidenced in one study that showed a higher risk of autism following maternal bereavement specifically in the third trimester of pregnancy (Class et al. 2014). Nevertheless, the association between prenatal stress and autism is ambiguously supported; for example, a study by Rai et al. (2012), based on data from two large population studies, found no link between major life events in pregnancy and autism.

Similarly, the risk for ADHD related to prenatal stress exposure has also been reported to be higher in males than in females (Li et al. 2010; Loomans et al. 2011). However, not all studies documenting the association between prenatal stress and ADHD have found sex-specific results (Class et al. 2014; Ronald et al. 2011). Additionally, Class et al. (2014) reported a greater risk for ADHD in children who were exposed to stress specifically in late pregnancy.

Prenatal distress has also been found to enhance the risk of conduct disorder (Glasheen et al. 2013; MacKinnon et al. 2018), an association that has also been shown to be particularly pronounced in boys (Glasheen et al. 2013). Other mental health outcomes linked with prenatal distress exposure include eating disorders (St-Hilaire et al. 2015), borderline personality disorder (Winsper et al. 2015), and psychosis (Fineberg et al. 2016). Moreover, the risk for schizophrenia related to prenatal stress exposure also appears to be higher in male offspring (Fineberg et al. 2016). Nevertheless, in a review of prenatal stress effects on a risk of schizophrenia (Lipner et al. 2019), the authors concluded that the results of studies are mixed and that the question of whether specific types of prenatal stress or timing of exposure have differential effects remains unresolved.

Biological Mechanisms

The DOHaD hypothesis contends that maternal stress in pregnancy can affect the developing fetus through stress-based alterations in maternal biology, with potentially long-lasting implications for the offspring's health. However, some doubts have been expressed regarding the causality of such associations. For example, women who experience stress during pregnancy are more likely to be living in poverty, which represents an environmental factor that is directly linked with child outcomes (Lefmann and Combs-Orme 2014). They might also smoke or drink alcohol more frequently and lack an appropriate diet and adequate physical activity (Goodwin et al. 2017; Hurley

et al. 2005; Schetter and Glynn 2011). Moreover, pregnant women who are stressed are more likely to also be stressed in the postpartum period (Field 2011; Lin et al. 2017), which might, in turn, lead to less favorable parenting practices (Huizink et al. 2017; Schechter et al. 2017) and difficulties in bonding (Figueiredo and Costa 2009). In fact, maternal stress in pregnancy is related to several factors that are linked with child outcomes; thus, the effects of stress are difficult to disentangle from those of other related factors. In addition, it is reasonable to expect that mothers who appraise their pregnancy period as being more stressful have specific genetic predispositions that may be passed onto their children.

It can thus be difficult to determine whether direct biological mechanisms connect maternal prenatal stress and child psychopathology in addition to indirect pathways, such as behavioral, and shared genetic factors (Glover 2019). Is it indeed biological fetal programming that mediates, at least partially, the association between prenatal stress and offspring psychopathology? Based on results from animal studies, this question can be answered affirmatively. Animal research provides strong evidence that offspring exposed prenatally to maternal stress are affected in several ways, including changes in HPA axis activity (Maccari et al. 1995), functional and structural alterations of the brain (Adrover et al. 2015; Charil et al. 2010; Coe et al. 2003), epigenetic changes (Jensen Peña et al. 2012; Weaver et al. 2004), and alterations in gut microbiota (Bailey et al. 2004), all of which also relate to variations in behavioral outcomes, such as increased fear behavior and distractibility or reduced sociability (Austin et al. 2005a).

Moreover, studies with human subjects have shown that stress experienced by mothers during pregnancy holds a stronger association with child outcomes than stress experienced by fathers during the same period, which implies that the effects of prenatal stress cannot be attributed solely to shared genes (Capron et al. 2015). Although the biological pathways suggested in animal research may also apply to humans, there are considerable differences between humans and animals on physiological and neuroendocrine levels (Glover et al. 2010). Overall, the mechanisms by which prenatal stress may affect human offspring are emerging, and research has explored several systems that could be involved.

One frequently studied domain is HPA axis functioning. The end product of the HPA axis—that is, the stress hormone cortisol—has been hypothesized as a leading agent in the association between prenatal stress exposure and child outcomes. It has been assumed that maternal stress results in increased cortisol levels that, in turn, lead to a higher fetal exposure to cortisol, affecting the development of the fetal and child nervous system (Davis et al. 2017; Graham et al. 2019). Indeed, higher cortisol levels in amniotic fluid have been found to predict lower scores in cognitive development in 17-month-old infants (Bergman et al. 2010). Higher maternal cortisol levels have also been associated with decrements in child cognitive performance at 7 years of age (LeWinn et al. 2009).

However, the results of the studies are conflicting, reporting both positive and negative effects of fetal exposure to higher cortisol levels. For instance, higher levels of maternal cortisol in late pregnancy have been shown to enhance fetal neurodevelopment (Glynn and Sandman 2012) and cognitive development in infancy and middle childhood (Davis and Sandman 2010; Davis et al. 2017). Making matters even more complex, maternal cortisol levels do not always correspond to maternal levels of perceived distress, which is especially true later in pregnancy, where there is often a weak or no association between perceived stress and cortisol levels (Davis et al. 2011; Voegtline et al. 2013; Werner et al. 2013).

Given the lack of association between maternal perceived stress and cortisol levels in late pregnancy, it is unlikely that the effects of maternal stress in pregnancy on child outcomes can be explained primarily by an increase in maternal cortisol levels. Therefore, other pathways have been investigated, including downregulation of the placental enzyme 11β-HSD2 (Bowers and Yehuda 2016; Monk et al. 2016; O'Donnell et al. 2012; Togher et al. 2017). 11β-HSD2 converts cortisol to an inactive form (i.e., cortisone), thus regulating the degree of maternal cortisol passing through the placenta to the fetal compartment. When this enzyme is downregulated, possibly through epigenetic changes on gene regulation (Seth et al. 2015), the fetus may become exposed to higher levels of cortisol without increases in maternal levels. Indeed, Glover et al. (2009) observed that the association between maternal and amniotic fluid cortisol varies based on maternal anxiety status, with a stronger association occurring among more anxious pregnant women. For all women, levels of 11β-HSD2 decrease during the third trimester to enable a higher proportion of maternal cortisol to circulate in the placenta, a process that is necessary for fetal lung maturation and preparation for birth; however, if maternal cortisol levels have been high for a longer period, the fetus becomes exposed to atypical cortisol levels, with a potential programming effect on its development and health (DeSocio 2018). Monk et al. (2016) observed the association between greater maternal stress and higher placental DNA methylation of *HSD11B2*, which, in turn, was linked with lower coupling of fetal movements and heart rate, an indicator of less mature CNS development.

Prenatal stress has been associated with other epigenetic changes. The most frequently studied epigenetic mechanism is DNA methylation, consisting of the addition of methyl groups to the promoter region of genes. Since the HPA axis is considered the main regulator of the stress response, research in this area has focused on the association between prenatal stress and methylation of a glucocorticoid receptor gene (*NR3C1*). Methylation of this gene prevents the expression of the glucocorticoid receptors in the hippocampus, resulting in suppression of negative feedback that turns down HPA axis activity when cortisol levels are too high for an extended period (DeSocio 2018). Variation in *NR3C1* regulation has been studied in the placenta as an indicator of variation in cortisol that may reach the fetus; it has also been studied in other samples thought to be representative of children's biology.

Conradt et al. (2013) reported that maternal depression was related to greater placental DNA methylation of *NR3C1*, which in turn predicted lower self-regulation and higher hypotonia and lethargy in infants. Also, maternal emotional distress during pregnancy was linked with methylation of *NR3C1* in cord blood (Harris and Seckl 2011; Hompes et al. 2013), and changes in *NR3C1* methylation have been associated with a higher risk of psychopathology (Dadds et al. 2015; Tyrka et al. 2016). Investigating the effects of intimate partner violence during pregnancy on *NR3C1* methylation, Radtke et al. (2011) found no effect on methylation in the mothers but did find an effect in their adolescent children. The link between maternal distress and offspring methylation of *NR3C1* is further supported by a meta-analytic study by Palma-Gudiel et al. (2015), which reported a significant correlation between stress in pregnancy and methylation levels at a CpG site located at the *NR3C1* promoter. Regulation of other genes also seems to be involved in the association between maternal prenatal distress and child behavior (Cao-Lei et al. 2017).

Maternal immune response might also be a pathway by which maternal prenatal stress exerts its effects on the fetus. Research has indicated that not only infection but

also maternal psychosocial stress elicits a release of the proinflammatory cytokines. More specifically, depressive symptoms in pregnant women have been found to be associated with higher levels of circulating proinflammatory cytokines interleukin (IL)-6 and IL-15, tumor necrosis factor (TNF)-α, and C-C motif chemokine 3 (CCL3) (Christian et al. 2009; Osborne et al. 2019). Another study reported higher levels of IL-1β and IL-6 in association with stress in pregnant women (Coussons-Read et al. 2007). Maternal infections during pregnancy have been linked with neuropsychiatric disease in offspring later in life (Brown 2011), yet the evidence for the mediating role of maternal cytokines is still emerging. Existing studies are mostly based on animal models, and those conducted in humans have shown no effect of most of the proinflammatory maternal cytokines on the offspring's psychopathology; positive associations have been found between specific maternal cytokines (e.g., TNF-α or IL-8) and neuropsychiatric disease in the offspring, but they have not always been successfully replicated in other studies (Rakers et al. 2017).

Nevertheless, recent research has suggested an association between maternal cytokines (IL-6) and infant brain changes and cognitive development. Spann et al. (2018) observed an association between maternal IL-6 levels in pregnancy and resting state functional connectivity in newborn brain and toddler cognitive outcomes, suggesting that maternal immune activation in pregnancy influences the human nervous system in both the short and long term (Spann et al. 2018). In addition, Graham et al. (2018) found that above-average concentrations of maternal proinflammatory cytokine IL-6 during pregnancy is associated with larger newborn right amygdala volume and stronger left amygdala connectivity in the newborn, which are in turn associated with lower impulse control at 2 years of age.

A promising area of research is the role of the microbiome in prenatal stress programming. Altered gut microbiota composition has been linked with metabolic and immune disorders and with brain development and behavior (O'Mahony et al. 2017). Recognizing this association has led to establishing the so-called gut-brain axis (Bercik et al. 2012). Communication between gut microbiota and the brain appears to be bidirectional, such that the brain exerts influence on gut microbiota, and the gut microbiota affects neurodevelopment (de Weerth 2017).

Distress and anxiety experienced in pregnancy have been associated with changes in the composition of the maternal intestinal and vaginal microbiome (Gur et al. 2017; Hechler et al. 2019; Jašarevic et al. 2015), suggesting that the microbiome might be a link between prenatal stress and neurodevelopment (Gur et al. 2015). Although offspring gut colonization has long been thought to commence during birth by passage through the birth canal and to develop with subsequent breastfeeding, the "sterility of the uterus" dogma has been challenged by several studies, indicating that offspring gut microbiome colonization may occur in utero. Nevertheless, studies are only beginning to investigate the intrauterine transmission of microbes from mother to fetus resulting in fetal colonization (Chong et al. 2018).

Additional/Moderating Influences

The inconsistency in research findings indicates that exploration of moderating factors that buffer or exacerbate the effects of prenatal stress on fetal and child outcomes

is paramount. As previously mentioned, the intensity of prenatal stress may modulate its effects on offspring, with some authors suggesting that moderate levels of stress might even be beneficial and others showing that the opposite is true for high levels of prenatal stress (DiPietro et al. 2006; Laplante et al. 2008). Nevertheless, researchers have indicated that these positive effects, such as advanced maturation and resilience to stress in later life, do not come without cost, because prenatal stress is associated with alterations in brain development (Van den Bergh et al. 2017). Moreover, it may be the case that the potential benefits of prenatal stress only manifest under specific circumstances, such as a supportive postnatal environment and high-quality parental care (Hartman et al. 2018).

Although the timing of prenatal stress may also play a role, to date research has not identified a particular period more vulnerable to stress. It is more likely that the effects of stress differ depending on the gestational period in which the exposure occurs, concurring with sensitive windows for the development of specific brain regions (Van den Bergh et al. 2017). For example, first- and second-trimester exposure has been associated with effects on cognitive development, and the first trimester of pregnancy has been linked with behavioral problems (Van den Bergh et al. 2017). Further research is needed to corroborate these initial findings about specific effects of stress at specific gestational ages.

The term *prenatal distress* covers various types of stress whose effects need to be disentangled despite their intercorrelation. For example, depression and anxiety are often comorbid, but they may have differential effects on the developing child. As indicated, several authors have reported that anxiety, not prenatal depression, is associated with temperamental features in infants (Austin et al. 2005b; Chong et al. 2016). Nolvi et al. (2016) identified only pregnancy-related anxiety (and not general anxiety or depression) as being related to infant temperament. On the other hand, suboptimal cognitive functioning has been associated with prenatal depression but not anxiety (Koutra et al. 2013). Research has also shown the differences between the effects of natural disasters (i.e., objective hardship due to exposure to the event) and their subjective appraisal, demonstrating that their effects often diverge and that they may exert differential effects for specific child outcomes. For example, McLean et al. (2019) observed that internalizing problems were associated with objective disaster-related hardship, whereas Moss et al. (2017) found that only maternal subjective distress, and not objective hardship related to the flood, was directly associated with delays in child motor development.

Moreover, sex-specific differences in the effects of prenatal stress imply that child sex may modify prenatal programming. In their review, Sutherland and Brunwasser (2018) reported that sex-dependent results were found primarily in studies evaluating the impact of prenatal stress on nervous system development and temperament. Girls were found to be at a higher risk of elevated negative emotionality and reactivity, anxiety, and internalizing symptoms and displayed delayed motor and cognitive development more frequently if exposed to stress in utero. Boys, on the other hand, showed reduced reactivity and emotionality and had a higher risk of externalizing problems and schizophrenia.

These findings can be interpreted within an evolutionary framework. Male fetuses are more vulnerable to stress in terms of viability, which manifests in a diminished secondary sex ratio (males to females born) in the context of prenatal stress (Walsh et al. 2019). Although it threatens viability in males (where the fittest are more likely to sur-

vive), prenatal stress leads to a higher vulnerability in later development in females, who are disposed to develop strategies for surviving in an adverse prenatal environment but pay the price of being more susceptible to delayed neurodevelopment, increased reactivity, and mood-related problems (Sandman et al. 2013). In fact, higher reactivity and greater vigilance in a stressful environment could have been an evolutionary advantage for females, who looked after the children, whereas males may have benefited more from lower stress reactivity so as to better explore the environment and face potential dangers (Glover and Hill 2012). Thus, both males and females are likely affected by prenatal stress, but the consequences and developmental domains concerned appear to differ (Van den Bergh et al. 2017). It is of note that sex-specific differences in the effects of prenatal stress may contribute to the well-known sex differences in psychopathology, particularly an increased risk for internalizing problems in females (Hicks et al. 2019).

Family socioeconomic status is another factor to consider as a moderator of the effects of prenatal stress on child outcomes. As indicated, positive effects of moderate levels of stress are found in higher-income populations, where families have more economic, social, and cultural resources that are expected to buffer the potential detrimental effects of stress (DiPietro 2012; Laplante et al. 2008). Given the adverse effects of low socioeconomic status on child development (Bradley and Corwyn 2002), we can expect that the positive effects of moderate doses of stress do not apply to disadvantaged populations, who are also more prone to experience extreme stress. For example, Robinson et al. (2016) reported that women from ethnic minority groups are more likely to experience depression and anxiety during pregnancy than are women who identify themselves as white.

The effects of prenatal stress may also be modulated by state policies to support women during pregnancy. Comparing the levels of depression and anxiety symptoms in pregnant women in the United States and the Netherlands, Gartstein et al. (2020) found higher levels of depression and anxiety in the U.S. population. The authors hypothesized that different workplace and health care policies (e.g., access to health care and paid maternity leave) in those countries may have contributed to different levels of stress in pregnancy. Thus, the strength of the effects of prenatal stress might be modulated not only by the difference between low- and high-income countries but also by disparities in the support provided to pregnant women and new mothers in Western cultures that are economically similar.

Currently, research has indicated that maternal stress in pregnancy is associated with a prior maternal history of childhood trauma (e.g., abuse, neglect) and may thus function as a pathway underlying the intergenerational transmission of maternal trauma to offspring. Maternal childhood trauma has been found to be associated with several adverse outcomes in the offspring, including altered autonomic nervous system regulation (Gustafsson et al. 2017), altered brain structure (Moog et al. 2018), and behavioral problems (Plant et al. 2017). There is evidence that women with a trauma history are more likely to experience distress in pregnancy, especially symptoms of depression or anxiety (Ghosn et al. 2019; Plant et al. 2017). Interestingly, Plant et al. (2013) found that maternal childhood maltreatment and prenatal depression combined (but neither separately) predicted a higher risk of adolescent antisocial behavior in the offspring. Moreover, women with childhood trauma show raised placental cortisol-releasing hormone (Moog et al. 2016) and elevated levels of the proinflammatory

cytokine TNF-α in pregnancy (Blackmore et al. 2011), which may suggest that intergenerational transmission of trauma involves placental-fetal stress physiology and immune system activation.

Social support is another factor to be considered in the context of prenatal stress, but it is seldom measured. A positive effect of partner support in pregnancy on maternal emotional well-being and infant temperament was reported by Stapleton et al. (2012). Zhu et al. (2015) observed an interaction between prenatal stressful life events and social support in an analysis stratified by child sex, such that boys whose mothers experienced severe stressful events accompanied by lower social support were at a higher risk of developing ADHD symptoms. Walsh et al. (2019) reported that controlling for social support largely mitigated the effects of prenatal stress on birth outcomes.

Women who experience prenatal stress are more likely to experience stress in the postnatal period as well (Field 2011; Lin et al. 2017). To avoid confounding by postnatal stress, most recent studies focusing on the effects of prenatal stress have controlled carefully for this variable. Postnatal stress may nevertheless moderate the association between prenatal stress and child neurodevelopmental outcomes. As previously described, there are conflicting findings regarding the nature of such moderation: on the one hand, postnatal stress has been found to exacerbate detrimental effects of prenatal stress (Hartman et al. 2020); on the other hand, some authors have observed more optimal outcomes for children whose mothers experienced congruent levels of both pre- and postpartum stress, regardless of its intensity, suggesting that postnatal stress may actually result in favorable outcomes if combined with comparable levels of prenatal stress (Sandman et al. 2012b).

Screening, Treatment, and Prevention

There are bidirectional psychological and biological influences between the mother and her fetus or child, which underscores the need for a dyadic approach to treatment that takes into consideration both the mother's and the child's well-being (Monk et al. 2019a). For example, in addition to the woman's own experience of distress during pregnancy, that distress can lead to adverse fetal and child neurobehavioral outcomes, which can also in turn produce increased distress for the mother in a dyadic back-and-forth relationship between mother and child. Although the precise mechanisms of transmission from mother to child (i.e., the mechanisms by which maternal prenatal distress can transcend to the fetus) are not yet fully understood, a complete understanding of these pathways is not necessary to provide treatment, especially when considering how distress or symptoms of depression and anxiety are modifiable with access to adequate health services (Monk et al. 2018).

When maternal distress during pregnancy goes unidentified by health care professionals, most women will not seek treatment for themselves (MacLennan et al. 1996). To ensure that distressed pregnant women do receive treatment, the first step is to perform routine screening for prenatal mental health issues as recommended by leading professional and government organizations. As of 2015, the American College of Obstetricians and Gynecologists (ACOG) issued a formal recommendation that all obstetrical care providers screen women for depression and anxiety at least once during pregnancy, in addition to screening in the postpartum period (American College of Ob-

stetricians and Gynecologists 2018). The U.S. Preventive Services Task Force (USPSTF) also recommends screening for maternal depression during and after pregnancy (Siu et al. 2016). These recommendations by ACOG and USPSTF are supported by conclusions in a systematic review that demonstrated that screening for depression during both pregnancy and postpartum can lead to 1) reduced prevalence of depression, and 2) increased remission (O'Connor et al. 2016). (For specific recommendations on screening and measures to use, please consult Chapter 13, "Depressive Disorders," Chapter 19, "Anxiety Disorders and Insomnia in the Perinatal Period," and chapters on individual disorders.)

However, in addition to screening for prenatal depression and anxiety, screening for adverse childhood experiences may also be warranted, given that women who have a history of early life trauma are more likely to experience depression and anxiety during pregnancy (Letourneau et al. 2019). The standard measure of assessing a history of trauma is the Adverse Childhood Experiences questionnaire (Felitti et al. 1998), a 10-item self-report scale that has been validated in both research and clinical settings (Glowa et al. 2016) and is suitable for use during pregnancy (Monk et al. 2018). Given that obstetrical care providers and other women's health providers play a key role in the evaluation and management of women who survive sexual assault, ACOG recommends routine screening for a history of sexual assault, including screening during pregnancy (American College of Obstetricians and Gynecologists 2019).

Interventions that focus on treating prenatal distress can improve women's experience during pregnancy and prevent postpartum depression (Monk et al. 2018). Full recommendations for treatment modalities are given in the chapters on anxiety (Chapter 19) and depression (Chapter 13) and include specific psychotherapies (e.g., rational-emotive behavior therapy; Anton and David 2015) and mindfulness-based cognitive therapy adapted for women with perinatal depression (Dimidjian et al. 2015), as well as pharmacotherapy where indicated. In addition, interventions aimed at reducing distress among women who may not be identified as having clinically significant illness can be helpful. Practical Resources for Effective Postpartum Parenting, a dyadic treatment that begins in pregnancy and is designed to teach women about infant cues and sleep patterns, has been associated with reduced symptoms of maternal depression and anxiety and with less infant fussiness and crying behavior at 6 weeks postpartum (Werner et al. 2016).

When prevention is focused on improving mood during pregnancy, this offers an opportunity to foster more positive representations of the child in utero. These approaches, in turn, can carry over into the quality of the mother–child attachment and promote the healthy development of the child (Glover and Capron 2017). Screening, prevention, and treatment of maternal pre- and postnatal stress are intended to improve the mental health and well-being of both the mother and her child, and evidence supports the positive effects they bring to both.

Special Considerations

Regardless of whether one engages in research or clinical practice, there are considerations to be made when working with women who are experiencing distress during pregnancy. When designing a study, interpreting results, or considering potential clin-

ical applications, confounding factors must be taken into account both in the pre- and postnatal environment. For example, a common factor to consider when investigating the influence of maternal prenatal mood on child outcomes is maternal *postnatal* mood. Other examples, among many possible confounds or factors, include maternal social support, socioeconomic status, maternal age, child sex, child gestational age at birth and birth weight, birth complications, maternal history of trauma, race, ethnicity, and cultural background.

The generalizability of findings should also be considered, especially given the lack of diversity in trial samples, which do not match the U.S. population. For example, Latinx and Black Americans represent nearly one-third of the U.S. population, yet comprise only 6% of participants in federally funded clinical trials (Coakley et al. 2012). Lack of diversity in research is both an ethical and a scientific problem because race and ethnicity can lead to increased risk for disease and decreased likelihood of responding to treatment (Monk et al. 2019a). In prenatal stress research, the communities and minority groups who are underrepresented are often those at greater risk of prenatal stress. Thus, greater diversity in sampling is needed to better reflect the reality of women who are disproportionately exposed to adversity throughout pregnancy and the postpartum period.

A final and fundamental consideration in research and clinical practice that supports women with prenatal stress is how to not blame the mother. Researchers and clinicians who work with women during pregnancy can engage in thoughtful, deliberate, and dynamic practices such that women and mothers are not blamed for ways in which their fetus or child's development can be affected. Research and clinical practice in this domain have the purpose of supporting women's health and experience during pregnancy, as well as supporting the health of their fetuses and children. Pressure can be relieved by reinforcing how prenatal stress is only one of a multitude of factors that can influence fetal and child development and by emphasizing that support is being provided for both the mother and the child's health and well-being, as individuals and as a dyad.

Conclusion

Several decades ago, David Barker formulated his hypothesis that adult disease might be programmed in utero. This hypothesis was extended from physical to mental health outcomes, including the hypothesis that environmental factors occurring early in life—including maternal stress—can alter neurodevelopment and increase risk of later psychiatric disorder. Evidence has been provided to support the association between prenatal stress and child developmental outcomes, including psychopathology, yet further identification of mechanisms and the role of moderating factors remain to be discovered. Although clinical, translational, and basic researchers continue to make new discoveries in DOHaD research as it relates to maternal stress and child outcomes, clinicians can rely on evidenced-based interventions to provide women and their future children with support.

Key Points

- Prenatal (di)stress includes daily hassles, perceived stress, and major life events and a range of mental health problems, such as depression and anxiety.
- Prenatal (di)stress is associated with adverse neurobehavioral outcomes throughout fetal, infant, and child development.
- Traumatic events prior to pregnancy can influence prenatal (di)stress.
- The influence of prenatal (dis)tress can be moderated by factors such as socioeconomic status and social support.
- Evidence-based screening tools are available to identify prenatal (di)stress.
- Evidence-based interventions are available for the treatment of prenatal depression and other mood disturbances.
- Careful considerations must be made to avoid blaming mothers and women for the influence of prenatal (di)stress on child outcomes.

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