Chapter 3
Maternal Influences on the Developing Fetus

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“For behold, the moment that the sound of thy greeting came to my ears, the babe in my womb leapt for joy.” Luke 1:44

Observations of a link between pregnant woman and fetus, and speculation on its nature abound throughout history, literature, and across cultures. Despite the ubiquity of the phenomenon, relatively little is known about the manner in which the development of the fetus is influenced by the maternal psychological context. Scientific inquiry into the nature of this relationship has been historically hampered not by lack of interest, but by lack of access to the fetus. Although this changed considerably in the 1980s with the development of real time obstetric ultrasound, the prenatal period is the only time in development when interaction between mother and offspring cannot be directly observed and evaluated.

As discussed earlier in this volume, the scientific focus of fetal neurobehavioral assessment has been typically directed at the fetus, and not at the maternal–fetal pair. However, as early as the 1930s, the Fels Longitudinal Study included the first systematic scientific inquiry into factors that influence neurobehavioral functioning of the human fetus. Potential fetal influences considered included exposures such as cigarette smoking and nutritional factors as well as maternal psychological factors of emotionality and stress [1, 2]. Although the methods of access to the fetus and measurement of fetal heart rate and motor behavior were quite rudimentary, many of the questions posed then remain now as active areas of research. The preliminary findings from this project could have served to provide a broad substrate for a new field of scientific study. However, research into whether and how
normal variation in maternal psychological state may influence the fetus was not intensively pursued in depth until much later in the century when, presumably, ultrasound technology facilitated access to the fetus and scientific inquiry.

Since the early 1990s, the Johns Hopkins Fetal Neurodevelopment Project has been collecting information focused on documenting normal human development and the factors that affect it. Our initial focus was on assessment of the developing fetus, much in the same way one would approach infant assessment. However, a number of anecdotal observations during the course of early data collection, as well as descriptions of maternal–fetal interactions by participants, changed this. These included evident accelerations of the audible signal generated by the fetal heart rate monitor when pregnant women related distressing stories and numerous anecdotes by participants to the effect of “I know that when I do ‘X,’ the fetus will do ‘Y.’” As a result, we reoriented our focus away from the fetus alone to the maternal–fetal dyad. Because there are no direct neural or circulatory connections between the pregnant woman and fetus, any fetal response to maternal psychological state or other experience that does not impinge mechanically on the uterine environment (e.g., maternal change in posture) requires signal transduction. As a result, a data collection system was developed to collect maternal psychophysiological data simultaneously with fetal neurobehavioral data. Maternal data collection includes heart period, a measure derived from a three-lead electrocardiogram, and respiration; in combination these provide a measure of respiratory sinus arrhythmia, which is an indicator of parasympathetic tone [3]. In addition, electrodermal activity, which reflects changes in conductivity of the skin, is measured by two electrodes applied to the fingertips. Skin conductance is mediated by the eccrine glands, which are singularly innervated by the sympathetic branch of the autonomic nervous system [4]. Fetal neurobehavioral data are collected using an actocardiograph, a fetal monitor that uses Doppler technology to detect fetal heart rate and motor activity. Maternal and fetal data are simultaneously digitized at 1,000 Hz, using streaming software on a PC-based system that permits analysis of each in relation to one another and to experimental manipulations. The routine monitoring period is 50 min in length. A schematic of this system is presented in Fig. 3.1. This chapter will review the information collected to date by the Johns Hopkins Fetal Neurobehavioral Development project that links the functioning of the maternal–fetal pair and, when possible, embeds it within the context of other current research findings.

Contemporaneous Associations Between Maternal Psychological Functioning and Fetal Neurobehavior

There has been significant interest in the role of maternal stress experienced during pregnancy in relation to outcomes ranging from preterm birth [5] to child development [6]. Although this subject will be returned to later in this chapter, the existing literature in this area stimulated our interest in documenting the potential effects of maternal stress in situ in an effort to understand potential mechanisms. The rationale
for doing so was that if there are persistent perinatal or postnatal developmental effects of maternal prenatal psychological functioning, there should be evidence for alterations to fetal development while the mediating biological influence was active. In a longitudinal study conducted at 24, 30, and 36 weeks of gestation, fetuses of women \( n = 52 \) who appraised their lives as more stressful and reported more frequent stresses or “hassles” that were specific to pregnancy were more motorically active [7]. However, fetal motor activity was also elevated in women who regarded themselves as more affectively intense and expressed greater negative vs. positive emotional valence toward pregnancy. These findings support another report of increased fetal motor activity in more anxious women [8]. More recently, the link between increased levels of pregnancy-specific stress and higher fetal motor activity was also detected from 24 to 38 weeks of gestation on a larger sample \( n = 112 \) [9], and in this case, variability in fetal heart rate was also higher. Although the tendency might be to conclude that the increased activity associated with greater maternal stress is an ominous outcome, higher levels of fetal motor activity were significantly predictive of more optimal motor and reflex maturation in the first few weeks of life [9]. This is consistent with the results generated by the Fels Study, which noted that greater fetal motor activity was predictive of advanced motor development at 6 months of age [10].

These and other findings described later in this chapter highlight the importance of measuring aspects of the maternal psychological experience that are most relevant to study participants. We have found that what women are most emotionally invested in during pregnancy, from both a positive and negative standpoint, is pregnancy. As unremarkable as this observation might seem on its surface, failure to measure pregnancy-related psychological factors will result in under-ascertainment of the maternal psychological milieu. As a result, we developed long and brief versions of
a Pregnancy Experience Scale, which measures pregnancy-specific uplifts and hassles [11, 12]. Scoring focuses on the frequency and intensity of pregnancy-specific experiences that are perceived to be hassles and/or uplifts, as well as a composite of the degree of hassles relative to uplifts to ascertain the emotional connection to pregnancy. Other research teams have also employed measures of pregnancy-specific stress or anxiety [13, 14]. Within our own and others’ research, it is not uncommon for significant results to be detected only for the pregnancy-specific measures.

Regardless of the instruments used, studies that rely on paper and pencil assessments of maternal psychological states or traits are limited in their ability to infer causality between the maternal psychological experience during pregnancy and fetal neurobehavior for a number of reasons. Correlations among measures of stress, depressive symptoms, and anxiety during pregnancy are high and remain relatively stable from pregnancy through 2 years postpartum [15], suggesting that commonly used psychological scales that purport to measure “stress” actually contain broader elements linked to other psychological attributes, including temperamental traits. These characteristics are known to affect maternal caregiving behavior in the postnatal period. Thus, postnatal measurement and control for these attributes is necessary to separate prenatal from postnatal influences on child outcomes.

The range of maternal psychological measures that are associated with fetal neurobehavior, and their persistence over time once pregnancy is over, raise the possibility that measurement of “prenatal stress” is neither specific to pregnancy nor specific to stress. Thus, in the studies described earlier, there is the possibility that both fetal motor activity and maternal psychological attributes reflect a shared genetic contribution without a causal relation. A recent investigation of the influence of a prenatal factor (i.e., maternal cigarette smoking) on child outcomes (i.e., child antisocial behavior) illustrates this issue. Comparisons between offspring conceived with in vitro fertilization using embryos from the mother and those conceived with donor embryos revealed associations between prenatal smoking and child behaviors only in the former [16]. This suggests that when child behavioral outcomes are linked to maternal smoking, it is less a result of biological effects of exposure to smoking on the developing fetus, and more, or perhaps only, a reflection of shared inheritance with characteristics of women who choose to smoke during pregnancy. It is not unlikely that a similar case could be made for findings linking prenatal maternal affect or stress to postnatal child behavior. Finally, the putative mechanism inferred in studies of stress and pregnancy, activation of the hypothalamic–pituitary–adrenal (HPA) axis, is of questionable validity since psychological assessments provided by nonclinical samples of women are largely unrelated to levels of HPA by-products, including cortisol [13, 14, 17, 18].

Fetal Response to Experimental Manipulation of Maternal State

A more effective, but methodologically challenging, way to evaluate whether the maternal psychological state affects the developing fetus is to manipulate maternal state and observe whether there is a fetal response. This approach provides both a
temporal link between the dependent and independent measures and greater potential for revealing mechanisms. In the 1960s, investigators tried a variety of manipulations designed to alarm pregnant women and typically observed fetal tachycardia as a response [19]. We relied on a less threatening procedure, the Stroop Color–Word test, which is a challenging cognitive–perceptual task. Others have also employed this task in studies designed to evaluate fetal responsiveness to induced maternal stress [20, 21]. As expected, the procedure generated a clear physiological response in our sample of pregnant participants ($n = 137$). Fetuses responded to the manipulation, which lasted for about 4 min, with increased variability in heart rate and suppression of motor activity [22]. Once the manipulation was over, these values reverted to baseline levels, although male fetuses showed greater rebound in motor activity. There was moderate stability over time in the degree of both the maternal physiological response and the degree of fetal reactivity, suggesting that individual mothers and fetuses have their own characteristic response patterns.

The second manipulation used that was designed to activate maternal arousal was a labor and delivery documentary shown at 32 weeks of gestation to women who also participated in the Stroop study. The stimulus film included women relating their birth experiences interspersed with labor and delivery scenes. Again, maternal physiological data confirmed the effectiveness of the manipulation and again, fetuses responded with decreased motor activity, but in contrast to the Stroop intervention, decreased heart rate variability [23]. However, examination of the fetal response to a specific component of the documentary – the first graphic birth scene – revealed a somewhat different pattern of responsiveness. Fetuses of women who had not given birth before showed a transient increase in motor activity during this scene. This suggests that maternal influences on fetal neurobehavior may have biphasic elements and generate both acute (i.e., rapid and transitory) and more tonic (i.e., persistent and incremental) effects. This could also serve to reconcile the observation of higher levels of fetal motor activity linked to psychological attributes as described in the previous section with those reported here.

Our third manipulation was a relaxation procedure designed to examine how the fetal response to maternal arousal reduction may differ from arousal induction as effected through the Stroop task and labor and delivery film. A guided-imagery audiotape was used to induce an 18-min period of relaxation in pregnant women ($n = 100$) at 32 weeks of gestation. The manipulation generated the expected reduction in maternal psychological and physiological tension based on self-report measures of relaxation and physiological measurement of maternal respiration, heart rate, and skin conductance. The fetal response included decreased heart rate and increased heart rate variability but attributing these to the relaxation procedure itself could not be distinguished from simple maternal rest. However, there was a clear suppression in fetal motor activity during the manipulation, which recovered after the relaxation protocol concluded [24].

Although these studies have successfully demonstrated that the fetus responds to induced changes in maternal psychological state, they have been relatively unsuccessful in determining how this happens. In each study, change scores were
computed for maternal physiological and fetal neurobehavioral responses from baseline to the manipulation (i.e., reactivity), and from the manipulation to the postmanipulation periods (i.e., recovery). However, significant associations between the degree of maternal and fetal responsiveness were not detected in all cases, and when they were detected, the magnitude of the association was typically modest, a phenomenon reported elsewhere [21]. In general, associations between maternal heart rate and fetal measures are weakest; those with maternal skin conductance somewhat stronger. However, the intrauterine environment is affected by more than the predominantly autonomic indicators measured by our data collection system. Concurrent maternal salivary cortisol and umbilical blood flow data collected in the relaxation study provided an opportunity to examine the potential role of HPA activation and oxygen transfer in understanding the observed fetal response in that protocol. However, detected associations were also few and modest. A decline in maternal salivary cortisol was significantly associated with the decline in fetal movement observed from baseline to the relaxation period, and the increase in fetal heart rate variability was associated with the degree of decline in umbilical artery resistance [24]. However, the degree of shared variance accounted for by these associations was 9% or less. Thus, understanding of the manner in which maternal experiences are transduced to the fetus remains incomplete.

If the relaxation manipulation had been implemented prior to the two stressful procedures, it would have been tempting to speculate that the fetus “relaxed” when the mother relaxed. Rather, because motor activity suppression is the same pattern of fetal response noted to other maternal manipulations, we offer another possibility: that the observed fetal responses in all of the studies were elicited by fetal alerting to sensory-based alterations in the intrauterine milieu. Fetal heart rate responses have been observed within seconds of maternal manipulations that impinge on the intrauterine environment, including maternal postural changes [25] and auditory stimuli [26]. A similarly rapid onset of a fetal response to induced maternal psychological stress, including increased fetal heart rate variability, has been reported in nonhuman primates [27].

Studies based on recordings conducted from within an intact uterus in animal preparations have found that the uterus is a fairly noisy place, with prominent maternal vasculature, digestive, and vocal sounds [28]. We suggest that sudden accelerations or decelerations in maternal heart rate and accompanying blood pressure and gastric motility changes that are elicited by variation in maternal psychological state provide the fetus with a changing uterine sensory environment. This may induce a fetal orienting response, consistent with the observation of suppressed cardiac variability and motor activity observed in the results reviewed here. Thus, women who have temperamentally more intense and volatile affect may present a different level of daily stimulation to fetuses throughout pregnancy than those who are more even-tempered. The results showing greater activity levels in fetuses of more affectively intense women that appraise their lives as stressful may indicate a biphasic or rebound effect of such lability on fetal neurobehavior.
Temporal Associations Between Maternal and Fetal Functioning

The next series of studies was targeted at investigating whether maternal and fetal measures are temporally related during undisturbed conditions. Maternal and fetal heart rate are correlated when averaged over periods of time ranging from 50 min to 24 h such that women with faster heart rates have fetuses with faster heart rates. However, an association such as this does not imply that one drives the other. To examine the nature of the temporal relationship, time series analysis was applied to continuous streams of two maternal measures, heart rate and skin conductance, and two fetal measures, heart rate and motor activity, collected during an undisturbed monitoring period of 50 min. Data were analyzed for 137 maternal–fetal pairs measured longitudinally at 20, 24, 28, 32, 36, and 38 weeks of gestation. Cross-correlation coefficients were computed for each cross-lagged value ranging from 0 s (i.e., coincident) to ±100 s. Results indicated that maternal and fetal heart rate were unrelated; that is, there were no systematic relations between change in one and change in the other. Therefore, any time independent associations that may exist between maternal and fetal heart rate must be generated by secondary processes that mediate both. However, clear associations emerged for maternal skin conductance and fetal motor activity with a time lag of 2 s, that is, the association between changes in these measures peaked at a 2 s interval. The magnitude and shape of this cross-correlation function did not change during the period of gestation evaluated. However, the direction of the association surprised us: fetal movement preceded maternal skin conductance changes. Put most simply, fetal motor activity stimulated a small maternal sympathetic “jolt” 2 s after it occurred. An equally consistent, but slightly lower in magnitude, association between fetal movement and maternal heart rate was also demonstrated.

Working with colleagues, these findings were subsequently replicated in a sample of 195 maternal–fetal pairs in Lima, Peru measured using the same methodology and longitudinal intervals. Cross-correlation results again yielded no relationship between maternal and fetal heart rate, but similar associations between maternal skin conductance and both fetal parameters, with the same temporal lag. Figure 3.2 presents the associations between fetal motor activity and maternal skin conductance in both samples of maternal–fetal pairs. Women generally detect only the largest and most sustained fetal movements, which means that the maternal response is evoked in the absence of perception most of the time. Since the fetus moves frequently, approximately once per minute or slightly more, during the second half of pregnancy, it would appear that pregnant women neither habituate nor become sensitized to this internal signal. In addition, stability was observed in the magnitude of these associations such that maternal–fetal pairs that show higher levels of synchrony at 20 weeks maintain higher levels through term.

The remarkable similarity in results generated from maternal–fetal pairs that are separated by geography, ethnicity, and socioeconomic prosperity suggests that such microanalytic techniques can provide information regarding fundamental properties.
of the synchrony within the maternal–fetal relationship. It is possible that fetal movement may generate an autonomic response mediated by adrenergic feedback mechanisms resulting from perturbations to the uterine wall. Although the mechanism is unknown, the results point to a role of the fetus in effecting a maternal response, indicating that the maternal–fetal relationship is bidirectional in nature.

A seminal paper by Bell [36] challenged the prevailing belief that parent–child interaction was a unidirectional phenomenon with the child as recipient of parental action. This led to the now well-accepted view of the maternal–child relationship as dynamic and transactional. A similar model has been applied in understanding the effects that rodent offspring have on the development of the maternal nervous system [37]. We have proposed [29] that sympathetic activation of the mother by the fetus may contribute to observed decrements in cognitive performance associated with advancing pregnancy [38, 39] by interfering with parasympathetic processes that are required for maintenance of attention. In turn, the coincident dampening of responsiveness to external physical and mental challenges [40–42] may allow heightening of responses to internal signals. Thus, periodic sympathetic surges generated by fetal activity may serve to entrain maternal arousal patterns to the behavior of the fetus with implications for the impending demands of newborn care.

**Relationship Between Maternal Psychological State During Pregnancy and Postnatal Developmental Outcomes**

As noted earlier, our original impetus for examining the maternal–fetal relationship was based on the reports that maternal psychological stress during pregnancy negatively affected infant and child development. To date, we have found no evidence to support this notion, and in two studies, we have found a somewhat facilitative effect of maternal distress during pregnancy on child outcomes. In the first, higher levels of maternal prenatal anxiety, nonspecific stress appraisal, and depressive symptoms were associated with better motor development (i.e., PDI scores) on the Bayley Scales of Infant Development when children (n=94) were 2 years old. Mental Development Index (MDI) scores were associated with higher prenatal anxiety and depressive symptoms [43]. Analyses controlled for postnatal maternal psychosocial values at 6 weeks and 2 years postpartum. The only deleterious effect of prenatally measured attributes involved pregnancy-specific stress. Offspring of women who perceived pregnancy more negatively than positively showed somewhat poorer emotional regulation and attention.

**Fig. 3.2** Cross-correlation functions for fetal movement–maternal skin conductance collected longitudinally at six gestational ages on maternal–fetal pairs in Baltimore and Lima. The y-axis depicts the strength of the temporal association at multiple points from ±40 s from the origin. The x-axis shows the strongest association between fetal movement and subsequent maternal skin conductance at +3 s. (Reprinted with permission: DiPietro et al. (2006) Prenatal development of intrafetal and maternal-fetal synchrony. Behav Neurosci 120:687–701, American Psychological Association)
Because developmental assessments such as the Bayley Scales do not include evaluation of information processing, a more recent study utilized brainstem auditory evoked potentials (BAEP) as an indicator of neural development. Results indicate that greater pregnancy-specific stress (but not nonspecific anxiety) averaged over the second half of pregnancy was negatively associated with transmission speed within components of the BAEP waveform [9]. Faster transmission indicates enhanced maturation of the neural components of the auditory pathway; thus a negative association indicates that maternal stress had a maturative effect. There is a developing body of evidence that might be germane to these findings. That is, higher maternal cortisol after 31 weeks of gestation is associated with more advanced physical and neuromuscular neonatal maturation [44] and higher MDI scores when infants are 1-year old [14] but cortisol levels earlier in pregnancy show either no, or the opposite, association with outcomes. Thus timing of exposure to maternal cortisol levels during pregnancy may be a critical element.

However, we also found that maternal pregnancy-specific stress was positively associated with neonatal irritability as assessed during a neurological examination [9], a finding that partially supports other studies that have detected associations between maternal stress and/or anxiety and reduced infant behavioral regulation [45–47]. However, early infant irritability is a temperamental characteristic and not a phenomenon that portends impeded developmental outcomes. Thus, if there is a link between prenatal maternal psychological factors and early irritability, it should not be regarded as indicative of damage to the developing nervous system.

Our inability to detect deleterious effects of maternal psychological functioning on developmental outcomes or neurological development may seem to contradict the existing literature. However, examination of a number of widely cited studies purporting to show damaging effects of maternal stress, anxiety, and/or depression on infant outcomes reveal a number of significant methodological and interpretative problems. The most problematic has been the reliance on maternal report of child outcomes as opposed to measuring child outcomes by observational data collection. It is well-documented that maternal perception of child behavior and development is contaminated by maternal psychological characteristics in the direction of the reported findings. That is, women who are more anxious or stressed perceive their children to be more difficult, thereby inextricably confounding the dependent and independent measures in a direction that ensures detection of positive associations. Another common limitation is failure to measure and control for postnatal maternal psychological functioning since it is clear that women who are anxious or stressed during pregnancy remain so through at least the first 2 years of their child’s life [15]. The postnatal influence on child-rearing as a function of maternal psychological status is also well-known; thus observed associations may be environmentally, as opposed to biologically, mediated.

Animal models provide the most compelling support for a link between prenatal stress and developmental deficits [48], but functional deficits are not uniformly found and some studies report benefits [49, 50]. Most importantly, animal models of stress rely on repeated and systematic experimental manipulations, which are very different from the nature of observational studies of psychological attributes.
of women. These issues have been discussed in depth elsewhere [51]. Our findings are in agreement with the long-standing viewpoint that the human brain requires sufficient, but not excessive, stress to promote neural development both before [52] and after birth [53]. Participants in our studies and similar studies in pregnancy based on volunteer samples tend to be fairly well-educated, financially stable women, who are free from significant psychopathology. Although they experience significant levels of stress and anxiety, it is likely to be qualitatively different from that experienced by impoverished or clinically treated groups of women. Thus, the upper range included in these studies might best be regarded as reflecting “moderate” stress as opposed to more toxic or debilitating exposures.

Summary and Future Directions

This review was not intended to be a comprehensive examination of the maternal influences on the fetus but rather to illustrate a progression of studies designed to reveal the complexities of the maternal–fetal relationship. There is perhaps no relationship in life as profound as the first one, and much of the understanding of how each member of the dyad influences the other awaits discovery. Since the degree of synchrony within individual maternal–fetal pairs shows evidence of being a stable characteristic of that pair, the next question is whether the degree of maternal–fetal synchrony presages the degree of postnatal synchrony in maternal–child interaction within given pairs. Are women who are more physiologically responsive to fetal movements more responsive to infant behavior? Does the degree to which the fetus responds to maternal changes in psychological state translate to an infant’s success at serving as an elicitor of caregiving? Efforts to address these questions are currently underway in our laboratory using a maternal–infant physiological and behavioral interaction paradigm at 6 months postpartum. In any case, it is clear that just as neurodevelopment does not commence with birth, neither does the maternal–child relationship.

References


