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Behavioral perinatology: Biobehavioral processes in human fetal development

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Abstract

Behavioral perinatology is an interdisciplinary area of research that involves conceptualization of theoretical models and conduct of empirical studies of the dynamic time-, place-, and context-dependent interplay between biological and behavioral processes in fetal, neonatal, and infant life using an epigenetic framework of development. The biobehavioral processes of particular interest to our research group relate to the effects of maternal pre- and perinatal stress and maternal–placental–fetal stress physiology. We propose that behavioral perinatology research may have important implications for a better understanding of the processes that underlie or contribute to the risk of three sets of outcomes: prematurity, adverse neurodevelopment, and chronic degenerative diseases in adulthood. Based on our understanding of the ontogeny of human fetal development and the physiology of pregnancy and fetal development, we have articulated a neurobiological model of pre- and perinatal stress. Our model proposes that chronic maternal stress may exert a significant influence on fetal developmental outcomes. Maternal stress may act via one or more of three major physiological pathways: neuroendocrine, immune/inflammatory, and vascular. We further suggest that placental corticotropin-releasing hormone (CRH) may play a central role in coordinating the effects of endocrine, immune/inflammatory, and vascular processes on fetal developmental outcomes. Finally, we hypothesize that the effects of maternal stress are modulated by the nature, duration, and timing of occurrence of stress during gestation. In this paper, we elaborate on the conceptual and empirical basis for this model, highlight some relevant issues and questions, and make recommendations for future research in this area.

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Keywords: Behavioral perinatology; Pregnancy; Fetal development; Stress; Placenta; Corticotropin-releasing hormone (CRH); Neuroendocrine; Immune/inflammatory; Vascular

1. Introduction

Developmental processes involved in transforming a single-cell human embryo into a fully functioning organism within a mere span of 40 weeks are exceedingly complex and fascinating; indeed, one would be hard pressed to come up with any other example in the physical or biological world that even begins to approximate the sheer elegance of intrauterine development. Biologists over the ages have asked the question: Does the genetic material of the fertilized egg already contain a full set of building specifications for the organism? Over the last decade or so, there has been a major paradigm shift in developmental biology regarding fundamental concepts of how the central nervous system and the rest of the organism develops and functions. The answer to the above question is now believed to be an unequivocal “no”. Genes and environment are no longer considered to exert separate influences, and development is viewed not as a gradual elaboration of an architectural plan preconfigured in the genes, but rather as a dynamic interdependency of genes and environment characterized by a continuous process of interactions in a place- and time-specific dependent manner, and involving short- and long-term information storage, whereby genetic and epigenetic processes,\textsuperscript{1} at every step of

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\textsuperscript{1} For the purpose of this discussion, we use the term ‘genetic’ to refer to the effects of variations in DNA sequences on protein physiology, and the term ‘epigenetic’ to refer to alterations in gene expression and protein physiology without changes in DNA sequences (e.g. genetic imprinting via DNA methylation).
development, become represented in the evolving structural and functional design of the organism [1–3]. According to this epigenetic view of development, events at one point in time have consequences that are manifested later in the developmental process, and afferent activity has a profound influence on the developmental trajectory [4]. In other words, it appears that within the constraints imposed by the heritable germ line at conception, each developing organism plays an active role in its own construction. This dynamic process is effectuated by evolving various systems during embryonic and fetal life to acquire information about the nature of the environment, and to use this information to guide development. In the context of this formulation, not only does environment play a necessary role for development to occur, but the nature of the environment may play either an advantageous role for normal or optimal development, or a pernicious role to harm development [5].

Behavioral perinatology is broadly defined as an interdisciplinary area of research that involves conceptualization of theoretical models and conduct of empirical studies of the dynamic time-, place-, and context-dependent interplay between biological and behavioral processes in fetal, neonatal, and infant life using an epigenetic framework of development. The biobehavioral processes of particular interest to our research group relate to the effects of maternal pre- and perinatal stress and maternal–placental–fetal stress physiology. Our choice of stress and stress physiology is guided by the following two major considerations: First, empirical studies in humans and animals support a significant role for pre- and perinatal stress as an independent risk factor for adverse developmental outcomes [6]. Second, stress and stress physiology offer an excellent model system for the study of early developmental processes because it appears that the developing fetus acquires and incorporates information about the nature of its environment via the same systems that in a developed individual are known to mediate adaptation and central and peripheral responses to challenge/stress (i.e., the neuroendocrine, immune, and vascular systems) [7,8].

We propose that behavioral perinatology research may have important implications for a better understanding of the processes that underlie or contribute to the risk of at least three sets of outcomes: prematurity, adverse neurodevelopment, and chronic degenerative diseases in adulthood. Each of these classes of adverse health outcomes represents major public health issues in the United States and other developed nations; their prevalence is characterized by substantial disparities along factors associated with sociodemographic disadvantage and racial/ethnic minority status (which we and others have argued may, in part, reflect the effects of variations in stress and stress physiology in affected populations), and growing evidence supports a crucial role for early developmental process in their origins [4,9–12].

2. Biobehavioral model of prenatal stress and stress physiology in human fetal development

From a biological perspective, the term “stress” is used to describe any physical or psychological challenge that threatens or is perceived to have the potential to threaten the stability of the internal milieu of the organism (homeostasis). The neuroendocrine, immune, and vascular systems play a major role in adaptation to stress. The principal effectors of these adaptive responses are the corticotropin-releasing hormone (CRH) and locus ceruleus–noradrenaline (LC–NA)/autonomic (sympathetic) neurons in the hypothalamus and brain stem, which regulate the peripheral activities of the hypothalamic–pituitary–adrenal (HPA) axis and the systemic/adreno-medullary sympathetic nervous system (SNS), respectively. Activation of the HPA axis and LC–NA/autonomic system results in the systemic elevation of glucocorticoids and catecholamines, respectively, which act in concert on target tissues to mobilize and redistribute available resources, and also to maintain or effect a return to the state of homeostasis [8,13].

The adoption of an epigenetic framework for early development, wherein the organism plays an active role in its own construction by evolving systems to acquire and use information about the nature of the environment to guide development, gives rise to two important questions. First, how do the fetal and maternal compartments communicate with one another? And second, in light of the fact that the fetal nervous system is itself in a state of evolution and has yet to acquire its full repertoire of structural and functional capabilities, what are the modalities available to the developing fetus to receive, process, and act on information acquired from the environment? There are no direct neural, vascular, or other connections between the mother and her developing fetus. One of the remarkable adaptations of pregnancy is the evolution in early gestation of a transient organ of fetal origin—the placenta. All communication between the maternal and fetal compartments is mediated via the placenta through one or both of two mechanisms: the actions of maternal and fetal factors on placental activity, or transplacental passage of blood-borne substances. In addition to the long-recognized multiple roles played by the placenta, it now appears that the placenta may also take on some functions that are usually ascribed to the central nervous system, i.e., the capability of receiving, processing, and acting upon certain classes of stimuli. Indeed, we propose that one of the important roles of the placenta is to act on behalf of the fetus as both a sensory and effector organ to facilitate the transduction and incorporation of environmental information into the developmental process.

Based on our understanding of the ontogeny of human fetal development and physiology of pregnancy and fetal development, we have articulated a neurobiological model of pre- and perinatal stress. Our model proposes that chronic maternal stress may exert a significant influence on fetal developmental outcomes [6,12]. The effects of maternal
stress may be mediated through biological and/or behavioral mechanisms. Maternal stress may act via one or more of three major physiological pathways: neuroendocrine, immune/inflammatory, and vascular. We further suggest that placental corticotropin-releasing hormone (CRH) plays a central role in coordinating the effects of endocrine, immune/inflammatory, and vascular processes on fetal developmental outcomes. Finally, we hypothesize that the effects of maternal stress are modulated by the nature, duration, and timing of occurrence of stress during gestation (see Fig. 1).

Starting very early in gestation, the placenta produces hormones, neuropeptides, growth factors, and cytokines, and appears to function in a manner resembling that of compressed hypothalamic–pituitary target systems [14]. The physiology of placental CRH serves as an excellent illustration of our concept that the placenta acts in some ways as a sensory and effector organ on behalf of the fetus. CRH, a 41-amino acid neuropeptide of predominantly hypothalamic origin, is one of the primary mediators through which the brain regulates the activity of the HPA axis and the physiological responses to stress and inflammation [8,15,16]. During human pregnancy, the CRH gene and receptors are also richly expressed in the placenta. Placental CRH is identical to hypothalamic CRH in structure, immunoreactivity, and bioactivity [17]. The expression of the CRH gene increases exponentially in the placenta over the course of gestation, resulting in the production of placental CRH and its release into the maternal and fetal compartments. With respect to the role of the placenta as an effector of fetal development, we and the others have proposed various crucial roles for placental CRH in regulating human reproductive biology, including implantation, modulation of maternal and fetal pituitary–adrenal function, participation in fetal cellular differentiation, growth, and maturation, and involvement in the physiology of parturition [17,18]. With respect to the role of the placenta as a sensory organ, several lines of evidence have now converged to suggest that the activity of placental CRH is, in turn, regulated by characteristics of the maternal and intrauterine environment. For example, in vitro and in vivo studies have demonstrated that placental CRH output is modulated in a positive, dose–response manner by all the major biological effectors of stress, including cortisol, catecholamines (NE), oxytocin, angiotensin-II, both forms of interleukin-1, and hypoxia [19–22].

3. Prenatal stress and fetal developmental outcomes: overview of epidemiological findings

Disruption of reproductive function in mammals is a well-known consequence of stress. Results from experimental approaches in animal models strongly support a causal role for prenatal stress as a developmental teratogen, with large effects of even relatively mild behavioral perturbation in pregnancy on outcomes including, but not limited to, maternal–fetal physiology, length of gestation, and fetal growth [6,23–27]. Psychosocial/behavioral stress in human pregnancy has also been associated with outcomes at various points along the developmental continuum, including fertilization and conception, early pregnancy loss (spontaneous abortion), fetal structural and functional developmental outcomes (malformations, physiological activity, neurobehavioral maturation, growth), the length of gestation, infant birth weight, neonatal neurological optimality, neonatal complications, infant neurodevelopmental indices related to cognition, affect, and behavior, and childhood and adult psychopathology [6]. In humans, the length of gestation and fetal growth/infant birth weight are the outcomes that have been most commonly studied and found to be associated with maternal stress during pregnancy. We recently conducted a comprehensive review of human empirical research published in English-language journals over the past 12 years (1990–2001) and identified 98 empirical reports that examined the association of maternal psychosocial stress and/or social support with pregnancy outcomes related to the length of gestation and birth weight. Findings from this review are consistent with our own previously published studies in this area and support the notion that pregnant women reporting high levels of psychosocial stress and/or low levels of social support during pregnancy are significantly more likely to deliver earlier/preterm and a smaller/low birth weight infant [28–31]. Moreover, the effects of maternal stress appear to be independent from those of other established obstetric and sociodemographic risk factors. The effects of maternal stress are observed across the entire range of the outcome distribution, as opposed to only at one end of the distribution. Subjective measures of stress perceptions and appraisals are more strongly associated with adverse outcomes than measures of exposure to potentially stressful events or conditions. In many instances, the effects of stress are moderated by other person or situation characteristics, such as maternal age, body mass index, occupation, personality, and coping styles.
In terms of the magnitude of the effect, pregnant women reporting high levels of stress are at approximately doubled risk for preterm birth or fetal growth restriction compared to women reporting low levels of stress (the adjusted relative risk ratios vary between 1.5 and 2.5).

Based on these findings, we suggest the following two implications of this research: (1) Maternal psychosocial processes in pregnancy are at least as important and warrant the same degree of further consideration and study as other established obstetric risk factors, because the overall magnitude of their independent effect size on prematurity-related outcomes is comparable to that of most other obstetric risk factors. (2) There is, however, a compelling need to improve the specificity and sensitivity of stress measures as predictors of adverse outcomes. Clearly, not all women reporting high stress deliver preterm/low birth weight. The above-described findings in humans, including the modest effect size, taken together with the findings of a large magnitude of effect of prenatal stress in animal models, emphasize the importance of better measurement in humans of psychosocial stress and the dynamics of the interplay between stress, person- and situation-specific contextual factors, and biology. For example, without exception, every published human study of maternal psychosocial stress at the individual level has relied on self-report measures of retrospective recall of psychological state and affect over time. Self-report, summary measures of an individual’s states and experiences over time rely on autobiographical memory (as opposed to semantic memory), which is as much a matter of reconstruction as of accurate recall, and is known to be highly susceptible to numerous, systematic biases that adversely impact accuracy [32,33]. Thus, a consequence of unsatisfactory measurement of psychosocial stress in the context of behavioral perinatology research is the difficulty in ascertaining whether the modest effect sizes observed in the human literature are a function of “true” weak or small effects of prenatal stress on birth outcomes, or of deficiency in measurement procedures.

4. Prenatal stress and physiological processes in human fetal development: role of placental cotricotropin-releasing hormone

Fetal growth and development involves a complex interplay of factors and signaling molecules within the maternal, placental, and fetal tissues. Pregnancy is associated with major alterations in physiological function, including changes in hormone levels and control mechanisms (feedback loops) that are crucial in providing a favorable environment within the uterus and fetus for cellular growth and maturation and conveying signals when the fetus is ready for extraterine existence [14]. Fetal maturation and parturition are tightly synchronized processes. Recent advances have implicated placental CRH as one of the primary endocrine mediators of parturition and fetal development [17,18,34–37].

4.1. Placental CRH and parturition

It is well recognized that a shift in the balance from a progesterone-dominant to an estrogen-dominant milieu over the course of gestation results in a sequence of events in the gestational tissues to promote labor, including gap junction formation, expression of oxytocin receptors, and synthesis of prostaglandins [17,38]. In most mammals, this shift is effected by the conversion of progesterone to estrogen because it lacks the enzyme 17-hydroxylase required for this conversion. Instead, the placenta utilizes another precursor hormone—dehydroepiandrosterone sulfate (DHEA-S)—which is produced by the fetal adrenal zone, to synthesize estrogen (estriol (E3)) [36,39,40].

Placental CRH is believed to coordinate and control the physiology of parturition via its actions on the fetal endocrine system (fetal HPA axis) and within the gestational tissues. Placental CRH has recently been shown to directly and preferentially stimulate DHEA-S secretion by human fetal adrenal cortical cells [41]. Placental CRH also exerts direct actions on the uterus and cervix to augment changes produced by estrogen on these tissues by interacting with both prostaglandins and oxytocin, the two major uterotonic agents that stimulate and maintain myometrial contractility at term and during labor [17,18,38].

The overwhelming evidence from clinical studies of CRH and parturition that we and the others conducted suggests that women in preterm labor have significantly elevated levels of CRH compared to gestational age-matched controls, and that these elevations of CRH, assessed in some studies as early as 15 weeks gestation, precede the onset of preterm labor [42–52]. Studies that conducted serial assessments of CRH over the course of gestation found that compared to term deliveries, women delivering preterm not only had significantly elevated CRH levels but also a significantly accelerated rate of CRH increase over the course of their gestation [44,48,53]. Moreover, we have shown that the effects of placental CRH on spontaneous preterm birth are independent from those of other biomedical risk factors [50].

4.2. Placental CRH and fetal growth

Placental CRH is believed to also regulate fetal growth via its effects on placental perfusion and fetal cortisol production. Placental CRH elevations are associated with decreased uteroplacental flow and hypoxemia—known risk factors for fetal growth restriction [54,55]. Fetal cortisol plays a critical role in organ growth and maturation [56], and placental CRH also may participate in this process via its positive feedback loop with fetal cortisol [35,36,57]. Several clinical studies have found that CRH levels in maternal and/or cord blood at the time of delivery are significantly higher in low birth weight/SGA births [52,58–60].
4.3. Placental CRH and immune-inflammatory processes in pregnancy

Microbial infection and inflammation in the gestational tissues has emerged as one of the major risk factors for adverse birth outcomes such as early preterm birth (<30 weeks gestation) and adverse neurodevelopmental outcomes such as white matter brain damage and cerebral palsy [61,62]. These adverse outcomes in the setting of infection are believed to result from the actions of pro-inflammatory cytokines secreted as part of the maternal and/or fetal host response to microbial invasion [63,64]. Pro-inflammatory cytokines have been shown to promote spontaneous labor and rupture of membranes via their actions in the gestational tissues to stimulate the synthesis and release of prostaglandins and metalloproteases, in the fetus to stimulate the production of inflammatory cytokines, cortisol, and DHEA-S, and in the placenta to stimulate corticotropin-releasing hormone (CRH) synthesis and release [21,22,65–68]. Endocrine and immune processes extensively cross-regulate one another in pregnancy. For example, the pro-inflammatory cytokine interleukin (IL)-1 stimulates the production of placental CRH, and CRH in turn regulates cytokine production by immune cells. Because maternal stress is associated with preterm birth, abnormalities in the regulation of CRH and the production of pro-inflammatory cytokines may be a mechanism that could form the pathophysiological basis for this association [63].

Although maternal stress and infection have each been implicated as risk factors in preterm birth and the effects of stress on immune function are well established, very little research to date has examined the nature of the stress—infection—immune relationship in human pregnancy. Our review of the relevant literature found only two studies linking maternal stress with immune processes in human pregnancy [69,70], and one in vivo study reporting that women in preterm labor with microbial invasion of the amniotic cavity had significantly higher CRH levels than those in preterm labor without infection [49].

4.4. Placental CRH and fetal neurodevelopment

The developing human central nervous system may be more vulnerable to environmental perturbations than any other system because it develops over a much longer period of time (11–12 years); it has limited repair capabilities; its units have highly specific functional roles; the blood–brain barrier is not fully developed in utero; and the sensitivity of neurotransmitter systems, which is set during critical developmental periods, affects the organism’s response to all subsequent experience [71]. However, the influence of the maternal and intrauterine environment on the developing human fetal brain is poorly understood, in part, because the assessment and quantification of human fetal brain development presents many theoretical and methodological challenges [72,73]. To date, we have performed three studies in an effort to quantify and examine the influence of biobehavioral processes on fetal brain development.

The first study was performed on a sample of 84 fetuses at 31–32 weeks gestation to examine the ability of the human fetus to learn and recall information. Three series of vibroacoustic stimuli were presented at pseudorandom intervals over the fetal head, and fetal heart rate (FHR) responses to the first series of 15 stimuli (S1) were compared to responses to an identical second series of 15 stimuli (S1) separated from the first set by the administration of a single novel stimulus of different intensity and frequency (S2). A significant habituation pattern of responses was observed across trials for both series of stimuli, but this habituation pattern was attenuated for the series following the novel stimulus. These findings suggest that the 32-week-old human fetus may be capable of detecting, habituating, and dishabituating to an external stimulus, and support the premise that areas of the human fetal central nervous system critical for some aspects of learning and memory have developed by the early third trimester [74].

In a subsample of 33 mother–fetus pairs from the above study, the relationship was examined between maternal (placental) levels of CRH and the above-described fetal pattern of habituation and dishabituation in response to external stimulation. Results indicated that the fetuses of mothers with highly elevated CRH levels did not respond significantly to the presence of the novel stimulus, thereby providing preliminary support for the notion that abnormally elevated levels of placental CRH may play a role in impaired neurodevelopment, as assessed by the degree of dishabituation [75].

We performed nonlinear statistical analyses on our complete sample of 156 mother–fetus pairs studied at 31–33 weeks gestation. These analyses of FHR arousal and reactivity data, using a nonlinear repeated-measures model with auto-correlated errors within subjects and independence across subjects, suggest a host of maternal processes, including factors related to prenatal stress, elevated levels of placental hormones, and the presence of obstetric risk conditions, exert significant influences on the fetus and predict individual differences in patterns of fetal responses to external challenges. Our results specifically indicate the following: fetuses exhibited a significant, nonlinear FHR increase in response to the vibroacoustic stimulation protocol; baseline FHR, presence of uterine contractions during trials, and characteristics of the challenge protocol such as intertrial interval significantly influenced the magnitude of FHR responses; after accounting for the effects of baseline FHR, uterine contractions, and characteristics of the challenge protocol, maternal conditions related to psychological and physiological stress (i.e. psychosocial stress levels, placental CRH concentrations, umbilical blood flow, and presence of maternal medical risk conditions) were significantly associated with the pattern of FHR responses; after an initial response period, fetuses exhibited a FHR response...
decrement to subsequent stimuli, indicating habituation; a two-parameter growth curve (power) model to assess habituation rate accounted for approximately 70% of the variance in FHR response; and fetal sex and conditions related to maternal stress (i.e. maternal ACTH concentrations, presence of medical risk conditions) were significantly associated with the rate of habituation [76]. Thus, this set of findings provides further support for the role played by the prenatal environment, including placental CRH, in modulating aspects of human fetal brain development that underlie processes related to recognition, appraisal, response, memory, and habituation.

4.5. Stress and placental CRH function

Placental CRH is stress-sensitive. As mentioned earlier, a series of in vitro studies by Petraglia and colleagues [20–22] have shown that CRH is released from cultured human placental cells in a dose–response manner in response to all the major biological effectors of stress, including cortisol, and catecholamines. In vivo studies by our group [77] and other investigators [78–80] have found significant correlations among maternal pituitary–adrenal stress hormones (ACTH, cortisol) and placental CRH levels. Moreover, we and the others have reported that maternal psychosocial stress is significantly correlated with maternal pituitary–adrenal hormone levels (ACTH, cortisol) [81]—both of which are known to stimulate placental CRH secretion. Some [43,44], but not all studies [82], have also reported direct associations between maternal psychosocial processes and placental CRH function. Thus, depending on the chronicity of the stressor, the resultant increase in CRH production may be a critical factor that contributes to the early initiation of spontaneous labor and impaired fetal growth [18,83].

The fetus may also be directly sensitive to maternal stress [84,85]. Romero et al. [68] have recently described a condition, “Fetal Inflammatory Response Syndrome (FIRS),” characterized by a multi-system fetal stress response in human pregnancy, with activation of endocrine and immune systems, including elevated fetal cortisol/dehydroepiandrosterone sulphate (DHEA-S) ratio and elevated levels of inflammatory cytokines in fetal circulation [86,87], all of which are important biochemical mediators of fetal development and spontaneous preterm birth.

5. Conclusions, issues, and future directions

Adverse fetal developmental outcomes and their sequela are recognized as significant health problems in the United States. Women reporting high levels of pre- and perinatal stress are, on average, twice as likely to experience an adverse outcome as women reporting low levels of stress. Although the magnitude of this effect of prenatal stress is comparable to that of other “established” obstetric risk factors, the specificity and sensitivity of these measures as predictors of adverse outcome(s) in any individual pregnancy is, at best, only modest. These self-report measures of psychosocial stress rely exclusively on retrospective recall, and may be subject to numerous, systematic biases that undermine measurement validity. Moreover, these measures do not capture several important dimensions that are known to moderate the stress and adverse health outcome relation, such as individual differences in psychological or biological responsivity to potentially stressful circumstances in the subjects’ everyday lives, and individual differences in the context-specificity of stressful responses. Recent advances in momentary experience sampling methodology now afford the opportunity of not only minimizing biases associated with retrospective recall measures but also of assessing the dynamic interplay of psychological, behavioral, and biological processes in natural, everyday settings. We suggest that these new methods hold great promise in addressing many of the shortcomings in the stress and fetal development literature, and recommend importing and adapting these methods to conduct ambulatory studies of psychological, biological, and behavioral processes in human pregnancy.

Stress-related physiological parameters such as placental CRH and pro-inflammatory cytokines have been shown to significantly predict the risk of adverse fetal developmental outcomes. However, studies have examined the role of these parameters separately and have uniformly reported low specificity and sensitivity. For example, low levels of placental CRH in pregnancy are a good negative predictor of preterm birth but high levels are a poor positive predictor. Similarly, the absence of intrauterine infection is a good negative predictor of early preterm birth, but the presence of intrauterine infection/inflammation is a poor positive predictor. This may suggest that parameters such as placental CRH and infection/inflammation are, in and of themselves, necessary but not sufficient causes of adverse outcomes. Rather than propose other “novel” physiological parameters, we suggest that these major parameters need to be examined simultaneously to determine the manner in which they interact to predict risk of adverse developmental outcomes. We are not aware of any study that, for instance, has looked systematically at both endocrine and immune/inflammatory processes in human pregnancy. We suggest this is a critical future direction for this work because it is well known that endocrine and immune processes extensively interact to moderate the stress and adverse health outcome relation, do not capture several important dimensions that are known to undermine measurement validity. Moreover, these measures do not capture several important dimensions that are known to moderate the stress and adverse health outcome relation, such as individual differences in psychological or biological responsivity to potentially stressful circumstances in the subjects’ everyday lives, and individual differences in the context-specificity of stressful responses. Recent advances in momentary experience sampling methodology now afford the opportunity of not only minimizing biases associated with retrospective recall measures but also of assessing the dynamic interplay of psychological, behavioral, and biological processes in human pregnancy.
logical dysregulation that may even precede the index pregnancy. We are not aware of any studies that have examined stress and stress biology processes in women before they became pregnant to track the physiological and psychosocial transitions from nonpregnant to pregnant state, and we suggest this is an important direction in order to better understand individual vulnerabilities for the adverse effects of prenatal and perinatal stress.

Finally, to return to the concept of an epigenetic framework of development, it appears that embryonic/fetal developmental processes ultimately represent the dynamic interplay between two sets of information systems (i.e. fetal and maternal DNA) and two sets of cellular machinery (i.e. the fetal and maternal environments). We are not aware of any studies to date that have examined the physiological genomics of stress-related systems and pathways in human pregnancy, and suggest this is yet another important future avenue for this line of research.

Some 60 years ago, the Fels study of early development, probably the first systematic investigation of factors that affect development before birth, suggested that "such factors as... (maternal) emotional life and activity level during gestation may contribute to the shaping of physical status, behavioral patterns, and postnatal progress of the children they bear" [88]. Clearly, although we have come a long way since then, the study of the interface between biology and behavior in prenatal life continues now more than ever before to hold great promise in realizing the full implications of this statement to shed light about the nature of our origins and their consequences for our health and well being.

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