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REVIEW ARTICLE

The association between pregnancy processes, preterm delivery, low birth weight, and postpartum depressions—The need for interdisciplinary integration

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Pregnancy and peripartum/perinatal periods are characterized by significant biologic as well as psychosocial processes and changes that influence the 2 individuals at focus (mother and fetus), as well as their interactions with the immediate environment.

Multiple intertwined pathologic pregnancy processes (hormonal, biologic, stress and other mental occurrences) may lead to fetal distress, preterm delivery (PTD), low birth weight (LBW), and other delivery complications as well as to postpartum disorders. PTD and LBW in particular have been demonstrated to be associated with significant mortality as well as short- and long-term morbidity. Underlying processes and risk factors for PTD, LBW and postpartum disorders may overlap. Their impact on the offspring is compounded.

Currently, the multiple clinical and research disciplines that are concerned with the various aspects of pregnancy, delivery, and postpartum period are not conceptually and practically integrated. Specifically, obstetricians are more concerned with delivery complications, whereas mental health professionals are concerned with postpartum depression. An interdisciplinary approach is needed for better understanding of developmental processes and the development of measurements and interventions to prevent long-term impact on the offspring.

According to the World Health Organization (WHO) World Health Report 2001,[1] for the year 2000 maternal (495,000) and perinatal conditions (2,439,000) accounted for 2,934,000 deaths (5.3% of the total worldwide), which is very comparable to the deaths from HIV/AIDS (2,943,000; 5.3%). The burden of disease, in disability adjusted life years (DALYs) was even higher: 34,480,000 (2.3% of the total, 4.9% of women) disability years from maternal conditions, plus 91,797,000 DALYs (6.2% of the total) from perinatal conditions (compared with HIV/AIDS: 90,392,000 DALYs, 6.1%).

The individual and public health impact of maternal and perinatal conditions call for understanding of their underlying mechanisms, patterns, and risk factors to treat affected women and prevent the impact on their offspring.

A major impediment to efficient progress is the relative fragmentation of the domain. Here we will assess the data concerning physical and mental adversities during pregnancy, their influence on delivery outcomes, and their association with postpartum disorders. The

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data may be interpreted as suggesting a common denominator and overlapping pregnancy processes leading to both adverse delivery outcomes and postpartum disorders. Both have been demonstrated to cause negative impact on offspring and their development that may be cumulative. Integration of biologic, endocrine, and obstetric knowledge and efforts—with the realm of psychiatric-mental knowledge, research, and possible interventions—is needed.

Anxieties, stress, and depressions during pregnancy

Pregnancy is perceived by many as a period of happiness in anticipation of motherhood. However, depressive, anxiety, stress, and distress symptoms are quite prevalent during pregnancy. The prevalence of depression during this period has been estimated at 10% to 15% and prevalence of various anxiety disorders among pregnant women has been estimated at 10%.[2-10] Some estimates are even higher.[11] Pregnancy per se may be a stressful life event,[12] especially when it is unplanned and occurs in a complicated psychosocial situation.

Recent review of the literature[13] demonstrates that although prevalence of Diagnostic and Statistical Manual, fourth edition (DSM IV)[14] diagnoses during pregnancy is not much higher than the prevalence during other periods, the prevalence of stress, depressive symptoms, and distress may be much higher. This is demonstrated especially in specific vulnerable populations: Prevalence among black teenagers has been estimated at 42%,[15] among unmarried women at 44.4%,[16] among black and Hispanic women at 51%,[17] and among inner-city pregnant women at 41.7%,[18] prevalence is especially high among women of low socioeconomic status.[19]

Anxiety and stress during pregnancy have been reported to cause negative pregnancy outcomes such as preterm delivery (PTD) and low birth weight (LBW) of infants.[3,20-29] Depression during pregnancy has been reported to be associated with preeclampsia.[30] Even depression as early as the first trimester of pregnancy has been suggested to be associated with high risk of PTD and LBW of the infant.[31] The impact of depression during pregnancy may still be controversial,[32] whereas the impact of anxiety/stress is quite well accepted.

PTD and LBW

PTD (birth before 37 weeks of pregnancy) is of major public health concern. It occurs in about 10% of births. PTD rates are especially high (more than 20%) among poor, inner city, and minority pregnant mothers. Despite improvement in many health indicators, the rate of PTD has not decreased over the last 3 decades.[33] In the United States, the rate of PTD actually increased to 11.9% of pregnancies during 2001.[34] PTD is associated with 70% to 80% of neonatal mortality and increased morbidity in both developed and developing countries.[35-37]

Furthermore, PTD is a major determinant of neonatal and infant morbidity. Surviving infants may be at a high risk of damage to the central nervous system resulting in disorders such as cerebral palsy, neurodevelopmental deficiencies, chronic respiratory problems, intraventricular hemorrhage, infections, retrovental fibrophasia, and necrotizing enterocolitis[37] as well as long-term neurologic and developmental impairments, mental and cognitive dysfunctions, increased rate of cardiovascular disorders, hypertension, diabetes, and other somatic disorders.

LBW (birth weight <2500 g, which is not always associated with PTD) is also associated with increased infant morbidity and mortality.[38,39] LBW has been suggested to be associated with development of diabetes,[40] cardiovascular disease,[41] and schizophrenia,[42] as well as other conditions, though it may well be that LBW is mainly an indicator of fetal deficiencies during pregnancy that may be the causal factor(s), and LBW is not a culprit in its own right.

Despite progress in the field of obstetrics and gynecology, the predictive value of currently substantiated risk factors for PTD and LBW is rather low and there are no effective treatments to prolong gestation once preterm labor commences.[43]

There are several main pathogenic pathways for PTD: (a) activation of the maternal and/or fetal hypothalamo-pituitary-adrenal (HPA) axis, through maternal and/or fetal stress; (b) inflammation (systemic or decidual chorioamniotic); (c) decidual hemorrhage; and (d) pathologic distention of the uterus.[44] There may be some overlap between these processes.

It has been demonstrated that psychological and/or social stress may be a significant independent risk factor for PTD.[20-22,45-49] However, not all women reporting high levels of psychosocial stress also have PTD, suggesting that some women are more vulnerable to consequences of stress or its associated mechanisms.[48] Stress leading to PTD may be general, because of situational facts related to life in poverty, as chronic lack of resources, unhealthy living conditions, crime, and lack of personal safety. Rearing many previous children and single motherhood, as well as stress situations that are culture specific, especially in developing countries, are also general situational stressful conditions. Other stresses may be pregnancy specific, including maternal fears related to outcome of pregnancy, labor, ability to be a good mother, and infant's health.[20,21,50,51] Hard physical work may also result in poor fetal growth and preterm birth,[48] especially in developing countries where other contributing factors are prevalent.

Timing of stress is of importance; stress during early pregnancy may have a higher impact on PTD compared with later stress.[52]

The importance of social context, culture, and general living conditions is suggested by reports that in the United States, LBW is more prevalent and profound in disadvantaged neighborhoods regardless of individual levels of poverty and other risk factors.[53,54] These community psychosocial-cultural aspects are more profound in developing countries.[48,55-58]

The social context of pregnancy-related stress may be related also to nutritional deficiencies. A general deficiency referred to as "maternal depletion syndrome"[59] is prevalent in developing countries. It is attributed to inadequate maternal supply compared with expanded fetal demand. The deficiencies may be on several levels involving quantity as well as quality of nutrients. The deficiency is compounded by multiple successive pregnancies and births, lactation, chronic inadequate nutrition, inadequate maternal weight gain during pregnancy, and general poverty. The contribution of mental disorders and cumulative exhaustion to "maternal depletion" is still undetermined. The depletion may lead to LBW of the fetus, PTD, delayed infant development, and poor long-term outcomes for the offspring. The timing of deficiency is of importance, even when a severe famine occurs.[60] Early famine may be associated with PTD, whereas late pregnancy famine may be associated with very low newborn weight. In most cases the nutritional deficiency factors are probably more subtle. Specific nutritional deficiencies have been suggested to be associated with PTD. Interestingly similar deficiencies have been associated with depression and postpartum depression (PPD), (eg, deficiency in omega-3 fatty acids[61,62]). Fasting or nonfrequent meals may also lead to PTD.[63] Hobel and Colhane suggest[48] that fasting may lead to elevated corticotrophin-releasing hormone (CRH) levels and therefore initiate a stress response leading to PTD.

In consideration of the multiple sources of psychosocial stress, Hobel and Colhane[48] suggest the need of multilevel studies, using multilevel statistics that incorporate social, economic, and community characteristics.[64]

I believe that additional levels are needed.

Postpartum symptoms and disorders

The DSM IV[14] indicates that postpartum disorders are distinguished not by their phenomena but by their timing. Any major depressive, manic or mixed episode, bipolar I disorder or bipolar II disorder, as well as brief psychotic disorder should get a postpartum specifier if it occurs within 4 weeks postdelivery. Most publications estimate that PPD affects 10% to 15% of women.[2,8] Anxiety disorders are estimated to affect another 10% of new mothers.[5,9]

A more detailed review of the literature reveals that the reported prevalence of PPD varies among countries, affecting between 0% to more than 60% of new mothers. In the United States the reports vary between 3.7% and 48.6%. This is despite the fact that most surveys used the same instruments: the Edinburgh Postnatal Depression Scale (EPDS)[65] or the Beck Depression Inventory.[66] Indeed, the diversity may be attributed to cultural, socioeconomic, genetic, and reporting style differences between countries and cultures. A closer assessment of the United States reports demonstrate that most (but not all) reports of high prevalence of PPD symptoms included a large number of inner-city women with diversified ethnicity (mostly Hispanics, but also Asians[11,18,67]). Single women with low socioeconomic status (SES) have been overrepresented in these samples.[68] Although earlier reviews suggested that socioeconomic and ethnic variables did not necessarily influence prevalence of PPD, more recent reports suggest that low SES and poverty, as well as being a single mother are associated with PPD. Because many inner-city poor women are black or Hispanic, the overlap between these factors still needs to be disentangled.

Most attention concerning postpartum phenomena focused on PPD. It is currently assumed that the phenomena of PPD are similar to those of major depressive disorder (MDD). This may be correct if the heterogeneous nature of the current DSM-IV entity of MDD is not considered. However, a multitude of other diversified clusters of symptoms, syndromes, and behavioral entities have been described (for review refer to Brockington[69]) ranging from the very prevalent postpartum blues to the severe but infrequent (0.1%) postpartum psychosis, with many proposed mental entities in between. They may be described as mental disorders appearing during the period in focus, such as posttraumatic stress disorder.[70-76] Various anxiety disorders[5,9,77-83] and disorders of the mother-infant relationship[69] have been also described. Other central nervous system (CNS) postpartum disorders (eg, epilepsy), episodes of autoimmune disorders and other hormonal (eg, thyroid dysfunction), and general disorders are commonly almost ignored in psychiatric literature and practice and their association with mood, behavior, and cognitive symptoms is still not well recognized.

It is plausible that there are diversified postpartum disorders. The delineation of these disorders and their overlap with one another, as well as their distinction or lack of thereof, from descriptive entities during other periods of women's and men's lives, is still unclear. Whether a descriptive homogenous approach is sufficient may also need reassessment. Cross-cultural variations in symptom expressions and reporting styles were

documented for several affective disorders. It is quite plausible that in a group of disorders such as postpartum disorders whose reported prevalence so vastly varies from culture to culture, variations in symptoms' expression exist and may contribute to the reported different rates.

Predictors (risk factors) of post partum disorders

More than 70 (partly overlapping) risk factors of PPD have been reported. They may be clustered as reflecting past lifetime history and family history of mental disorders, past and current (during pregnancy and postpartum) socioeconomic factors, disturbed family relations and relations with the immediate environment, factors relating to the recent pregnancy as well as delivery and early postpartum periods, factors related to the infant, hormonal, biologic, and genetic factors, and cultural factors.

Several risk factors have been reported quite consistently—mostly previous PPDs, depression during recent pregnancy, lifetime history of depression, family history of mental disorders, stressful life events (especially postpartum distress), and lack of social support. Only a few studies were prospective,[3,84,85] most were limited to 1 or a few relevant aspects (eg, psychosocial or hormonal) and almost all were searching for risk factors for a single entity of PPD. Most attempts were quite disappointing, yielding low predictive rates. Two recent reviews[86,87] document the low sensitivity and specificity of current tools. In Austin's words: "In order to achieve this (a clinically useful tool) it is likely that a broader set of risk factors will need to be used."[86] Furthermore, different PPDs may be the result of different underlying mechanisms, vulnerabilities and risk factors. Therefore, characterization of targeted differentiated PPDs may lead to development of specific predictors for each of them.

Relation among PTD, LBW, and PPD

The 3 situations—PTD, LBW, and PPD—may be an outcome of similar or partially overlapping pregnancy processes. There is quite an overlap of risk factors leading to both adverse delivery outcomes and postpartum mental disorders. This overlap is more apparent regarding environmental, mother-supply/fetus-demand deficiencies and stress-related factors. It is unlikely that there is a causal effect of LBW/PTD on PPD (unless the infant's special needs severely affect the mother). It may be, however, that LBW/PTD are predictive factors for PPD.

The overlap between the 2 profiles of risk factors is shown in Table I. This table also shows that stress-related hormonal processes during pregnancy may be shared by LBW/PTD and PPD. They may be components of the common underlying mechanisms.

Table I Pregnancy risk factors for PTD/LBW and for PPD

	PTD/LBW	PPD
Low SES	+	+
Lack of social support	+	+
Race (↑ in African-American)	+	+
(↓ in Hispanics)	+	?
Single motherhood	+	+
Poverty	+	+
Inner city, disadvantaged communities	+	+
Stress	+	+
Physical and/or psychological trauma	+	+
Repeated major stressful events	+	+
Anxiety during pregnancy	+	+
Early psychosocial stress	+	+
Drug and alcohol abuse	+	?
Smoking	+	?
Early menarche	+	?
Mother's age: ↑adolescent, ↑ over age of 35 y	+	+
↓ Maternal BMI	+	?
Infrequent meals	+	?
Maternal nutritional deficits	+	+
Maternal inflammations, infections (Incl. periodontal diseases, STD)	+	?
Multiple births	+	?
Artificial reproductive technologies	+	?
High dose of fluoxetine to depressed mothers	+	?
High placenta/fetal weight ratio	+	?
Previous history of PT/LBW or PPD	+ (?)	+ (?)
↑ CRF	+	?
↑ Estriol (marker of fetal adrenal activity)	+	?
↑ Cortisol	+	+?
↑ Proinflammatory cytokines (TNFα, IL-1, IL-6)	+	?
↑ Prostaglandines	+	?
↑ Oxytocin	+	?

BMI, Body mass index.

Hormonal processes associated with stress during pregnancy

Stress during pregnancy may be psychological as well as physiologic. The 2 types may lead to the same consequences concerning birth-related adversities, as well as depressions during pregnancy and postpartum.

The HPA system and the placental-adrenal (PA) system as well as the immune system may be components of that link. The association between the physiologic and psychological stress processes is bidirectional. For instance, high levels of psychosocial stress and low levels of social support may cause suppression of the

Table II Hormones involved in stress-related depression and in PTD

	Stress/depression	PTD
CRH	↑	↑
Cortisol	↑	↑
DHEA	↓?	↑
DHEA-S	↓?	↑
TNFα, IL-1, IL-6	↑	↑
Norepinephrine	↑	↑
Angiotensin II	↑	↑
Vasopressin	↑	↑
Oxytocin	?	↑
Estrogen sensitivity	↑	↑
Progesterone withdrawal	?	↑

immune system.[88,89] Infections and high levels of interleukins may stimulate CRH secretion and the stress system.[90]

In the context of interaction between biologic and mental processes and outcomes, the initial focus is on the HPA axis that is considered to be the main hormonal system involved in stress. The main drive of the system is the hypothalamic CRH, which stimulates secretion of the pituitary hormone adrenocorticotropic hormone (ACTH), which in turn stimulates secretion of cortisol. The HPA system is normally regulated by negative feedback loops. CRH is also involved in immunologic and behavioral responses to stress.

During pregnancy, CRH is also a main secretory product of the placenta.[91-93] In the placenta, cortisol and other glucocorticoids stimulate CRH release,[92] as opposed to the negative-inhibitory feedback action on the hypothalamus.

During the second half of pregnancy, plasma CRH levels increase exponentially, with a simultaneous decrease in the CRH-binding protein (CRH-BP). The outcome is even higher levels of bioactive CRH that reaches a peak during delivery and then rapidly decreases postpartum.[94-97] Maternal stress[98] as well as fetal stress or hypoxia[99] increase mother and/or fetus plasma cortisol levels and because of the positive stimulating effect this causes an increase in placental CRH.[100] Maternal and fetal stresses are also associated with an increase in norepinephrine, angiotensin II, and vasopressin, all compounds that stimulate CRH release in the hypothalamus as well as in the placenta.[92,93,101]

The increase in CRH levels in the mother's plasma toward the end of pregnancy is normal, but in mothers who deliver preterm, the increase has been reported by some but not all to appear earlier and to be noticeable already in the second trimester,[94] indicating that the trajectory toward PTD may start already early in pregnancy and may be recognized then (potentially leading to development of preventive interventions). This issue is still in need of further elucidation.

Stress-induced stimulation of the fetal HPA axis increases production of fetal adrenal dehydropiandresterone sulfate (DHEA-S). The fetal DHEA-S reaches the placenta where it is converted to estrone (E_1) and estradiol (E_2) and after 16 hydroxylation in the fetus' liver, also to estriol (E_3). The increase in E_2 and E_3 contributes to onset of term and PTD.[102,103]

The close association between fetal, placental, and maternal HPA and PA systems is supported by the high correlation of maternal CRH levels and fetal cortisol levels during the second half of pregnancy in noncomplicated pregnancies. Lockwood et al[96] suggested that the fetus is actually driving the timing of delivery. Activation of his/her HPA axis may drive a CRH-mediated "placental clock" that triggers the onset of parturition in term or preterm.[44]

The abrupt CRH withdrawal once the placenta is delivered and its impact on the mother's HPA axis equilibrium may also be at least a major contributing factor to the development of PPD. This notion has not been adequately investigated. So far the focus of the few studies on hormonal withdrawal has been on the apparent gonadal hormones withdrawal and its possible prevention and treatment.[104-107]

Fetal distress and PTD may also be driven by amniochorionic and maternal systemic inflammation. It is of interest that the epidemiologic profile of women at risk for PTD includes some of the risk factors for sexually transmitted diseases (STD), as well as for pregnancy and PPD (inner city, poor, minority, young single mothers).

Women with PTD, especially those with infections, show an increase in cytokines such as interleukin-1 (IL-1) and tumor necrosis factor α (TNFα) as well as IL-6, which is secreted by the placenta affected by IL-1 and TNFα.[108] Activation of the cytokines network may lead to increased placental apoptosis and PTD.[44] The involvement of the immune system in general and specifically of interleukins, in the pathophysiology of depression is recently receiving more attention and is subject to substantial research. To my knowledge, however, this has not been adequately elucidated in the context of PPD and its possible association with PTD.

As shown in Table II, the hormonal changes that are associated with PTD are quite similar to those associated with depressions, especially with stress-related depressions (a subtype of depressions associated with alterations in the HPA system).

Influence of stress and depressions during pregnancy on children

A series of retrospective epidemiologic studies has demonstrated an association between LBW and PTD, which are considered to be indicators of adversities

during pregnancy, childhood,[109] and adulthood[110] as well as hypertension, coronary heart disease (CHD), hypercholesterolemia, glucose imbalance, and noninsulin-dependent diabetes mellitus.[111-118] These reports led to the theory, formulated mostly by the group led by Barker, that adversities during pregnancy contribute to a trajectory towards various disorders during adulthood.

Initially the theory of fetal origin of adult disorders ("The Barker Theory") stressed mostly biologic processes during pregnancy and their physical outcomes. However, it has been reported that exposure of pregnant mothers to the Dutch famine winter of 1944 to 1945 during their second trimester of pregnancy was associated with increased risk of MDD in their adult offspring.[119,120] The specificity of risk that pregnant mother's exposure to malnutrition is related to adult mental disorders in their offspring may be indicated by the reports that the cohorts who were exposed earlier in pregnancy had high risk of schizophrenia,[121] whereas those whose mothers were exposed at a later stage of gestation were at a higher risk for MDD. Not all types of pregnancy adversity may have the same impact, as suggested by the finding that influenzas during the second trimester of pregnancy were not associated with a high risk of schizophrenia in a British cohort.[122] The same group[123] reported association between offspring's schizophrenia and some pregnant mothers' somatic obstetric complications. The obstetric complications were different from those of pregnant mothers of offspring with affective psychoses. Studies examining LBW as an indicator of adversities during pregnancy[125] in British, Dutch, and Finnish cohorts, have reported it to be associated with schizophrenia of the adult offspring.[121,123,124] Increased risk of depressions in those born with LBW was reported by Barker's group,[126] based on their United Kingdom cohorts. Increased rate of suicide was also reported in the same cohort.[127] Although the currently available data are based mostly on retrospective evaluations, they strongly suggest that the environmental impact on human mental and physical development commences in utero.

Influence of maternal postnatal depression and stress on children

Children of women with PPD have been suggested to perform worse on cognitive and behavioral measures[128-134] and to exhibit high rates of increased attachment.[130,131,135] Disturbed mother-baby interaction of depressed mothers has been suggested to be a predictor of poor infant cognitive outcomes at 18 months.[136] Because child abuse and neglect are prevalent worldwide, it is of importance to assess the contribution of the mother's mental status to the parent-baby interaction. To our knowledge that has not been adequately studied (refer to Brockington[69]). Exposure to subsequent relapse of maternal depression (after the first year) probably increases risks of children to develop poor cognitive outcome.

Depressed mothers have been reported to express behaviors that have negative impacts on children, including being intrusive or withdrawn, disengaged, not interacting with their infants,[137,138] and being less sensitively attuned to their infants.[131]

Parental (mother) depressive symptoms have been suggested to be the most consistent predictor of future negative parenting behaviors (yelling, hitting, shaking,).[139] If maternal depression is prevented, it has been suggested that problems in the infant (behavioral, insecurity, overattachment, behavioral inhibition, and decreased IQ) also may be prevented or at least reduced.[131,140]

Though very compelling and intriguing, these reports are based on selected groups of patients who were evaluated with variable assessment tools with different designs and definitions of clinical entities as well as of timing.

Prevention of stress-related PTD

The recognition that stress during pregnancy may lead to adverse outcomes of delivery has been leading to stress-reducing interventions. Cognitive behavioral psychotherapy aimed at helping pregnant women to cope effectively with specific stressful situations of their lives has been reported to improve psychological well-being and reduce PTDs, provided that the interventions were applied to selected populations of women and individuals at risk.[21,141-146] However, when the risks were general (eg, community related), the same interventions were ineffective.[141] General improvement of social support was reported to be ineffective as well.[141,147,148] It did provide some improvement in delivery outcomes only when delivered by well-trained professionals who focused on women with very low social support to start with (refer to Orr's Review[149]). Interventions should be applied as early in the gestation as possible[52] and be aimed at specific coping situations relevant to the specific individual. Educational programs by nurses may be helpful[150-152] though results are not consistent.[153]

Conclusion

It is currently well substantiated that the external and in utero environment have an impact on delivery outcomes. Furthermore, adversities during pregnancy may influence the trajectory of offspring toward long-term developmental problems and disorders. It may also be plausible that the same processes influence the mother

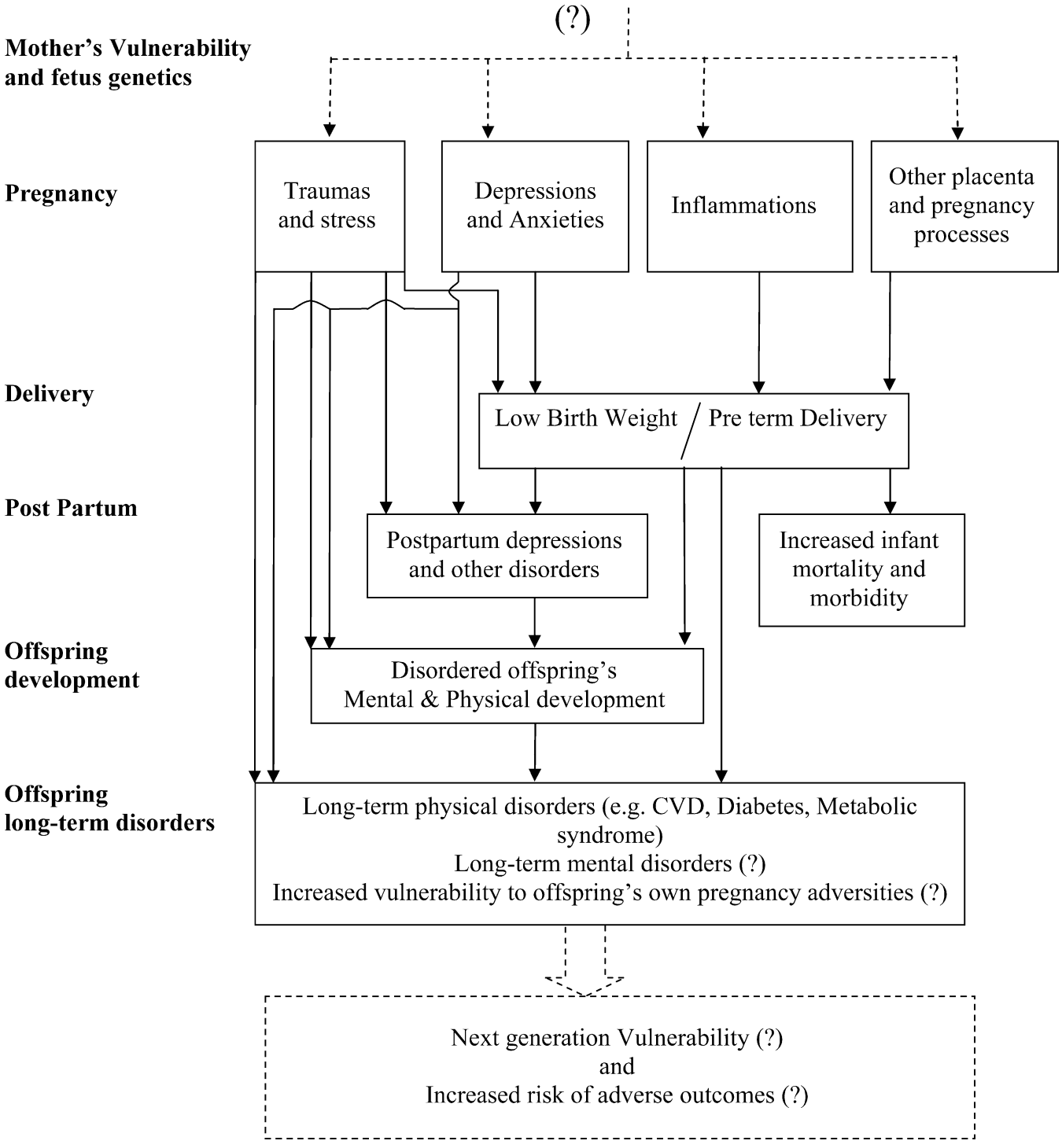

Figure The multiple compounded adversities leading to short- and long-term disorders of offspring.

not only during pregnancy but also postpartum and probably even beyond that period. The placenta plays a mediating role between the mother's physical supplies and the fetus's demand as well as between the mother's pregnancy adversities and the fetus's adverse responses. Furthermore, in the case of the mother's physical and mental stress, the placenta, through its endocrine functions, may amplify adversities and actively influence the fetus, delivery outcome and offspring vulnerability to future adversities.

Adversities during pregnancy may also contribute to **PPD** that is compounded by the corticotrophin-releasing factor (CRF) withdrawal when the placenta is delivered.

The associations between pregnancy processes, delivery adversities, and PPDs call for an interdisciplinary,

broad, comprehensive approach that is needed to address the multidimensional interactive processes involved.

As is presented in the Figure, pregnancy adversities, adverse delivery outcomes, and postpartum mental disorders may have a compounded assault on the offspring's physical and mental development and long-term vulnerability to disorders. That process may start before pregnancy. Some women may be more vulnerable to pregnancy adversities than others. Their inherited susceptibilities as well as past experiences may contribute to the offspring's genetics. Both mother vulnerability and offspring genetics may contribute to response to external and internal pregnancy adversities.

To my knowledge, individual predisposition to pregnancy adversities and their negative effects on delivery outcomes and beyond have not been sufficiently elucidated. Not all women respond to general calamities and stressful environmental situations with adverse outcomes. Therefore, identifying the women who are vulnerable to adverse outcomes may contribute to better understanding of underlying mechanisms as well as prevention of adverse response when warranted.

The adversities during pregnancy may be cumulative and compounding of previous events. The dynamically evolving vulnerability of the mother from one assault to another as well as possible effects of positive inputs and occurrences in reducing vulnerability, have not been clarified either. The genetic and epigenetic transfer of these vulnerabilities to offspring is an intriguing issue that once elucidated may have clinical implications for targeted preventive efforts not only for the individuals it involves but also on transfer of vulnerabilities and disorders from generation to generation.

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