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Adverse obstetric and neonatal outcomes in women with mental disorders

Silvia Hoirisch-Clapauch [a,*], Benjamin Brenner [b], Antonio Egidio Nardi [c]

[a] Department of Hematology, Hospital Federal dos Servidores do Estado, Ministry of Health, Rio de Janeiro, Brazil
[b] Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus and Technion Institute of Technology, Haifa, Israel
[c] Institute of Psychiatry, Federal University of Rio de Janeiro and National Institute for Translational Medicine (INCT-TM), Brazil

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ABSTRACT

The brain and the placenta synthesize identical peptides and proteins, such as brain-derived neurotrophic factor, oxytocin, vascular endothelial growth factor, cortisol, and matrix metalloproteinases. Given the promiscuity between neurochemistry and the mechanism of placentation, it would be expected that mental disorders occurring during pregnancy would increase the risk of adverse obstetric and neonatal outcomes. Indeed, expectant mothers with anxiety disorders, post-traumatic stress disorder, schizophrenia, or depressive disorders are at higher risk of preterm birth, low-birth-weight and small-for-gestational-age infants than controls. These mental illnesses are accompanied by a procoagulant phenotype and low activity of tissue plasminogen activator, which may contribute to placental insufficiency. Another risk factor for pregnancy complications is hyperemesis gravidarum, more common among women with eating disorders or anxiety disorders than in controls. Severe hyperemesis gravidarum is associated with dehydration, electrolyte imbalance and malnutrition, all of which may increase the risk of miscarriages, of low-birth-weight babies and preterm birth. This paper reviews some aspects of mental disorders that may influence pregnancy and neonatal outcomes.

Introduction

A number of peptides and proteins are produced by both the brain and the placenta. Oxytocin, for example, is synthesized in amnion, chorion, decidua, and neurons. In the peripartum period, oxytocin not only controls labor and milk ejection, but also regulates anxiety, mood symptoms and other complex mechanisms of social cognition and behavior, including neonate recognition and bonding between mother and baby [1]. Brain-derived neurotrophic factor, a well-known neurotrophin, and matrix metalloproteinases (MMPs) have a major role in adult neurogenesis and neuroprotection against excitotoxicity, and also participate in the processes of embryo implantation, trophoblast invasion, placental angiogenesis and vascular remodeling [2–4].

Among other substances that play a dual role in the central nervous system and the placenta are somatostatin, neurotensin, enkephalin, cortisol, insulin-like growth factor 1, vascular endothelial growth factor and the transcription factor cyclic AMP-responsive element-binding protein (CREB).

Given the promiscuity between neurochemistry and the mechanism of placentation, it would be expected that women with mental disorders would be at increased risk for obstetric complications. Unsurprisingly, depressive disorders, anxiety disorders, post-traumatic stress disorder, schizophrenia, and eating disorders occurring during pregnancy are independent risk factors for adverse obstetric and neonatal outcomes [5] (Fig. 1).

Depressive disorders

Periods of sadness are inherent aspects of human experience. While grief is a normal response to pregnancy complications, major depressive disorder is a disabling illness that increases the risk for adverse obstetric outcomes. If untreated, antenatal depression is associated with worsening of the psychiatric condition that may lead to suicide attempts, and with increased risk of a postpartum episode.

According to the American Psychiatric Association [6], the diagnosis of a major depressive disorder requires at least five of the following features to be present during the same 2-week period, one of them being depressed mood or loss of interest. With the exception of weight change and suicidal ideation, each criterion must be present nearly every day: (i) depressed mood most of the day; (ii) marked diminished interest or pleasure in all or almost all activities most of the day; (iii) insomnia or hypersomnia; (iv) psychomotor agitation or retardation; (v) fatigue or loss of energy; (vi) feelings of worthlessness, or excessive/ inappropriate guilt; (vii) diminished ability to think or concentrate, or indecisiveness; (viii) recurrent thoughts of death, suicide ideation or suicide attempt; (ix) weight loss when not dieting, or weight gain. The diagnosis also requires that symptoms cause significant distress or impairment in important areas of functioning, such as social or professional activities. Besides, the episode should not be attributable to any

* Corresponding author: Silvia Hoirisch Clapauch, MD, Atlantica 434-1101, CEP 22010-000 Rio de Janeiro, Brazil. Tel.: +55 21-99973-7500. *E-mail address:* sclapauch@ig.com.br ().

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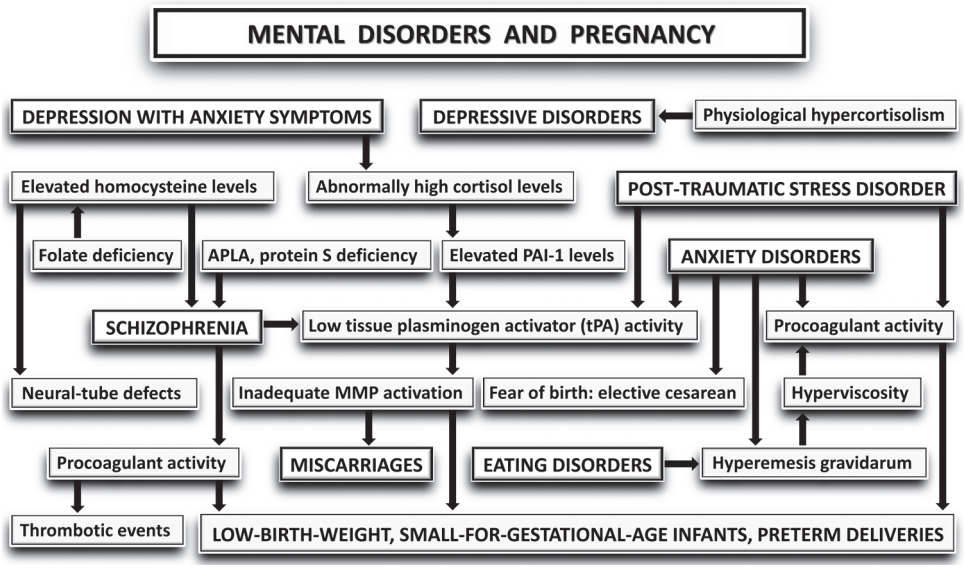

Fig. 1. Legend: PAI-1: plasminogen activator inhibitor-1; MMP: matrix metalloproteinase; APLA: antiphospholipid antibodies.

substance effect, and the symptoms must not be related to another medical condition. Importantly, depressive disorders are often accompanied by anxiety.

Elevated estrogen levels in pregnancy doubles the levels of corticosteroid binding globulin, resulting in low catabolism of cortisol by the liver, and a two-fold half-life of cortisol in plasma [7]. As a result, a steady rise in cortisol during normal pregnancy is noted, peaking during the third trimester at about two and three times non-pregnant values. Mothers with comorbid depression and anxiety synthesize an excessive amount of cortisol that further increases the already high levels of cortisol seen in normal pregnancies [8].

Chronic hypercortisolism may hinder fertility. In addition, a high percentage of pregnancies with Cushing's syndrome are complicated by fetal wastage, intrauterine growth restriction, preterm deliveries and neonatal death [9]. Elevated levels of cortisol that accompany severe depressive disorders may also increase the risk of pregnancy complications, such as recurrent unexplained miscarriages [10]. Although it has been reported that more women who use antidepressants miscarry than unexposed women [11], it is possible that women who require antidepressants have a more severe clinical course that could influence the obstetric outcome.

In 1992, Steer et al. [12] alerted to the fact that mothers with depressive symptoms had more than three times the odds of preterm birth, of low-birth-weight or small-for-gestational-age infants than mothers without depressive symptoms. These results were not confirmed in meta-analyses, possibly because treatment became more effective over the years. Nonetheless, it is indisputable that antenatal depression poses a modest but statistically significant risk of preterm birth and low-birth weight [13].

One possible explanation for the adverse obstetric events found in mothers with depressive disorders involves elevated levels of plasminogen activator inhibitor (PAI)-1, a finding consistently reported in depressive disorders. Both placental angiogenesis and vascular remodeling – required to sustain fetal growth – depend on extracellular matrix degradation by MMPs, such as MMP-2 and MMP-9 [4]. MMPs are secreted as latent enzymes, whose activation depends on stromelysin-1, also known as MMP-3, and on plasminogen [4]. MMP-3 is activated by plasmin and both plasminogen and plasmin are inhibited by PAI-1.

If a depressive episode increases the risk of adverse obstetric events, pregnancy itself increases the risk of having a depressive episode. It seems that high cortisol levels contribute to depressive episodes that affect 12% of pregnant women [14]. Cortisol levels are inversely related to dopamine levels, which plays a pivotal role in reward-motivated behavior, and to serotonin levels, which regulates mood, appetite and sleep.

Anxiety disorders and post-traumatic stress disorder

Fear is an adaptive reaction to real threat or perceived imminent threat, while anxiety corresponds to anticipation of future threat. The two responses overlap, but fear is usually linked to the fight-or-flight reaction, whereas anxiety is often associated with apprehension and physical tension. Anxiety disorders differ from transient fear or anxiety by being persistent and/or by an out-of-proportion response [6]. Although some level of anxiety may be experienced by most pregnant women without affecting pregnancy results, anxiety disorders – which include generalized anxiety disorder, social anxiety disorder, specific phobia, panic disorder, and agoraphobia – may increase the likelihood of adverse obstetric and neonatal outcomes.

Acute and chronic stress are characterized by platelet activation and increased levels of factors VII, VIII, XII, fibrinogen and von Willebrand factor antigen. While in acute stress tissue plasminogen activator (tPA) levels increase and fibrinolysis is activated, in chronic stress tPA levels decrease and PAI-1 levels increase, and therefore fibrinolysis is inhibited [15]. It is possible that increased procoagulant activity and decreased fibrinolytic activity, inherent to chronic anxiety symptoms, could increase the risk of adverse obstetric and neonatal outcomes seen in women with anxiety disorders, by causing placental vessel thrombosis. Of note, several studies indicate that acute cortisol reactivity to laboratory stressors may be blunted during pregnancy [8].

Panic attacks are highly stressful situations. As such, they may hasten the clotting time and induce a hypercoagulable state, similar to what is observed in procedures likely to provoke acute anxiety, such when the specific phobia patient fears needles [16]. Mothers with panic disorder have a higher risk of preterm deliveries and small-for-gestational-age infants than controls, especially if a panic attack is experienced during gestation [17].

Another problem significantly associated with anxiety disorders is excessive vomiting [18]. Severe hyperemesis gravidarum is associated with dehydration, electrolyte imbalance and malnutrition, all of which may increase the risk of miscarriages, of low-birth-weight babies and preterm birth. The risk is even higher if hyperemesis is associated with low pregnancy weight gain [19]. Also, compared