Prenatal depression and stress – risk factors for placental pathology and spontaneous abortion

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Abstract

Prenatal stress and depression affects 10–25% of pregnant women and is associated with disruption of fetal neurodevelopment, higher rates of placental abnormalities, preeclampsia, spontaneous abortion, or preterm birth. Markers of genetic vulnerability are catechol-O-methyltransferase, monoamine oxidase-A, variation of serotonin transporters, low levels of dopamine-beta-hydroxylase, and brain derived neurotrophic factor Val66Met (BDNF), while hyperactivity of HPA (hypothalamic–pituitary–adrenal) axis and massive release of endogenous cortisol, regulated by metalloproteinase-1, -2, -3 and -9, and are involved both in depressive symptoms and neurodevelopmental abnormalities in fetus. In women with prenatal stress and depression which suffered spontaneous abortion were observed placental abnormalities as regular shape and necrotic villi, decidua with large areas of necrosis, acute inflammation and effusion areas correlated with increase in proinflammatory factors, immune deficit and infections, hyaline type fibrosis, intervillos and deciduous intense hemorrhage, associated with increase of vascular endothelial growth factor. Taking into account the important societal and economic costs becomes important for an interdisciplinary approach, in which pregnancy and its risks are a central point for women mental health.

Keywords: placental barrier dysfunction, placental abnormalities, low level of 11beta-hydroxysteroid dehydrogenase type 2, psychosocial stress.

Introduction

Depressive disorder is common in women before or during pregnancy, and can cause obstetrical complications represented by disrupted fetal neurodevelopment, structural changes and abnormalities of the placenta, early miscarriage, premature birth, fetal distress incompatible with survival, and post-partum psychotic manifestations. Clinical markers for effects of prenatal depression and stress are reduced birth weight, and smaller head circumference [1–3].

Interdisciplinary approach of the prenatal depression represents a necessity now, in the context of numerous difficulty of interpretation for this complex pathology, surrounded by a vicious circle, the majority of studies highlighting just the etiopathogenic value of spontaneous abortion or premature birth for depressive disorder. The role of depression during pregnancy as a risk factor for obstetrical complication remains little known and under valued. The current biological perspective in addressing depressive disorder generates the possibility of achieving a particular etiopathogenic model to explain the consequences of this disorder on the mother and fetus.

It is known that prenatal depression affects 10–25% of pregnant women and is associated with higher rates of placental abnormalities, preeclampsia, spontaneous abortion, premature delivery, and complications requiring intensive care [4].

Materials and Methods

Multidisciplinary and retrospective studies which aimed to highlight the correlation between spontaneous abortion and prenatal stress and depression on a sample of 12 female patients, in which prenatal depression symptoms associated with family and social high level of psycho-stress, have been retrospectively identified, based on previous psychiatric evidences mentioned in medical records. After the moment of obstetrical intervention, the level of social stress was evaluated by two subscales of Social Stress Indicators (SSI) [5, 6] first one assessed stress of patient and his family in the last 12 months, and second the level of chronic stress in nine domains of the present life (finance, family, social, environment, workplace, marriage, parenting, housing, health); bigger scores indicate a high level of stress. Severity of depressive symptoms was assessed by using the Patient Health Questionnaire (PHQ-9), a screening tool where scores of 5, 10, 15, and 20 represent cut points for mild, moderate, moderately severe and severe depression, respectively [7, 8].

Material of histopathological study was represented by the placenta expelled with the product of conception during spontaneous abortions, after 12 weeks of gestation from the Clinics of Obstetrics and Gynecology, Emergency County Hospital of Craiova, Romania, between January 1 and June 30, 2013, and processed in the Laboratory of Anatomic Pathology of the same Hospital unit. From our research were excluded the patients with intrauterine death of fetus, trauma injuries, and severe medical conditions of the mother.

Processing was carried out by standard techniques of paraffin inclusion, with the following steps: 10% formalin
flush, washing with water or 80% alcohol, dehydrating (graded alcohol), clarifying (benzene, toluene, and xylene), and waxing. Usual staining Hematoxylin–Eosin (HE) was used.

**Results**

For all 12 patients included in our study, the scores obtained on the SSI subscales indicate a high level of social stress (over 25 on the first one, respectively over 60 on the second one), especially on the items related with family and financial present status (SSI 1 = 27.33 ± 2.49, respectively SSI 2 = 76.42 ± 8.98). These scores showed the important impact of social chronic stress before and during the pregnancy, the effects of the stressor being amplified also by the specific vulnerability of female gender.

The results of PHQ-9 questionnaire have showed also that for all 12 patients, symptoms of depressive disorder were present in moderately severe and severe degree; all scores obtained were over 15 cut point and were positively correlated with the data from the medical history of the patients (PHQ-9 = 19.67 ± 2.77). It was observed that the self-harming or suicidal tendencies were slight for all patients from our study group.

Optical microscopic observation highlighted placental abnormalities, which can be correlated with the biological mechanisms.

Placental villi, which are present in the examined placentas of all 12 patients, are intermediary immature type. In the first two trimesters of a normal pregnancy, the trophoblastic villi form all around the embryo. They had a uniform appearance and are lined by trophoblast with a highly vascularized stroma. Also, as a consequence of a normal development process, the decidual cells appear after differentiation of the stromal cells. These are large cell with polyhedral aspect, having an eosinophilic cytoplasm, abundant and vacuolated, round and uniform nuclei, and distinct cell membranes.

In our study, the increase in proinflammatory factors can be correlated with regular shape and necrotic villi, and decidua with large areas of necrosis, which appear as eosinophilic and non-structured areas, associated with acute inflammation and effusion areas. The villous outline is slightly irregular, and villi are quantitatively reduced (Figure 1), while placental vascular abnormalities (increase of vascular endothelial growth factor) can be also related to hyaline type fibrosis (Figure 2).

Intravilli hyaline is disposed in close areas, with obliteration of the villous capillary, and the loss of their vascularity. It was observed the fibrosis of the villous stroma. The hyaline areas appear as some non-structured and non-cellular eosinophilic areas, while hyaline type villi have lacy appearances. It was observed intervillous and deciduous intense hemorrhage (Figures 2–4), and necrotic villi with regular shape (Figure 3).

Decrease of immunity and presence of infections was associated in our study with important areas of decidual necrosis associated with acute inflammation and effusion areas, in which are present numerous polymorphonuclears. Some areas of necrosis are present intervilli, appearing as non-structured eosinophil masses, and in deciduous it was highlighted the loss of normal architecture, with irreversible nuclear alterations, such karyopyknosis and karyolysis, and the presence of the inflammatory cells (Figures 5 and 6).

Histopathological evidence from spontaneous abortion in women with prenatal depression and stress confirmed our hypothesis that these psychiatric disorders are predictive risk factors for evolution of pregnancy, both for mother and fetus.

**Discussion**

Spontaneous abortion may be a factor for aggravation of depressive disorder, becoming a risk factor for the possible next pregnancy and post-partum depression or psychosis. Biology of prenatal depression suggest a level of genetic vulnerability that can be correlated with the positive history of the patients and their family of uni- or bipolar depressive disorder, addictive, impulsive-aggressive, or suicidal behavior. Emphasizing these vulnerabilities, there are benefits of potential enzyme markers for neurotransmitters release, the catechol-O-methyltransferase (COMT) and the monoamine oxidase-A (MAOA) [9], thus serotonin and dopamine being the most frequently studied neurotransmitters.
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Figure 3 – Necrotic villi and intense hemorrhage (HE staining, 100×, 12 weeks placenta).

Figure 4 – Decidua with acute intense inflammation (HE staining, 100×, 12 weeks placenta).

Figure 5 – Decidua with intense acute inflammation and effusion areas (HE staining, 100×, 12 weeks placenta).

Figure 6 – Decidua with acute inflammation and effusion areas and necrosis intervilos associated (HE staining, 40×, 12 weeks placenta).

In depressive disorder, specific correlations were found for genetic variation of serotonin transporters (5HTT) [10], while for dopamine were reported low levels of activity of dopamine-beta-hydroxylase (DBH) in unipolar depression [11] with unbalanced dopamine-norepinephrine ratio in frontal cortex [12], associated with dopamine hyperactivity commonly found in bipolar depression, or positive symptoms in schizophrenia. Also, genetic markers of neuroprotection highlight a specific vulnerability for brain derived neurotrophic factor Val66Met (BDNF) [13].

Exaggerating the role of serotonin in neurobiochemistry of depression, associated with unfavorable effects of proserotonin medication (Selective Serotonin Reuptake Inhibitors – SSRI) made by prenatal depression a chapter of interdisciplinary psychiatric pathology, with a limited psychopharmacological approach [14].

Prenatal depression or positive personal history for depressive disorder associated with psychosocial stress factors generated by pregnancy lead to a hyperactivity of HPA axis and massive release of endogenous cortisol that penetrates the placental barrier and cause changes in the neurodevelopment of fetus, in particular on the cognitive element. Exposure to high levels of maternal cortisol during pregnancy may be related to cognitive deficits in offsprings [15]. The same HPA (hypothalamic–pituitary–adrenal) axis hyperactivity generated by the prenatal stress associated with depression, from anxiety and partner relationship problems, to natural disasters, disrupt placental permeability through enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) that fails to decrease the high levels of cortisol [16].

In this context, it is considered that maternal stress may cause other changes in the placenta which affect fetal neurodevelopment, structural changes of fetal brain being in direct relation with placental changes and high levels of cortisol through decrease of physiological capacity of action for enzyme 11β-HSD2 [17], even just 10–20% of maternal cortisol passes to the fetus [18, 19] in the presence of stress during pregnancy. This relation can be associated with epidemiological data about preterm birth of 5–7% of live births in some developed countries [20], which represented 28% from of all early neonatal deaths (deaths within the first seven days of life) [21]. Also, about 12% of all clinically recognized pregnancies ended in a spontaneous abortion (SAB), from a total of 31% from all pregnancies (including both recognized and unrecognized losses) [22].

Concerning this data, the decrease of enzyme 11β-HSD2 activity can be considered a significant biological risk marker for spontaneous abortion or preterm birth.
and specificity, validity and fidelity of this marker are increasing when prenatal depression and stress are identified in the pregnant woman.

HPA axis hyperactivity and high level of placental cortisol are regulated by metalloproteinase-1, -2, -3 and -9 [23], while increase of matrix metalloproteinase-9 in placental villi and tissue inhibitors of matrix metalloproteases TIMP-2 can be important biological markers for recurrent pregnancy loss [24, 25] (Figure 7).

Figure 7 – Neurobiological model of prenatal depression and stress for placental barrier dysfunction risks.

The relation between high levels of cortisol and cognitive structures (hippocampus) vulnerability, both for mother and fetus, was observed also on animal model. On a previous 10 days study on Wistar rats, it was highlighted on rats treated with dexamethasone intraperitoneally administrated in saline solution equivalent to 0.2 mg/kg/day, that hippocampus was the most intensely affected, being observed intense pinocytosis and vacuolization. This experiment sustains the important risk of hypercortisolemia on hippocampus and cognitive structure of the brain [26] (Figure 8).

Figure 8 – (A and B) Histopathological changes in the hippocampus induced by dexamethasone (animal model). HE staining, 200× (Marinescu et al., 2009 [26]).

The prenatal stress is considered an independent factor for hypercortisolemia, functioning as a amplifier of HPA axis hyperactivity and association with prenatal depression constituted a high risk factor with an important influence...
on both women mental health and cerebral integrity and functionality of fetus brain, being also associated with psychosocial elements like past psychiatric history, childhood separation from the father, high neuroticism score [27], unplanned or unwanted pregnancy, lack of intimacy of the husband [28], low paternal care and high maternal protection [29]. Prenatal depression associated with psychosocial risk factors favored placental barrier dysfunction, having as direct consequences spontaneous abortion and preterm delivery, with an increased risk of preterm birth of 95% with any previous abortion, during the women reproductive history [30]. Thus, spontaneous abortion becomes a potential risk factor for emphasizing costs through increasing number of preterm deliveries, being the background of a social and economical catastrophic type model (Figure 3).

The effects on society and economy are also important, the burden of spontaneous abortion and preterm birth phenomena, clinical consequences of prenatal depression and stress, being estimate in United States at a minimum of $26.2 billion in 2005 ($51 600 per infant born preterm), with over 60% of costs, which means $16.9 billion ($33 200 per preterm infant) for direct medical care, and $1.9 billion ($3 800 per preterm infant) for maternal delivery costs [31]. Direct health care costs supported by employers for a preterm infant are 15 times higher than for a full-term infant ($41 610 vs. $2830) [32]. On long term, this burden is amplified by the vulnerability of the preterm infants for various medical (visual and hearing impairments, growth deficiency, chronic respiratory, gastrointestinal, and immune system conditions) and psychiatric (cerebral palsy, mental retardation, behavioral issues, learning impairment) complications, the care and special education services for these conditions cumulated to $1.1 billion ($2200 per preterm infant) [31]. At the level of a family with preterm infants the effects are also important, with disruption of daily life by providing special care for infants, decrease of financial status, and burden of behavioral and educational deficits [33] (Figure 9).

Our effort represents a first attempt based on theoretical and biological evidences and can be a start point for an interdisciplinary approach, in which pregnancy and their risks are a central point for women mental health. A series of evidence can be useful in medical daily practice: recognition of risks for psychopharmacological medication use in prenatal depression, the need for an early detection of depression and psycho-stress factors, therapeutically interventions based on limiting the effects of glucocorticoids excess and the need for an interdisciplinary monitoring of individuals at risk based on biological indicators.

Conclusions

Depressive disorder and prenatal stress may be considered as risk factors for spontaneous abortion. We consider as potential biological indicators for unfavorable evolution of pregnancy the proinflammatory factors, endothelial dysfunction markers, and immune indicators that can be validated by further studies. A major interest is represented by use of values for metalloproteinases and tissue inhibitors of matrix metalloproteases TIMP-2 as indicators for the risk of pregnancy loss when prenatal stress and depression occurred.

Author contribution

All authors have contributed equally to the manuscript.

References


