Wójcik Magdalena, Boreński Grzegorz, Szabat Przemysław, Poleszak Julita, Szabat Marta, Milanowska Joanna. Depression during pregnancy. Journal of Education, Health and Sport. 2019;9(3):465-473. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.2604908
http://ojs.ukw.edu.pl/index.php/johs/article/view/6728
https://pbn.nauka.gov.pl/sedno-webapp/works/908559

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 01.03.2019. Revised: 15.03.2019. Accepted: 25.03.2019.

Depression during pregnancy

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Abstract

Introduction: Depression during pregnancy seems to be dominated by the postpartum depression. It is important to remember about this condition and its symptoms as they are easy to be mistaken with mood changes and other behavioural changes common during pregnancy. Although we know the risk factors for this condition, we still do not know its complex etiology. Moreover, there is also not enough information about the treatment.
The aim of the study: The purpose of this systemic review was to collect and analyse causes and possibilities of treatment depression during pregnancy.
Material and method: Standard criteria were used to review the literature data. The search of articles in the PubMed and Google Scholar database was carried out using the following keywords: depression, treatment, pregnancy.
Description of the state of knowledge: Currently the most common treatment for pregnant women suffering from depression are selective serotonin reuptake inhibitors, especially citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine and sertraline. However, their potential side effects affecting the fetus is a controversial issue. The results of many studies are not consistent.

Summary: It is still not known how to treat depression during pregnancy properly. Psychotherapy, considered as a basic way of treatment, is always recommended. However, the usage of selective serotonin reuptake inhibitors is still open to debate.

Keywords: depression, pregnancy, treatment

1. Introduction

Clinical depression, which is also known as major depressive disorder, is common among women during childbearing [1,2]. In Europe 3-8% of pregnant women are prescribed antidepressants during pregnancy [3]. Serotonin reuptake inhibitors (SSRIs) are the most commonly used medicine [1]. SSRIs inhibit the serotonin transporter, which decreases the reuptake of serotonin into the presynaptic terminals and increases serotonin concentration in the synapses [4]. Chemical neurotransmitters are necessary to coordinate the development of neurons and brain circuits. Due to the fact that psychoactive drugs modulate components of neurotransmission, they may have an impact on prenatal stages of brain development [5].In animal models exposed in utero to serotonergic antidepressants, associations with autism-like behaviours in the offspring have been reported [6]. The serotonergic system is critical for neurodevelopment [7], so the possible effect of antidepressants on the safety of fetus may be disquieting.Determining the impact of antidepressants on health and fetal development is extremely important for increasing the awareness of pregnant women as to the consequences of their use.

Major depressive disorder (MDD) is a disease with complex etiology. World Health Organization predicts that MDD will be the main cause of disability in 2030 [8]. MDD is often associated with chronic illnesses or other mood disorders [9,10]. To diagnose depression the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) outlines the following criterion: The individual must be experiencing five or more symptoms during the same 2-week period and at least one of the symptoms should be either (1) depressed mood or (2) loss of interest or pleasure (Table 1).

Table 1.

Depressed mood most of the day, nearly every day.
Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (anhedonia).
Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.
A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down).
Fatigue or loss of energy nearly every day.
Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
Diminished ability to think or concentrate, or indecisiveness, nearly every day.
Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

To receive a diagnosis of depression, these symptoms must cause the individual clinically significant distress or impairment in social, occupational, or other important areas of functioning [8]. Risk factors for MDD development are endocrine abnormalities, cancers, adverse effects of drugs, stressful events and genetic factors [9].

2. Patophysiology

2.1 Endocrine system

Glucocorticoids, corticotropin releasing factor, glutamate, vasopressin, gamma-aminobutyric acid, serotonin may play and important role in development of MDD [9]. Brain reacts to acute and chronic stress by activation of the hypothalamic-pituitary-adrenal (HPA) axis. Glucocorticoids are released in larger quantities under the influence of activation of the HPA axis and ejection of corticotropin releasing factor. Steroids affects the overall metabolism and also affect behavior via direct actions on numerous brain regions [10]. Hypercortisolemia may be toxic to pyramidal neurons in the hippocampus, can lead to atrophy of dendrites and inhibition of neurogenesis in the dentate gyrus of the hippocampus. Hypercortisolemia can also reduce a volume of hippocampus leading to dysfunction of brain areas related to emotion and reward circuitry [9]. This state can also lead to decrease function of glucocorticoid receptor in HPA axis. It could explain the hyperactivity of HPA axis in depression [13]. In patients with depression increased number of corticotropin releasing factor secreting neurons in hypothalamus and locus coeruleus was observed [14]. Overexpression of corticotropin releasing factor in transgenic mice induced depressive behaviors. Such an effect was also observed during the infusion of corticotropin releasing factor into the brain of transgenic mice [15]. Selective deletion of corticotropin releasing factor-1 receptors in limbic areas leads to antidepressant-like behaviors in mice [16]. Glutamate is main stimulant neurotransmitter in central nervous system. Higher concentration of glutamate was found in bran, plasma and cerebrospinal fluid in patients with depression [17]. Vasopressin has multiple functions as a hormone in the periphery, but also functions as a neurotransmitter in the brain. Vasopressin is synthesized and released from neurons of the hypothalamic suprachiasmatic nucleus [18]. Vasopressin affects mainly amygdala and bed nucleus of the striaterminalis. Higher concetrations of vasopressin were observed in patients with depression and it may be involved in over-reactivity of HPA axis. It affects HPA axis by interactions with V1b receptors, in response to chronic psychological stress. Expression of V1b receptors is increased in patients with depression [9]. Gamma-aminobutyric acid (GABA) and glutamate imbalance plays an important role in the development of depression [19]. GABA is an inhibitory neurotransmitter in central nervous system [20]. There is a hypothesis that the activation of the GABA receptors may produce antidepressant effects [9]. The serotonergic system is implicated in pathogenesis of MDD. Serotonin and its receptors are the major targets for depression therapeutic drugs. Increasing the level of serotonin gives the antidepressant effect. All antidepressant strategies have been shown to enhance 5-HT transmission in the brain of laboratory animals [21].

2.2 Immune system

The role of inflammation in major depression has been extensively documented. In patients with MDD, we observe:

- increased expression of pro-inflammatory cytokines and their receptors
- increased levels of acute-phase reactants, chemokines and soluble adhesion molecules in peripheral blood and cerebrospinal fluid [21].

Increased concentration of IL-1β, IL-6, soluble IL-2 receptors and tumor necrosis factor-alpha (TNF- α) in patients with depression have been reported [22]. IL-1β is expressed mainly in the hypothalamus, but is also expressed in the hippocampus, cerebral cortex and thalamus [23]. Psychological stress increases the level of IL-1β in hypothalamus and hippocampus causing activation of HPA axis, suppression of hippocampal long-term potentiation and down-regulated expression of brain-derived neurotropic factor (it plays important role in the regulation of neurogenesis, synaptic and structural plasticity, which are involved in the pathology of depression) [9]. Peripheral and central IL-1β administration

induces symptoms such as anorexia, weight loss, anhedonia, fatigue, impaired social interaction, memory dysfunction and impaired social interaction, which are also symptoms observed in patients with depression [24]. Blockade of IL-1β signaling reversed stress-like symptoms induced by IL-1β [9,25]. Mice with deleted IL-6 gene showed increased resistance to the development of depressive symptoms induced by stress [9]. TNF-α is a 17 kD secreted protein that exert biological effects mainly by binding to tumor necrosis factor receptor 1 and tumor necrosis factor receptor 2. TNF-α could activate HPA axis and activate indoleamine-2,3-dioxygenase, which is expressed in macrophages and dendritic cells in the brain and could through kynurenine pathway catabolize tryptophan which is the substrate for serotonin synthesis. Most of TNF- α receptors are in hypothalamus, hippocampus, and cortex – areas involved in antidepressant response and cognitive functioning [9,26]. Blocking the effects of TNF- α can contribute to relieving the symptoms of depression [26].

2.3 Role of Inflammation in perinatal depression

During early pregnancy, different kinds of natural immune cells such as natural killer cells, dendritic cells, macrophages, T-reg cells infiltrate the decidua around the invading trophoblast cell-layer, enhancing the recruitment and migration of immune cells by secretion of inflammatory cytokines - IL-6. The presence of these cells is beneficial for the development of pregnancy. Their lack may contribute to the disturbances in the development of the placenta or blastocyst implantation [22,27]. Mediators released by trophoblast and decidual cells such as TNF-α, IL-1β, IL-10, IL-8 increase the synthesis of mediators such as chemokines, prostanoids, histamine and serotonin which stimulate and guide placental processes. Furthermore, IL-6 and IL-11 increase expression of adhesion molecules in endometrial epithelial cells, that help in implantation and trophoblast invasion. Disruption of the balance in these processes can lead to neuropsychiatric disorders [23]. Th1/Th2 balance is important in pregnancy. It may facilitate the maintenance or rejection of fetus [28]. The factors secreted during pregnancy promote Th2 predominance. Th2 cytokines inhibit Th1 and macrophage inflammatory activity, preventing rejection of the fetus. Domination of pro-inflammatory Th1 over anti-inflammatory Th2 may contribute to the development of perinatal depression [22]. Th2 bias during pregnancy decreases cell-mediated immunity, that increase a risk of infections by influenza, Listeria monocytogenes or leprosy [29]. Increase of inflammatory cytokines such as IL-1β, IL-6, TNF-α is associated with perinatal depression. Increase of these is correlated with depression onset. We also observe brain function changes - reduced hippocampal activity associated with cognitive deficits, reduced memory, and poor behavioral performance [22]. Among others, increased level of cytokines and TLR signaling in response to psychological stress, during third trimester, may contribute to changes in the prefrontal cortex, anterior cingulate, hippocampus, neuroendocrine system and placental processes and the appearance of symptoms of depression. In pregnant women exhibiting major depressive disorder, we observe abnormal function of HPA axis. There are high levels of cortisol, hypothalamic-pituitary peptide hormones, catecholamines and low level of dehydroepiandrosterone in plasma [30]. Imbalance in immune system during pregnancy may generate a persistent dysfunction of HPA axis. Perinatal depression has the same features of inflammatory signals inducing the dysfunction of monoaminergic transmission systems as in MDD [22].

3. Depression and pregnancy

Postpartum disorders seem to be more common than depression during pregnancy. Postpartum disorders have been classified into five major categories [31]. Two of them known as postpartum blues or baby blues and postpartum depression are the most common. The risk of postpartum depression is increased by 25% if the patient has a history of major depression, moreover with the history of postpartum depression the risk of recurrence is

increased to 50% [32]. The etiology of peripartum depression is unclear [33]. There are studies which show that hormonal disorders (thyroid dysfunction) [33,34] and genetic predisposition [36] may have an impact on the occurrence of depression during or after pregnancy. The American College of Obstetricians and Gynecologists (ACOG) recommends screening for depression during each trimester of pregnancy [37]. There is a systematic review that focus on the risk factors of antepartum depression, considering 20 of potential predictor variables: anxiety, life stress, life events and negative life events, daily hassles, history of depression, social support and lack of it, also lack of a partner, domestic violence, relationships and its quality and some more [38]. Another study showed that depression during pregnancy is more common than postnatal depression yet it has been relatively neglected [39]. The hard part of diagnosing depression during pregnancy is that its symptoms are similar to the conditions that a pregnant woman experience normally such as disruptions in sleep, weight/ appetite changes, lack of energy or difficulties in concentration [40]. Another study regarding depression during pregnancy showed that pregnant women with the risk for the development of the perinatal depression were in average more depressed and anxious than the pregnant women who have not shown the risk of the development of the perinatal depression [41]. Risk factors for screening as depression positive during pregnancy or postpartum in study in Serbia were: low education level, low satisfaction with financial situation, high-risk pregnancy and depression during pregnancy [42]. It is known that pregnancy and the postpartum period are periods of increased vulnerability to psychiatric disorders [43]. There is a great need to diagnose depression during pregnancy as it can allow for early intervention. However, it raises a question how to diagnose it. The study about the validation of the Edinburgh Depression Scale (EDS) during pregnancy showed that it is a reliable instrument for screening depression during pregnancy. However, a lower cutoff is recommended [44]. Women with depression during pregnancy are at increased risk of preterm birth (PTB) and low birth weight (LBW) of their children [45]. In one of the studies about depression restricting a fetal growth, it has been shown that depressed women had a 13% greater incidence of premature delivery and 15% greater incidence of low birth weight than non-depressed women [46].

4. Depression during pregnancy - treatment

Selective serotonin reuptake inhibitors are the most common antidepressants prescribed during pregnancy [47]. Comparing to older tricyclic antidepressants (TCAs), they have better tolerability and safety. The most commonly used SSRI drugs are citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine, sertraline, and the SNRI drug venlafaxine [4]. They all increase extracellular serotonin and hyperserotonemia is found in about one-third of children with autism [48]. All antidepressants cross the placental barrier and are available to the developing fetus [5]. Many cohort and case-control studies examined the potential influence of antidepressants on developing autism spectrum disorder (ASD) in the offspring [48]. A meta-review of meta-analyses do not discourage the use of SSRIs during pregnancy. In case of depression having a negative impact on maternal or fetal well-being, the risk of ASD in the offspring is not a factor that should decide on the treatment [49]. Another case of SSRI exposure during pregnancy is that it may cause congenital malformations. Results of studies show that that there is no evidence that the association was specific to particular malformations [50]. However, other metaanalysis shows that exposure to paroxetine during first-trimester appears to be associated with a significant increase in the risk for cardiac malformation [51]. Another study regarding the impact of prescribing psychotropic medication during early pregnancy showed that it can result in higher risks of miscarriage, perinatal death and decisions to terminate a pregnancy in women with depression or anxiety [52]. Persistent pulmonary hypertension of the new-born (PPHN) is thought to be another

consequence of SSRI exposure. There is a study on large group of women which showed that there is a potential increased risk of PPHN associated with maternal use of SSRIs in late pregnancy. However, the absolute risk was small [53]. Another thing to discuss is increased neonatal morbidity and a higher rate of admissions to the NICU of new-borns associated with maternal use of antidepressants during pregnancy which was shown in large population study. In this study, after SSRI exposure during pregnancy 13.7% of the infants were admitted to the NICU compared with 8.2% in the population. However, the absolute risk for severe disease was low [54].

5. Summary

Depression during pregnancy is still not known well enough. The etiology is complex and many factors may contribute to its onset. Many patients with mild-to-moderate depression can be treated by individual and group psychotherapy [55]. A study of the impact of this kind of treatment shows that interpersonal psychotherapy is an effective method of antidepressant treatment during pregnancy and should be a first-line treatment [56]. In conclusion, most of the studies show that SSRI use during pregnancy is relatively safe for the development of the offspring. However, every woman requires an individual approach. Starting a therapy using SSRI requires strong indications as well as evaluation of the risks and benefits due to still lacking knowledge about its impact on developing embryo and fetus. Moreover, while planning the antidepressant treatment it may be worth considering new options in treatment such as psychobiotics with the mentioned above psychotherapy as a basic form of treatment.

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