Stress of Prematurity in Experience of COVID-19 Pandemic

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Stress is a process that triggers various physiological, hormonal and psychological mechanisms in response to a threat, which significantly affects the health of an individual. The COVID-19 pandemic introduced a lot of social changes that required constant adaptation to unfavorable conditions. Maternal stress and anxiety increase the levels of corticotropin-releasing hormone (CRH) in the placenta, which in turn affects the incidence of preterm birth and many other related maternal and neonatal complications.

Keywords: COVID-19 pandemic ; prematurity ; stress

1. Introduction

The premature birth of a child, defined as birth before 37 weeks of gestation, is becoming increasingly common worldwide. More than 50% long-term morbidity and circa 75% of perinatal mortality is caused by premature birth. Survived preterm children are at increased risk of developing neurological, respiratory and gastrointestinal complications [1].

2. Stress of Prematurity in Experience of COVID-19 Pandemic

Existing research suggests that SARS-CoV-2 infection may increase the risk of preterm birth and numerous pregnancy complications. There have also been reports of the potential placental transport of the virus and maternal-fetal transmission of the infection; however, the risk appears to be relatively low, and the number of reports confirming intrauterine transmission of the coronavirus is limited [2][3][4]. Conducted studies indicate that COVID-19 infection increases the risk of preterm birth compared to healthy women. This may be attributed to the inflammatory state resulting from the infection, which leads to the initiation of premature uterine contractions. Coronavirus infection can adversely affect the overall health status of pregnant women, manifesting in various symptoms such as fever, cough, muscle aches, gastrointestinal disturbances (diarrhea and nausea), and respiratory difficulties. Pregnant women are also more susceptible to developing pneumonia and acute respiratory distress syndrome, which carries the risk of severe oxygen deprivation for both the mother and the fetus. Severe COVID-19 infection can also serve as an indication for the premature termination of pregnancy for the health of the mother and the fetus, thus warranting iatrogenic preterm delivery [5][6][7][8][9][10].

Furthermore, COVID-19 infection increases the risk of gestational diabetes mellitus, gestational hypertension, preeclampsia, and intrauterine fetal demise [11].

Maternal psychological stress, or prenatal stress, as well as major stressful events (natural disaster, war, pandemic) during pregnancy, has been negatively associated with gestational age, weight and length of a child at birth. Furthermore maternal stress caused by psychosocial factors, such as single-parenting, food insecurity, or lack of physical activity, have been linked to lower birth weight [12].

Fetal programming is a concept described by sensation, receivement and reaction of the fetus to the intrauterine environment. Sensitive periods of fetal programming may lead to structural and functional changes in cells, tissues and organs, and therefore, long-term consequences [13]. Critical perinatal factors, involving: interactions between environment and genes, microbiota and microbiome changes, endocrine modulation, oxygen and nutrient accessibility from the placenta, duration of gestation and other environmental or genetic factors, have major influence on organogenesis and predisposition to diseases in the future [14]. The mechanisms of fetal programming in detail are currently not known, however the correlation between in utero stress and diseases such as atopic syndromes (e.g., asthma, eczema), metabolic complications, cardiovascular disorders, increased risk of infections and cancers, have been confirmed [15].

Excessive levels of glucocorticoids during pregnancy and programming of the hypothalamic-pituitary-adrenal (HPA) axis have significant impact in immune fetal development, which hypothetically may affect future offspring's health in oncology field, increasing the risk of lymphoma, hepatic and testicular cancer [16]. The impact of fetal programming is expressed especially in the last one—testicular cancer, which is initiated from primary germ cells or gonocytes, that go through improper differentiation during embryogenesis in pregnancy. Intrauterine concentration of estrogen, which increases circa 10 times in the female and 100 times in the male fetus, may affect invalid germ cells development. Moreover unequal maternal nutrition may also induce alternations in development of fetal cells with following risk of teratogenesis in metabolic, anthropometric and behavioral functions [17]. Another study suggested that fetal programming, by decreased size of placenta in association with large birth weight (LGA) and low placenta-to-birthweight ratio, may impact to increased risk of developing Wilms tumor in the offspring [18].

In conclusion the most common two factors, which influence on fetal programming are pregnancy nutrition and stress [13]. However other adverse intrauterine events, including maternal anxiety, depression, mental or metabolic diseases have their significant impact as well. Many studies reported that maternal anxiety or stress was linked to fetal tachycardia, sudden decreases or increases in fetal heart rate (FHR) and enhancement of fetal motor activity and breathing [19]. The most significant place of fetal programming is the human placenta, as a sensory and effector organ, which detects stress signals and activates the promoter region of the corticotropin-releasing hormone (CRH), the precursor for ACTH and β-endorphin. High levels of placental CRH are associated with preterm birth due to its endocrine, autocrine, and paracrine roles and also increasing in levels of the prostaglandins and estriol. Placental CRH during pregnancy is a significant mediator through placental receptors and vasodilatator in myometrium to potentiating mechanisms of contractions and relaxations [20].

The consequences of perinatal stress, as preterm birth and low birth weight, affects also on brain development and reduction in regional brain volume, including the prefrontal cortex, the premotor cortex, the medial temporal lobe, the lateral temporal cortex and the postcentral gyrus, which are associated with a variety of cognitive functions [19]. Thomason et al. research reported poorer connectivity between superior frontal and motor regions among neonates born preterm, which suggest impaired spontaneous motor activity in this group [21].

Maternal stress mechanism, by excess exposure of glucocorticoids, may change in utero environment in association of adverse cardio-metabolic and cardio-vascular outcomes in their offspring, such as obesity and overweight, insulin resistance, diabetes, hypertension, hyperglycemia and metabolic syndrome [22]. Van den Bergh et al. discovered that prenatal exposure of maternal stress increases the risk of unpleasant outcomes for offspring, including mental health disorders, poor cognitive functioning and behavior problems [23]. Sadman et al. found that psychobiological stress markers —especially in early pregnancy, leading to disrupted emotional regulation and impaired cognitive and motor functions during early childhood and decreased brain volume in areas associated with memory and learning [19]. Several studies suggest, that poor perinatal or fetal programming may contribute to increased risk of development psychological, neurological, or psychiatric disorders, such as schizophrenia, depression, anxiety, Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD) [24].

Maternal stress-involved endocrine alterations may also affect maternal cognitive brain functions and behavior. Pregnancy contributes to changes in structure and function of the brain in regions involving recognition, spatial memory and stress responsivity, which persist via lifespan [25]. Moreover Štěpáníková et al. research reported that prenatal, antenatal, or postnatal maternal stress may relapse increased risk of mental disorders, like depression among the mothers [26].

Another major concern in the modern obstetrics, that affect maternal and fetal health, is the increase of pregnancy-related cancer prevalence. The most frequent malignant tumor diagnosed during pregnancy is breast cancer, although the occurrence of other types, such as hematological, skin, or ovarian cancer, have been reported. Medical multidisciplinary interventions, especially personalized and integrated treatment, may prevent iatrogenic pregnancy complications, such as impaired fetal growth or preterm birth. Nanotechnology, as the reaction in the structures on a molecular level, improves biocompatibility, pharmacokinetics, targeting of the tumor and reduces systemic toxicity or drug resistance. Nanomedicine, as a field of nanotechnology, offers the opportunity to safe and effective application of antiblastic agents during the pregnancy. However, fetal exposure on nanoformulation, by transplacental transport is still an issue of the debate in gynecological and obstetric profession.

Stress is a common problem among pregnant women. United States data from the Centers for Disease—Control Pregnancy Risk Assessment Monitoring showed that nearly 75% of postpartum women reported at least one major stressful event in the year prior to the birth of their child [27]. It has been indicated that 1 in 5 pregnant women will have an anxiety disorder during pregnancy, while between 10 and 14% of pregnant women fulfill the criteria for a diagnosis of

major depression [28]. Pregnancy itself is associated with increased levels of experienced stress for pregnant women and the occurrence of psychological distress, anxiety disorders and depression, while the pandemic of coronavirus disease 2019 (COVID-19) has become an additional external stressor intensifying experienced stress and anxiety, additionally causing sleep disturbances in pregnant women [29][30][31]. As the level of experienced stress increases, an increase in cortisol release by the adrenal cortex is observed as a result of activation of the hypothalamic-pituitary-adrenal axis (HPA axis) [28][30][31][32]. In the third trimester of pregnancy, cortisol levels increase almost threefold, but as pregnancy progresses, hypothalamic production of corticotropic hormone (CRH) decreases, so that the HPA axis response to eustress and distress is suppressed [30] In addition, the fetus is protected from high maternal plasma glucocorticosteroid levels by the activity of the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which converts active cortisol into metabolically inactive cortisone [30][32].

The HPA axis can be overactivated by external stress-inducing factors. The consequence is an excessive release of endogenous cortisol and an increase of its concentration in the placenta, the process itself is regulated by metalloproteinase-1 (MMP-1), -2 (MMP-2), -3 (MMP-3) and -9 (MMP-9) [32]. A case-control study by Duran-Chávez et al. based on 129 cases of preterm birth proved that elevated levels of MMP-9 and decreased levels of MMP-2 are positively associated with the occurrence of preterm birth [33]. There is also an increase in the release of the pro-inflammatory cytokines IL-1β, IL-6 and tumor necrosis factor α (TNF-α) suppressing the response of the maternal immune system, which may increase the risk of preterm labor [31][34]. Another mechanism responsible for this phenomenon is also the constriction of placental blood vessels under the influence of cortisol, increasing blood pressure and the formation of pro-inflammatory changes responsible for the ischemia of the uterine muscle and, consequently, the occurrence of preterm labor, as well as intrauterine fetal growth restriction [35]. Overactivity of the HPA axis is also responsible for the occurrence of depression in pregnant women and an increase in the level of already experienced stress [32]. Pregnant women diagnosed with severe depression and anxiety have higher levels of the pro-inflammatory cytokines IL-6, IL-2, IL-9 and IL-17A [28]. Elevated levels of cytokines such as IL-2, IL-6 and IL-17 are also present in the cytokine storm in the course of COVID-19 [36], one of the obstetric consequences of which is an increased risk of preterm labor [37]. Inflammatory cytokines and metalloproteinases such as MMP-1, MMP-2 and MMP-9 are responsible for the cervical ripening, at the same time, increasing the risk of preterm labor [38]. With increased levels of placental cortisol, abnormalities in placental permeability and a decrease in 11β-HSD2 activity, which is a biological marker of spontaneous abortion and preterm labor, are observed, as increased levels of MMP-9 in placental villi and tissue inhibitors of matrix metalloproteinases 2 (TIMP-2) [32]. Even a small decrease in 11β-HSD2 activity can significantly increase fetal exposure to glucocorticosteroids due to the high concentration of these in maternal plasma compared to the concentration in fetal plasma. The result is a decrease in mean birth weight [30]. Studies have shown that vitamin D supplementation may lower endogenous cortisol levels and cortisol:cortisone ratio [39]. This fact could be used to investigate how to prevent the consequences of hypercortisolemia in pregnant women.

Also remarkable is the fact that chronic and repeated acute stressors through modulation of the HPA axis can affect the epigenome and transcriptome, consequently causing changes related to receptors for glucocorticosteroids [28].

Maternal stress as a risk factor for preterm birth remains a major cause of maternal morbidity and mortality worldwide [31]. Beyond the increased risk of preterm delivery, prenatal stress also increases the risk of gestational diabetes and pre-eclampsia [40]. A study by Garcia-Flores et al. in a mouse model showed that intergenerational maternal stress progressively shortens the length of gestation, with the rate of preterm births in the first and second generations at 13% and 11.1%, respectively [31]. A case-control study by Lilliecreutz et al. confirmed the relationship between the occurrence of stress and shortened pregnancy duration in humans, where among pregnant women who experienced stress, 54% of them gave birth prematurely with stress as an attributed risk factor [41]. Besides stress factors directly affecting the pregnant woman, the remaining question is whether common stressors with limited impact on daily life are also a risk factor for preterm birth. An analysis by Freedman et al. aimed to show whether the assassination of John F. Kennedy influenced the occurrence of adverse pregnancy outcomes in women between 1959 and 1965. For this purpose, they analyzed data from the Collaborative Perinatal Project and showed that exposure to the mentioned factor in the first trimester of pregnancy was associated with preterm delivery (hazard ratio (HR): 1.17; 95% CI: 1.05, 1.31). Exposure in the third trimester of pregnancy was associated with an increased risk of fetal acute inflammation in the placenta (odds ratio (OR): 1.34, 95% CI: 1.05, 1.71) [42]. The effect of prenatal stress on the development of placental pathologies, which can eventually lead to spontaneous miscarriage, has also been observed. In a study by Marinescu et al. placentas of patients with high levels of social stress who experienced spontaneous miscarriage were examined, and the most common conditions included regular shape and necrotic villi, decidua with large areas of necrosis, acute inflammation and effusion areas correlated with increase in proinflammatory factors, immune deficiency and infections, hyaline type fibrosis, intervillous and deciduous intense hemorrhage [32].

Due to the adverse effects of prenatal stress on pregnancy and perinatal outcomes, it is important to identify and mitigate pregnant women's exposure to stress early in order to prevent premature births. For this purpose, routine prenatal care should include screening for behavioral health problems and potential intervention [40]. Both untreated depressive and anxiety disorders and in utero fetal exposure to selective serotonin reuptake inhibitors (SSRIs) are associated with an increased risk of premature birth [41]. The use of benzodiazepines in combination with SSRIs is associated with an increased risk of adverse behavioral effects in infants [43]. That is why recently more and more hope has been associated with non-pharmacological methods of reducing stress during pregnancy. Methods with proven effects include meditation, biofeedback, yoga and expressive writing [28]. Data on yoga indicate that it improves quality of life by reducing stress, anxiety and sleep disturbances during pregnancy, and, in the absence of outdoor physical activity, may be effective in reducing the chance of pre-diabetes, obesity and metabolic syndrome [44]. Advantages of non-pharmacological interventions include the fact that those interventions are affordable, widely available and can all be applied without leaving home, which is particularly important in the context of the COVID-19 pandemic [28]. Used in combination with pharmacological treatment, it can be most effective for reducing perceived anxiety and stress levels in pregnant women [28].

Both the incidence of COVID-19 in pregnant women and the impact of this infection on pregnancy outcomes are still being investigated. Existing research suggests that SARS-CoV-2 infection may increase the risk of preterm birth and numerous pregnancy complications. There have also been reports of the potential placental transport of the virus and maternal-fetal transmission of the infection; however, the risk appears to be relatively low, and the number of reports confirming intrauterine transmission of the coronavirus is limited [3][4][5][45][46][47][48]. On the other hand, the presence of the virus in the mother's body is associated with vascular damage and complications such as hypercoagulability and deficient vascular perfusion [49]. Consequently, damage to the placenta may occur, which may facilitate vertical transmission [50]. Histologically confirmed changes in placental structure have appeared in symptomatic and asymptomatic women infected with SARS-CoV-2. To date, no adverse effects of placental damage in the course of virus infection have been observed for the child, although features of vascular malperfusion could be found in both the maternal and fetal parts of the placenta [46]. Reports of placental infection contributing to symptoms of fetal distress or stillbirth were much more common in the literature [45]. When comparing COVID-19 to other viral infections that can be acquired during pregnancy, such as CMV, Zika virus and rubella, there was also no characteristic congenital syndrome following prenatal exposure to SARS-CoV-2 [45].

Conducted studies indicate that COVID-19 infection increases the risk of preterm birth compared to women uninfected with the SARS-CoV-2 virus [51]. The authors of one study conducted on a large population of pregnant women in the United States observed that COVID-19 increased the risk of preterm birth by 60%. Taking into account the data collected from different countries, the rate of premature birth varies significantly between them and amounts to 14.3% to 61.2%. Despite the great diversity, there is a consensus that COVID-19 infection has an impact on the risk of preterm delivery. This may be attributed to the inflammatory state resulting from the infection, which leads to the initiation of premature uterine contractions. from one of the smaller studies there are reports of one type of immune cell. They express ACE2, which has the ability to cross the placenta, causing a more serious course of infection, infection of the placenta and premature birth [2][4][52]. Additionally, one study showed that women after 27 weeks of pregnancy were most often infected [53].

Coronavirus infection can adversely affect the overall health status of pregnant women, manifesting in various symptoms such as fever, cough, muscle aches, gastrointestinal disturbances (diarrhea and nausea), and respiratory difficulties. Pregnant women are also more susceptible to developing pneumonia and acute respiratory distress syndrome, which carries the risk of severe oxygen deprivation for both the mother and the fetus. Pregnant women with COVID-19 are compromised and less able to cope with the disease in general, especially when it comes to the effects of delayed diagnosis and overdue referral to treatment, when compared to non-pregnant women. The main reason is that advanced pregnancy brings about physiological and metabolic changes that have an impact on the immune system, cardiovascular function and, essential in this context, respiratory system [54]. Because the proper functioning of placenta depends on the flow of adequately oxygenated blood, the fetoplacental system, and maternal oxygen saturation during pregnancy, this virus frequently causes severe hypoxemia, which changes how oxygen is delivered to the placenta. Hypoxia and ischemia can be distinguished within the placenta through the increment in syncytial knots, while fetal hypoxia can be recognized within the circulation through the increment in erythroblasts and nuclear debris. Because the demand for oxygen rises dramatically during pregnancy, this change in blood flow and oxygenation caused by COVID-19 is extremely important because, with this compounding impact, there will inevitably be dysregulation in the oxygen supply to the placenta, resulting resulting in an increase in oxidative stress markers, which are associated with fetal health issues [55]. Meyer et al. research presented that when compared to women who were not hypoxic, women who required intubation or respiratory support due to COVID-19-related hypoxia more frequently demonstrated placental histology that showed villous

trophoblast necrosis [56]. Hypoxia and ischemia accelerate fibrosis in the villous stroma [57]. The conclusion which was reached in one of the most recent reviews describing changes in the placenta of pregnant women during the three years of the pandemic is that following viral infection, maternal hypoxia can result in reduced placental blood flow and maternal vascular malperfusion, which can lead to villous infarction, hypoplasia of the distal villi, and arteriopathy in the decidua. However, confirmation of the impact of the changes described will require long-term observational programs [58].

Severe COVID-19 infection can also serve as an indication for the premature termination of pregnancy for the health of the mother and the fetus, thus warranting iatrogenic preterm delivery [6][7][8][9][10]. Van den Bergh et al. in an international cohort study discovered that maternal and neonatal complications were significantly more common in women diagnosed with COVID-19. Most notably, there was an increased number of deliveries by caesarean section and such as hypertensive disorders of pregnancy and fetal distress. Also preterm delivery rates and poorer newborn weight, length, and head circumference at birth were associated with the diagnosis of maternal viral infection [49].

Considering the mental health of pregnant women, depression is still at the first place among all mental illnesses in this population group [59]. Stress and difficulty brought on by the pandemic may cause or exacerbate typical prenatal mental health issues, such as depressive symptoms, which have been reported to have a deleterious impact on maternal-child health. In research made by King et al. they discovered that compared to women who were pregnant before the epidemic, pregnant women during the pandemic were nearly twice as likely to have probable depression [60]. Additionally, Hessami et al.'s research indicates that stress levels remained elevated during the COVID-19 pandemic while symptoms of depression and anxiety increased from the early to mid-pregnancy period [61]. During COVID-19, stress levels remained high as signs of despair and anxiety grew from the beginning to the middle of pregnancy [62]. Preliminary research suggests that increased maternal stress and depressive mood symptoms correlate with impaired fetal brain development [63].

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