CHAPTER 17

COVID-19 AND PREGNANCY

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INTRODUCTION

Covid-19 disease is caused by SARS-CoV-2, an enveloped, non-segmented and single-stranded RNA virus. SARS-CoV-2 virus is included in the β subgroup of the coronavirus family. Covid-19 disease caused by the SARS-CoV-2 virus was declared as a pandemic by WHO on March 11, 2020. The virus is transmitted by droplets and the first entry point is the epithelial cells in the mucous membranes of the respiratory system such as the mouth and nose. Although there are studies showing that Covid-19 infection increases the risk of preterm birth in pregnant women, low birth weight, and postnatal intensive care needs of newborns, clear information about pregnancy loss, preeclampsia and vertical transition has not been reported definitively in the studies so far. Although it has been shown in previous studies that viral infection during pregnancy causes disorders such as fetal malformation and psychiatric disorder, there is no clear information so far that Covid-19 infection increases fetal malformations and long-term psychiatric and neurological disorders in the newborn.

Even though it has been reported that immunological, physiological and anatomical changes actually reduce the protection against viral infections during pregnancy, pregnant women experience Covid-19 infections with a

frequency and severity similar to other individuals due to unknown mechanisms. However, there is no clear and precise information on this matter yet. Covid-19 infection is seen in various spectra during pregnancy. They are either asymptomatic or can undergo a severe and fatal infection. Covid-19 infection can cause both morbidity and mortality and may lead to obstetric complications such as preterm birth and low birth weight during pregnancy. The transfer of the newborn to intensive care and the disadvantages of prematurity in cases such as preterm delivery and low birth weight contribute to the morbidity and mortality of the fetus. However, the role of Covid-19 infection in obstetric complications such as pregnancy loss and preeclampsia is not clearly known.

EPIDEMIOLOGY

Although the exact number of Covid-19 cases in pregnancy is not known, there are very few studies on this subject. In a study in the USA, the frequency in pregnant women admitted to the hospital was found to be 15.4%. In another study, the frequency of Covid-19 in pregnant women was reported as 12.2%. In a study evaluating the mortality rates during pregnancy, no change was observed in the mortality rate of pregnant and non-pregnant women and the mortality rate was found to be 0.2%.

PHYSIOLOGICAL CHANGES OBSERVED DURING PREGNANCY

Changes occur in all systems during pregnancy, especially physiological, immunological and anatomical changes. Pregnant women are considered to be more susceptible to viral infections because of these changes compared to other individuals in the society, because pregnant women, compared to other individuals, have been observed more affected by diseases caused by viruses from the same virus family including H1N1, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). However, there is no study in the literature showing that pregnant women are affected more than other individuals due to some unclear factors. No significant clinical difference was observed between pregnant women with Covid-19 infection and pregnant women without Covid-19 infection. The following major system changes are important for Covid-19 infection during pregnancy.

Immunological Change

Immunological mechanisms vary according to trimesters during pregnancy and accordingly cause changes in pro-inflammatory and anti-inflammatory responses. Proinflammatory process is dominant in the first trimester to allow blastocyst implantation and to prepare for delivery in the third trimester while anti-inflammatory response is dominant in the second trimester to ensure fetal growth. Therefore, during the first and third trimesters of pregnancy, the body is more vulnerable to viral infections. It can be considered that Covid-19 infection may progress more severe during these periods. Proinflammatory immune response in pregnant women with Covid-19 infection has been reported to be similar to non-pregnant patients with Covid-19 infection. TH1/TH2 balance generally tends to shift towards TH2 during pregnancy. A shift towards TH2 leads to a decrease in TH1 cellular immunity. Due to this decrease, the body cannot react adequately against microorganisms that have to live inside cells, such as viruses, and becomes more vulnerable to viral infections. The balance of regulator T (Treg)/TH17 cells ratio is important for embryonic implantation and a healthy pregnancy. Decreased Treg levels and increased TH17 levels are considered to be associated with miscarriage, pre-eclampsia, and preterm delivery during pregnancy. Studies have shown a decrease in Treg cells and an increase in TH17 cells in Covid-19 infection. The increased number of TH17 cells and their activation is blamed for the release of many proinflammatory cytokines into the body. This situation, called cytokine storm, is seen as an important cause of damage in maternal and fetal tissues.

The Covid-19 infection enters the body through droplets from the respiratory system. The SARS-CoV-2 virus enters the mucosal cell by binding to the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRSS2) receptor, which are mainly found in the respiratory tract and then in the intestinal mucosa, kidneys, endothelial cells, fetomaternal junction and some fetal tissues. Stimulation of the ACE2 receptor causes an increase in angiotensin 2 (AT2) release and a decrease in angiotensin 1-7 (AT1-7) release. After AT2 binds to the angiotensin 1 receptor (AT1R), the nuclear factor beta pathway is activated and, thus, causes an abnormal increase in IL-6, IL-1β, IL-10, TNF-α cytokines. The reduction of AT1-7 also causes the inflammatory response to decrease. Inflammatory cytokines such as IL-1 β, IL-2, IL-6, IL-7, IL-8, soluble TNF receptor1(sTNFR1), TNF-α, procalcitonin, C-reactive protein (CRP), ferritin, D-dimer, GM-CSF, IL-17, macrophage inhibitory factor 1-α (MIF1-α) have been reported to increase in Covid-19

patients. The number of Natural Killer (NK), CD4 and CD8 T cells and lymphocytes are decreasing in both Covid-19 infection and pregnancy. This leads to susceptibility to infection and increases the risk of transmission during pregnancy. It has been shown that IL-1β, IL-6, IL-8 and sTNFR1 are closely related to the severity of Covid-19 disease. The levels of CRP, IL-6, procalcitonin, ferritin and D-dimer have been found to be increased in proportion to the severity of Covid-19 infection. All of these immunological changes point to increased sensitivity to Covid-19 infection during pregnancy.

Covid-19 and Changes in Respiratory System During Pregnancy

Due to the increased estrogen and progesterone hormone levels during pregnancy, edema, hyperemia, increased mucus secretions and a decrease in mucus clearance capacity occur in the respiratory tract mucosa. Increasing estrogen level during pregnancy leads to an increase in the amount of hyaluronic acid in the mucosa and causes hydration and edema in the mucosal tissues. During pregnancy, the capacity of the lungs also changes due to the upward elevation of the diaphragm secondary to the expansion of the uterus. Functional residual capacity, decrease in expiratory reserve volume and residual volume, increase in inspiratory capacity and tidal volume are the reasons for these changes. Total lung capacity, lung compliance and first second expiratory volume do not change. During pregnancy, the need for oxygen also increases and the amount of oxygen consumed is 10% more than normal. This causes shortness of breath and dyspnea during pregnancy. Shortness of breath and dyspnea cause compensatory respiratory alkalosis secondary to frequent breathing of the mother. In addition, as the capacity of the lungs of pregnant women to clear mucus is reduced, this leads to lower respiratory tract infections. Due to all these changes in the respiratory system during pregnancy, it is predicted that Covid-19 infection may cause more serious clinical pictures.

Coagulation Changes and Endothelial Damage During Pregnancy

Thrombin production increases during pregnancy due to intravascular inflammation and this leads to a tendency to coagulation. Blood volume, cardiac output, stroke volume and heart rate increase and vascular resistance decrease during pregnancy. In addition to Covid-19 being a disease that mainly affects the respiratory tract, it has been reported that the SARS-CoV-2 virus binds to the ACE2 receptor in platelets and endothelium, causing the release of coagu-

lation factors, the secretion of inflammatory cytokines and the formation of leukocyte-platelet aggregates and, thus, thrombotic complications. Complications such as thrombotic disorders, sepsis and disseminated intravascular coagulation (DIC) have been reported in patients with severe Covid-19 infection. In large-scale studies, it has been shown that thrombocytopenia is concomitant to 18.8% to 36.2% of severe Covid-19 patients. Therefore, pregnant women should be followed carefully in terms of thrombotic complications and appropriate treatments should be planned. During pregnancy, due to the changes in the cardiovascular system, platelets and endothelial cells, the cytokine storm caused by binding of SARS-CoV-2 to ACE2 receptors in the endothelial cells in platelets tends to thrombosis and increases the incidence of clinical pictures such as thrombotic disorders (myocardial infarction, cerebrovascular occlusion, etc.), sepsis, DIC, multiple organ failure.

CLINICAL COURSE OF COVID-19 IN PREGNANCY

The clinical course of Covid-19 infection during pregnancy is similar to the clinical course in the community. It causes a wide range of clinical pictures from asymptomatic situations to situations requiring intensive care. During pregnancy, Covid-19 cause clinical symptoms such as fever and cough mainly, and myalgia, fatigue, dyspnea, sore throat, chest pain, weakness, headache, diarrhea, impaired taste and smell, nausea, vomiting, nasal congestion, muscle and joint pain, intrapartum and postpartum fever.

Covid-19 exhibits a clinical course in 5 subgroups over a wide range. These 5 subgroups include asymptomatic cases, mild and moderate cases, severe cases, critical cases and mortal cases. Symptomatic cases of Covid-19 disease are evaluated in 3 stages. Patients included in stage 1 exhibit flu-like symptoms. Stage 2 is divided into 2 subgroups as 2a and 2b and patients in stage 2a show signs of viral pneumonia, tachypnea, cough and fever while stage 2b includes hypoxia additionally. Patients with cytokine storm syndrome in which cytokines are released excessively, lung damage and multi-organ failure syndrome are included in stage 3. The presence of comorbid diseases such as diabetes, hypertension, chronic obstructive pulmonary disease and obesity in Covid-19 disease causes the clinical picture to become more serious. Tendency to gestational hypertension, gestational diabetes mellitus, thrombosis, preeclampsia, eclampsia, hemolysis, HELLP syndrome, asthma, hypothyroidism and obesity occurs, which can increase Covid-19 morbidity and mortality. The maternal and fetal effects of Covid-19 infection in pregnancy have not been

clearly understood yet. However, due to the fact that the infections caused by viruses such as SARS, MERS, H1N1, which are included in the coronavirus family, have more severe course during pregnancy, it has been considered that Covid-19 disease will also lead to more severe infections in pregnant women in the days when the first cases were observed. In the studies so far, it has not been clearly and definitively demonstrated that Covid-19 causes serious maternal and fetal morbidity and mortality in pregnancy as much as the disease caused by previous coronaviruses. Since the first case was heard, clinical courses similar to other individuals in the society have been observed in pregnant women. Although pregnant women with Covid-19 have been observed to have clinical courses similar with non-pregnant women, it has been observed that Covid-19 was more morbid in the presence of elderly maternal age, black race and comorbid conditions, according to some other studies. In studies comparing pregnant women with Covid-19 infection and pregnant women without Covid-19 infection, no significant difference has been observed in terms of mortality in pregnant women. Maternal mortality and the need for more intensive care have been reported in some studies. No clear and definite conclusion has been reached in the studies so far on this subject.

OBSTETRIC COMPLICATIONS IN PREGNANT WOMEN WITH COVID-19

There are still situations that are not fully clarified in the obstetric results of Covid-19. When the obstetric complications of Covid-19 are evaluated, no finding showing that it increases the complications in the first trimester has been detected until now. When the pregnant women with Covid-19 infection and those without Covid-19 infection have been compared in the first trimester, it has been observed that the pregnancy loss rates did not change. In a recent systemic study, it has been observed that pregnant women with Covid-19 infection increased the incidence of preterm delivery by 63.8%, low birth weight incidence by 42.8% and fetal distress frequency by 61.6%. In another study, it has been noted that pregnant women with SARS-CoV-2 infection had an increased possibility of preterm delivery and low birth weight, but the reason for this has not been clearly understood. In a study investigating pregnancy loss rates in pregnant women with SARS-CoV-2 infection, it has been found that pregnancy loss rate in pregnant women with Covid-19 infection was 2%. Pregnant women with positive Covid-19 and those without Covid-19

infection have been compared in terms of pregnancy loss and similar pregnancy losses have been found in another study. It has been found that the rates of Cesarean section increased in pregnant women with Covid-19 infection. Applications of the Cesarean section in pregnant women for reasons other than obstetric indications such as respiratory problems, risk of transmission and worsening of the clinical course that may occur in pregnant women with Covid-19 infection are the reason of this. However, Cesarean section should be decided according to the clinical condition of the mother and obstetric reasons. Covid-19 infection with no complication alone should not be considered an indication for Cesarean section.

Preterm Delivery

There are clues in systematic reviews that preterm delivery is increasing in pregnant women with Covid-19 infection. However, some studies have observed that preterm delivery does not increase. Preterm delivery can be induced or occur spontaneously in pregnant women with severe Covid-19 infection. There is no clear information in the literature about why preterm delivery occurs and why it is increasing in pregnant women with Covid-19 infection. In general, it can be predicted that preterm delivery may increase in pregnant women with Covid-19 infection. It is a known fact that preterm delivery increases morbidity and mortality in the newborn in the short, medium and long term. The likelihood of respiratory distress, respiratory distress syndrome, retinopathy of prematurity, bronchopulmonary dysplasia, sepsis, metabolic diseases, necrotizing enterocolitis, intraventricular hemorrhage and periventricular leukomalacia increases in premature babies. It should be kept in mind that preterm delivery may also lead to long-term complications such as cerebral palsy, learning difficulties, vision and hearing abnormalities, psychological disorders, growth disorders and chronic diseases. Therefore, care should be taken in terms of preterm delivery in pregnant women with Covid-19 infection.

Low Birth Weight

Low birth weight indicates births below 2500 grams. Low birth weight usually occurs due to intrauterine growth retardation and preterm delivery. Since preterm delivery and intrauterine growth retardation are more common in pregnant women with Covid-19 infection, the possibility of low birth weight in pregnant women exposed to Covid-19 infection also increases. Most of the

various studies on this subject report that low birth weight is more common in pregnant women with Covid-19 infection, while some studies state that it does not increase. Comorbid conditions such as high neonatal mortality, neurological disorders, psychological disorders, cardiovascular diseases and diabetes mellitus may develop due to low birth weight.

As a result, low birth weight is observed more frequently in pregnant women with Covid-19 infection compared to pregnant women without Covid-19 infection, and this increases neonatal morbidity and mortality. Pregnant women with Covid-19 infection need careful follow-up in terms of low birth weight.

Pregnancy Loss

There is no clear information on whether viral infections cause pregnancy losses and the mechanism that causes pregnancy loss is not clearly understood. It has been suggested that pregnancy loss may occur as a result of direct effect or as a result of the immunological response that occurs after the affection of trophoblasts and placenta by viral infections. The balance between TH1 and TH2 is crucial for a successful pregnancy and implantation. The change in Treg/TH17 ratio is also important for a successful pregnancy and implantation. It has been suggested that the increased tendency towards TH2 in pregnant women with Covid-19 infection may be a reason for pregnancy loss. It has been reported in most studies that no significant difference has been seen when pregnant women with and without Covid-19 infection were compared in terms of pregnancy loss. In contrast, some rare studies have argued that the rate of pregnancy loss and miscarriage increases in women with Covid-19 infection. As a result, although it has been considered that the increase in cytokines and inflammation that will occur due to the maternal immune response can theoretically lead to pregnancy loss because of detecting SARS-CoV-2 virus in placental and fetal cells in Covid-19 infection, most studies did not report a significant difference in terms of pregnancy loss and miscarriage.

Vertical Transmission

Since the presence of ACE2 receptors in placental and fetal tissues is known, it has been investigated in many studies whether Covid-19 infection is transmitted to the fetus vertically. In some studies, researchers observed that although the SARS-CoV-2 virus has been detected in placental villous stroma

and placental membranes, the possibility of vertical transmission has been found to be low. In some studies investigating vertical transmission, researchers detected the presence of the SARS-CoV-2 virus in the spinal cord blood, placental tissues and rectal swab samples of newborns. To date, there is no study on whether the newborn leaves a neurological sequel in the long term in maternal infections caused by coronaviruses. In maternal infections caused by other viruses, it has been found that neurological sequels develop in the baby in the long term, although the viruses have not passed the placenta and transmitted to the fetus. Therefore, there is concern that the babies of pregnant women with Covid-19 infection may develop neurological sequels in the long term. A clear reason for the mechanisms that cause these neurological disorders has not been found yet. These mechanisms are thought to be caused by direct tissue damage in the fetal nervous system by viral infection during pregnancy and indirectly due to the released cytokines due to fetal immune response. There are studies showing that viral infections that do not pass through the placenta cause brain damage in the fetus. It was stated in these studies that due increased amounts of cytokines, neurotransmitters and excitotoxic metabolites secreted from the placenta infected by the virus, there may be damage to the nerve cells of the fetus. Therefore, pregnant women with Covid-19 infection should be followed up carefully after delivery in terms of neurological sequels that may occur in their babies.

Psychological Disorders

In previous studies, it has been shown that some psychological disorders can be acquired by viral infection during pregnancy. It has been observed that disorders such as schizophrenia and psychotic disorders can occur after maternal viral infections. Although the cause of these psychological disorders is not known exactly, it has been argued that they may occur following changes in local gene expression of the placental and maternal viral transmission, changes in placental serotonin release, and changes in the release of Dopamine and Gamma Aminobutyric Acid (GABA) in fetal brain cells. Increased levels of TNFα, IL-8 and CRP in the maternal blood have been found to increase the risk of schizophrenia and psychotic disorder. Therefore, it should be kept in mind that in pregnancies infected with SARS-CoV-2 virus, cytokines, hormones and neurotransmitters, which are secreted after placental and possible fetal transmission and whose secretion amounts change, cause changes in the baby's brain and these may also lead to conditions such as schizophrenia and psychotic disorders.

It has also been shown that the risk of autism spectrum disorder is increased in babies of mothers with viral infections. Increased levels of serum IL-17a and IL-6 have been reported in mothers of babies with autism spectrum disorders. Since serum IL-17a and IL-6 levels are increased also in pregnant women with Covid-19 infection, they should be followed up carefully for the presence of autism spectrum disorder in their babies.

COVID-19 DIAGNOSIS DURING PREGNANCY

The diagnosis is made after the Real-Time Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test of the smears of the symptomatic and asymptomatic pregnant women suspected of having SARS-Cov-2 infection taken from the nasal, nasopharyngeal or oral mucosa. For differential diagnosis, P-A lung radiography, computed tomography of Thorax, Thorax US and hematological parameters are evaluated to support the definitive diagnosis. In Covid-19 infection, laboratory findings such as lymphopenia, leukopenia, leukocytosis, thrombocytopenia, increased erythrocyte sedimentation rate, anemia, and increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatinine kinase (CK), increased levels of bilirubin, CRP and ferritin levels. In addition, increased respiratory rate, decreased oxygen saturation and decreased PaO2/FiO2 ratio can be seen in the later stages of the disease. Besides, P-A lung radiography, computed tomography of Thorax, Thorax US can be performed for visualization of pulmonary lesions to support the diagnosis. However, computed tomography and radiographic images do not present a specific appearance and diffuse hyperechoic areas in the form of viral pneumonias involving the lung, ground glass appearance and thickened pleural bands and pleural effusion can be seen.

DELIVERY METHOD

There is no clear information in terms of delivery method for Covid-19-positive pregnant women. It has been reported that delivery method should be determined according to the clinical condition of the pregnant woman. Delivery time can be adjusted according to the severity of Covid-19 infection. It has been reported that normal delivery time should be expected in those with mild Covid-19 infection and delivery can be done at week 32 in those with severe Covid-19 infection. While planning the delivery method, it is

recommended to prefer Cesarean delivery according to obstetric indications, and if there is no indication, vaginal delivery should be preferred.

ADMINISTRATION OF ANTENATAL STEROID IN PREGNANT WOMEN WITH COVID-19 INFECTION

It has been stated that the administration of ACOG antenatal steroid will not change the clinical course of Covid-19 in pregnant women with positive Covid-19 between weeks 24 to 36 in the presence of routine indications, therefore it would be more beneficial to use it to reduce fetal morbidity. In order to prevent the increase in morbidity and mortality that may occur in conditions such as preterm delivery and low birth weight, corticosteroids should be administered based on the clinical condition of pregnant women with the risk of preterm delivery.

COVID-19 VACCINATION IN PREGNANT WOMEN

There is no clear information about vaccination to prevent pregnant women from Covid-19 infection. WHO does not recommend vaccination of pregnant women since there is no study in terms of side effects and fetal effects of vaccine in pregnant women. Although there is no clear information on the vaccination of pregnant women who work or are in risky positions, such as health care professionals, it has been reported that vaccination should depend on the common opinion of the patient and the physician.

BREAST MILK AND BREASTFEEDING

The nutrients in breast milk have many effects on growth factors, immunological factors, and on the growth of the baby and immune and neurocognitive development. Immunoglobulins in breast milk protect the baby against viral infections in the neonatal period. In pregnant women with Covid-19 infection, it has not been clearly shown whether a viral infection is transmitted to the baby through breast milk. However, the mother should be warned to take the necessary precautions during breastfeeding and breastfeeding should be encouraged, as it may be possible for the mother to infect her baby with the SARS-CoV-2 virus through droplets. Even if pregnant women with Covid-19

infection are taking medication, the mother should be encouraged to breast-feed the baby, as the drugs penetrate too little into the milk.

CONCLUSION

It is known that 66% to 88% of pregnant women with Covid-19 infection are asymptomatic. It should be kept in mind that pregnant women, even if they are asymptomatic, can be infected with the SARS-CoV-2 virus and infect those around. Therefore, appropriate screening programs should be carried out in pregnant women who admitted to the clinic. Pregnant women with Covid-19 infection should be followed up carefully in terms of conditions such as preterm delivery and low birth weight. Pregnant women with Covid-19 infection should be followed up in terms of psychological and neurological complications that may occur in their babies in the medium and long term.

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