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Review Article

The Overall Consequence of Antiviral Drugs Given to Pregnant Women with COVID-19

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ABSTRACT

During pregnancy, the anatomical structure of the respiratory system changes, and the virus transmitted by droplets and aerosols are more easily inhaled and difficult to remove by pregnant women. Women are generally more susceptible to various pregnancy-related complications and respiratory pathogens, increasing the risk of developing adverse pregnancy and neonatal outcomes. Anecdotal evidence suggests that pregnant women do not appear to differ from the general population in terms of disease transmission, and to date, there is no evidence of vertical transmission from mother to fetus. However, in another study, it is known that members of the coronavirus family are responsible for serious complications such as miscarriage, fetal growth restriction, and congenital anomalies during pregnancy. To date, only a few studies have reported relatively higher rates of adverse birth outcomes in women affected by SARS-CoV-2 infection in late pregnancy. This literature review presents the use of drugs used for the treatment of COVID-19 disease in pregnancy and pregnancy outcomes. It is also aimed to examine the effective control and management of SARS CoV-2 infection in the pregnancy, delivery, and postpartum period in line with the existing literature and guide health personals. Large-scale epidemiological studies are needed to evaluate the course of the infection during pregnancy and the effects of the drugs used on pregnancy and fetus.

Keywords: SARS-CoV-2; COVID-19; Antiviral drugs; Virus

INTRODUCTION

Coronaviruses are a large family of viruses. Some cause a variety of respiratory diseases in humans, ranging from mild colds to more severe conditions such as Severe Acute Respiratory Syndrome (SARS). This type of coronavirus is a new and previously undefined branch of the coronavirus family. A new type of coronavirus that affects the entire world and leads to an outbreak has been named SARS-CoV-2 by the World Health Organization (WHO). It is understood that, due to changes in the immune system during pregnancy, pregnant women may be more affected by respiratory infections. Conditions such as diabetes, inactivity, high blood pressure, cause more serious COVID-19 disease in pregnancy. Pregnancy is more likely to require intensive care than women who are not pregnant when they have a serious illness. For this cause, pregnant women can often be in a dangerous category concerning COVID-19 disease. Pregnant women exhibiting symptoms should have a test and, according to the outcome, adhere to the required isolation. There is no evidence that complications such as miscarriage and stillbirth are more common in women who experience corona during pregnancy. In pregnant women with COVID-19 disease, several studies have indicated an increased risk of premature birth. These babies will need to stay in neonatal intensive care as different complications may occur in babies born early (prematurely) [1].

With the spread of coronavirus, it is discussed how dangerous SARS-CoV- 2 infection is in pregnancy and how efficient the treatments will be. In this case, it has begun to investigate what effects the drugs used on the baby and pregnancy. Medicines are classified before being given to pregnant women and their doses are prepared individually. Antivirals and combinations, angiotensin receptor blockers, antimalarials, antihistamines,

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hormones, and antipyretics are among but are not limited to, different treatment choices. Specific medicines for COVID-19 disease have not been identified at this time when it comes to treatment, and taking old medications for new use in the treatment of COVID-19 disease has become an urgent strategy for the pandemic. In particular, drugs such as Chloroquine, Metformin, Statins, Lopinavir/Ritonavir, Glycyrrhizic acid, and Nanoparticle-Mediated Drug Delivery (NMDD) demonstrate superior maternal and fetal protection for pregnant women with SARS CoV-2 are worth considering. Nowadays, people only have to strive to select existing drugs based on their past antiviral experience and also to develop vaccines or direct-acting antiviral drugs or host-directed treatments. However, due to the presence of the fetus, many antiviral drugs are prohibited during pregnancy due to their proven teratogenicity. For example, Ribavirin is listed in the Federal Drug Administration (FDA) as a class X drug, but studies indicate that it is prohibited during pregnancy. Ribavirin has a drug safety rating of X in pregnancy by the FDA (Federal Drug Administration), indicating that its use is contraindicated for pregnancy. Far fewer clinical drug trials are conducted during pregnancy than in any other healthcare area. However, a complete risk assessment of drug safety in pregnancy and informing women exposed to the drug can both reduce pregnancy anxiety and prevent unnecessary pregnancy terminations. To treat pregnancy combined with COVID-19 disease as quickly, effectively, and safely as possible, available evidence and literature. Some of the drugs used to treat SARS CoV-2 infection are listed [2].

LITERATURE REVIEW

Remdesivir in pregnancy

Remdesivir is an antiviral drug. During SARS-CoV-2 infection, the drug has been used currently as a potential treatment for pneumonia. Remdesivir inhibits viral replication by inhibiting RNA-dependent RNA polymerase. Recent studies have observed shortened recovery time in pregnant patients with COVID-19 treated with Remdesivir. In a published article, a 39-year-old pregnant woman was told about the risks including unknown teratogenic side effects and benefits of the drug for obtaining the patient's permission. After following the workflow standard for the drug use, as the patient was symptomatic for less than 7 days, she received 200 mg IV Remdesivir on Day 1, followed by 100 mg of the drug for 4 days. The use of the drug was completed without any side effects, and looking at the data, the patient showed improvement during his hospital stay. The fetal activity was monitored every 8 hours using an external fetal monitor without detected any abnormalities. Supplemental oxygen was provided to maintain saturations 95%, as per the obstetrician's advice. Oxygen saturations were around 98-100% by NC (Nasal Cannula) route from 2 L and were reduced to room air at 95% saturation at the time of discharge on the sixth day [3].

In another study, a 3-month pregnant (trimester) woman with COVID-19 disease was examined. The patient complained of scarring stenosis 2 days after the first application. In the first 12 hours of admission, the ratio of oxygen saturation to inhaled oxygen fraction deteriorated significantly and the use of Remdesevir was decided. Twice a day evaluated by test; the fetal situation continued to be reassuring throughout the ICU (Intensive Care Unit) course. She was discharged on HD 9 after completing 8 of the planned 10 days of Remdesivir. On the phone follow-up 10 days after discharge, our patient reported exertional cough and shortness of breath but improved significantly from admission. No other fetal imaging was indicated at that time. After fully recovering from COVID-19 disease, the patient had an uncomplicated vaginal delivery at term. One of the noted side effects of Remdesivir is transaminitis. This drug can further complicate the interpretation of elevated liver enzymes in a population where they may represent preeclampsia, viral effect, or physiological elevation. While the patient was using the drug, her transaminases increased; it is reported that clear whether this is due to COVID-19 disease or Remdesivir. Additionally, a SARS-CoV-2 infection-approved patient was treated with Intravenous (IV) Remdesivir in Seattle and appeared to respond well with no side effects. Remdesivir is available for pregnant women with severe COVID-19 disease *via* the EUA (European Universities Association) as of May 1, 2020. Considering recent data that pregnant women with COVID-19 disease are more likely to be admitted to the intensive care unit than non-pregnant women of reproductive age and the need for invasive ventilation, strong support for Remdesivir's safety in pregnant women with high clinical recovery rates provides [4].

Lopinavir/ritonavir in pregnancy

The fixed combination Lopinavir/Ritonavir is widely used in the treatment of adults living with HIV. Lopinavir is a protease inhibitor prescribed in combination with Ritonavir, a CYP3A4 inhibitor of the cytochrome p450 isoform used as an enhancer to achieve therapeutic plasma concentrations. Lopinavir-Ritonavir is a U.S. (FDA) pregnancy category C drug used for HIV treatment. Category C means that animal reproductive studies have had an adverse effect on the fetus and that there are no adequate and well-controlled studies in humans; therefore, it is not known whether treatment with category C drugs will harm the baby. During pregnancy, the clearance of the free form of Lopinavir/Ritonavir is unchanged and experts do not recommend increasing the dosage of the drug (usually 400 mg lopinavir/100 mg ritonavir twice daily). Human data from the Antiretroviral Pregnancy Registry showed that the prevalence of birth defects among infants prenatally exposed to Lopinavir/Ritonavir was not significantly different from internal or external comparison groups. These data supported the safety level of Lopinavir and Ritonavir. It may be advisable, if possible, to avoid the oral solution during pregnancy due to its alcohol and propylene glycol content. Besides, several cases of Lopinavir/Ritonavir toxicity in treated preterm infants have been described, particularly hyponatremia and symptoms suggestive of adrenal insufficiency combined with hyperkalemia. These adverse effects were reported by the FDA in 2011 for a contraindication of this drug in preterm infants. It gave rise to a warning. In studies conducted today, it has been shown that this antiviral drug, which is mainly used in the treatment of HIV,

can be effective in coronavirus infection, and its teratogenic effect has not been observed when used in pregnant women [5].

Hydroxychloroquine in pregnancy

For several years, Hydroxychloroquine (HCQ), a 4-aminoquinoline derivative with antimalarial and immune-modulatory effects, has been used to treat malaria and immune disorders such as systemic lupus erythematosus. Chloroquine and Hydroxychloroquine are currently highly published as drugs for severe SARS CoV-2 infection, but efficacy data to date are very limited. The volume of distribution of these drugs is very high and potentially alarming for pregnant women and their half-lives are long; 10 to 30 days for Chloroquine and 30 to 60 days for Hydroxychloroquine, which results in prolonged exposure after stopping these drugs. Therefore, a woman who takes and discontinues one of these medicines before pregnancy may therefore be exposed during subsequent pregnancy. There is evidence of minimal fetal or maternal risk in case series of pregnant women with Hydroxychloroquine, systemic lupus erythematosus, and other autoimmune diseases. A recent meta-analysis of 800 women using Hydroxychloroquine during pregnancy did not find an increase in pregnancy complications or congenital malformations but noted a significant increase in spontaneous abortions that could be attributed to the underlying autoimmune disease. Hydroxychloroquine has been reported to be safe for use in pregnant women at doses of 200 mg once or twice a day. To date, any substantially increased risk of major malformations in general, as well as craniofacial, cardiovascular, nervous system, and genitourinary malformations in infants have not been found in the most recent systematic meta-analysis of Hydroxychloroquine use during pregnancy (200-400 mg/day from 3 months before and during pregnancy). Besides, there were no substantial changes in stillbirth rates, low birth weight, and prematurity. Nevertheless, another category of patients that should be considered when using HCQ is pregnant women. It is known that the drug crosses the placental barrier and that a small amount is secreted in breast milk. In light of the successful chloroquine treatment, the authors concentrate on the side effects of high doses, based on a study of higher chloroquine delivery volumes during pregnancy in a small group of women [6].

Corticosteroids in pregnancy

Corticosteroids are anti-inflammatory drugs. They are listed as US FDA category B drugs and are considered safe in the second and third trimesters of pregnancy when used in low doses. Corticosteroids are the most common treatment for preterm labor in women. Since it helps the fetus, corticosteroids are an important part of the treatment of premature birth. Unfortunately, this drug use has been associated with worse outcomes in COVID-19-positive patients. Until recently, Corticosteroid administration was not recommended in COVID-19 disease patients due to concerns about potentially delaying viral clearance. Antenatal glucocorticoids have a well-established neonatal advantage in women who are at high risk for preterm delivery within 7 days. Betamethasone and Dexamethasone are the only Corticosteroids recommended for inducing fetal lung maturity because they have the highest rate of placental transition with minimal mineralocorticoid effects of all Corticosteroids. The latest approved neonatal gain regimen is either Dexamethasone or Betamethasone. In methylprednisolone equivalents, a standard obstetric dosage of Betamethasone and Dexamethasone is 60 mg. Other Corticosteroids (e.g., methylprednisolone, prednisone, prednisolone, hydrocortisone) are not appropriate replacements since they are metabolized extensively by placental 11-b-hydroxylase steroid dehydrogenase-2, resulting in decreased placental transfer. In certain cases of SARS-CoV-2 infection, short-term methylprednisolone administration has been used to minimize lung inflammation and avoid acute respiratory distress syndrome, but there are no further details in cases of pregnancy. As a result, in the case of pregnant women with SARS-CoV-2 infection that need preterm delivery, strict caution should be exercised when using antenatal Corticosteroids [7].

DISCUSSION

Due to changes in their cellular immunity, pregnant women are vulnerable to intracellular organisms such as viruses, particularly respiratory pathogens, and those that cause severe infections. Besides, it is important to note that some treatments for COVID-19 symptoms in the mother may have more or less of an impact on the fetus. In symptomatic care and respiratory failure, this method is normal [8]. Antiviral treatment agents Remdesivir and Lopinavirritonavir (LPV/r) are both safe to use in pregnant women. Ribavirin is the medication that is used in non-pregnant COVID-19 infected patients and is not approved for use in pregnant women. Again, chloroquine, which has shown to be effective in many patients, is a drug that can be safely used in all three trimesters of pregnancy. Because of the low plasma level caused by the increased volume during pregnancy, high doses of Chloroquine may be required [9]. Dexamethasone has been shown to increase mortality in serious SARS CoV-2 infections. The drug has been shown to cross the placenta and have positive results during pregnancy. Dexamethasone for COVID-19 disease will not be considered long-term, although long-term steroids are not prescribed during pregnancy. Any measure to enhance the mother's condition in critically ill COVID-19 disease pregnant patients should be considered. Dexamethasone is not contraindicated during pregnancy, and if clinically recommended, should not be stopped [10].

CONCLUSION

As a result, any drug or its metabolites are given to a pregnant woman will be distributed to both the maternal and fetal compartments. Because fetal development is a dynamic process, the effects of drug exposure vary depending on the stage of development of the fetus at the time of exposure. As a result, in addition to the mother, the fetus must be considered a patient who will be exposed to the drug. Therefore, clinicians and pregnant women need to be aware of current preventive and management strategies to make appropriate decisions for the well-being of the mother and fetus.

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