



Evaluation of Updated Therapeutic Options For COVID-19 in Pregnancy and Lactation

Gebelikte ve Emzirme Döneminde COVID-19 Güncel Tedavi Seçeneklerinin Değerlendirilmesi

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ABSTRACT

A new respiratory tract infection caused by coronaviruses was identified in 2019 and called Coronavirus disease-19 (COVID-19). It has long been known that pregnant women are not more susceptible to viral illness. However, changes to their immune system in pregnancy can be associated with more severe symptoms. Pregnant women do not seem to be at higher risk than non-pregnant individuals of severe COVID-19 infection. There are currently no data suggesting an increased risk of miscarriage or malformations in relation to coronaviruses. There is no specific antiviral treatment for COVID-19. Therapeutic options for patients with confirmed COVID-19 have been recently updated as hydroxychloroquine and/or azithromycin, and favipiravir for severe pneumonia. According to updated national treatment guidelines for COVID-19, favipiravir is not recommended for use in pregnant or breastfeeding women, but lopinavir/ritonavir can be used as second-line therapy. Published experience with COVID-19 during breastfeeding is limited. The main risk of breastfeeding is the close contact between mother and baby. This paper presents a literature review regarding outcomes after use of hydroxychloroquine, azithromycin and lopinavir/ritonavir during pregnancy and lactation. Hydroxychloroquine and/or azithromycin use is not expected to increase the risk of birth defects and adverse effects in breastfed infants. Based on reports of human immunodeficiency virus- infected women, lopinavir/ritonavir use does not appear to increase the risk of adverse effects, and it may be chosen in life-threatening situations. It is important to pay special attention to the selection of drugs for COVID-19 and utilize the most up-to-date information to optimize outcomes for both infant and mother.

Keywords: COVID-19, drug, pregnancy, lactation

ÖZ

2019 yılında koronavirüslerin yol açtığı yeni tip bir viral solunum yolu enfeksiyonu tanımlanmış ve bu enfeksiyon Koronavirüs hastalığı-19 (COVID-19) olarak isimlendirilmiştir. Gebe kadınların viral hastalıklara daha yatkın olmadıkları uzun zamandır bilinmektedir. Ancak gebelikte bağışıklık sisteminde meydana gelen değişiklikler, gebelerin bu hastalıkları daha ağır bulgularla geçirmelerine neden olabilir. Ağır COVID-19 enfeksiyonu geçiren gebe olmayan kadınlarla karşılaştırıldıklarında gebe kadınlar, daha fazla risk altında gözükmemektedirler. Bugün için koronavirüslerin düşük, erken gebelik kaybı veya doğumsal defekterle bir ilişkisi olduğuna dair kanıt yoktur. COVID-19'un spesifik antiviral bir tedavisi bulunmamaktadır. COVID-19 tanısı almış hastalarda tedavi seçenekleri son olarak, hidrosiklorokin ve/veya azitromisin, ağır pnömoni olgularında favipiravir olarak güncellenmiştir. Güncellenmiş COVID-19 ulusal tedavi kılavuzuna göre, favipiravirin gebelerde ve emziren annelerde kullanımı önerilmemektedir. Lopinavir/ritonavir alternatif ya da kombine tedavi olarak diğer ilaçlara yanıt vermeyen gebelerde tercih edilebilir. Emzirme döneminde COVID-19 ile ilgili yayınlanmış veriler sınırlıdır. Emzirmede esas risk, damlacık yoluyla hastalığı bulaştırabilecek anne ile bebeğin yakın temasıdır. COVID-19 tedavisinde kullanılacak ilaçlar, fetus ve yenidoğana olası advers etkileri açısından dikkatle değerlendirilmelidir. Bu derleme gebelikte ve emzirme döneminde hidrosiklorokin, azitromisin ve lopinavir/ritonavir kullanımına ait literatür bilgisini sunmaktadır. Gebelikte ve emzirme döneminde hidrosiklorokin ve azitromisin kullanımının doğumsal kusur riskini artırması ya da yenidoğanda advers etkiye yol açması beklenmemektedir. Lopinavir/ritonavir tedavisi ile ilgili bilgilerimiz insan bağışıklık yetmezliği virüsü enfeksiyonu olan gebelere ait olmakla birlikte anne sağlığını tehdit eden durumlarda hem gebelikte hem emzirme döneminde bu ilaçlar kullanılabilir. Gebe veya emziren kadınlarda COVID-19 enfeksiyonunu değerlendirmek zor olabilmekle birlikte ilaç seçimi konusunda özellikle dikkatli olunmalı ve hem anne hem bebek açısından ideal sonuçlar için en güncel bilgiler kullanılmalıdır.

Anahtar Sözcükler: COVID-19, ilaç, gebelik, emzirme

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Introduction

Coronaviruses (CoV) are a family of viruses that can cause various degrees of respiratory, gastrointestinal, liver, kidney damage and neurological damage in humans and animals. They can cause different clinical outcomes from the common cold to more serious diseases such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) (1).

The number of people infected by the new CoV, which has become a global problem in 2020, is today expressed in millions. Since it was first reported in 2019 in Wuhan, China, as a result of the examination of cases of pneumonia of unknown etiology, this virus-related disease defined as “2019-nCoV” is called Coronavirus disease-19 (COVID-19). COVID-19, an infection with respiratory symptoms, fever, cough and dyspnoea, can cause pneumonia, severe acute respiratory infection, kidney failure and even death in more severe cases.

It has long been known that pregnant women are not more prone to viral diseases. However, changes in the immune system during pregnancy may cause pregnant women to experience these diseases with more severe symptoms. However, to date, there is no evidence that pregnant women are more susceptible to COVID-19 infection, or that those with COVID-19 infection are more likely to develop more severe pneumonia (2).

No malformation has been reported in babies born to pregnant women with coronavirus infection. Although some neonatal complications have been reported that may be associated with SARS and MERS infections, data on COVID-19 infection are still limited. According to the reports of 9 pregnant women who gave birth at 29-36 weeks of gestation with COVID-19 infection, no health problem occurred in babies, and no coronavirus was detected in amniotic fluid and milk samples (3). Although all women have given birth by cesarean section, no reason has been presented for the need for a cesarean section except for the presence of COVID-19 infection. Three of the babies born weigh less than 2500 grams and this has been associated with prematurity and preeclampsia. In another case report, 10 babies born from 9 women with COVID-19 pneumonia were observed, and 6 babies, including twins, were born preterm and had respiratory symptoms (4). A 35-week-old baby died of multiple organ failure; The coronavirus tests of 9 babies tested were negative. Published information on COVID-19 and breastfeeding is very limited. Researchers who conducted systematic reviews reported that no virus was found in measurements made on the milk of 13 mothers with COVID-19 infection. However, it should be kept in mind that this number is not sufficient to interpret the results (5).

Currently, there is no specific treatment for COVID-19 with proven safety and effectiveness. In patients with a confirmed diagnosis of COVID-19, antibacterials other than azithromycin are discontinued unless there is clinical or laboratory evidence of the presence of an additional bacterial pathogen. Hydroxychloroquine is also added to the treatment in patients

with suspected viral pneumonia (1). Although it was in the treatment plan in the first months when the infection started to spread, according to the treatment guideline of the Ministry of Health, oseltamivir is no longer used in treatment in patients whose diagnosis of influenza pneumonia has been ruled out (1,6). Favipiravir has been defined as an additional treatment option in patients with severe pneumonia who do not respond to the first treatment. According to the updated treatment options, use of hydroxychloroquine or lopinavir/ritonavir in pregnant women with a definite diagnosis of COVID-19 was deemed appropriate (Table 1). Although a treatment protocol for breastfeeding mothers has not been specified, it has been reported that favipiravir should not be used in pregnant women and nursing mothers (1).

The aim of this review is to re-evaluate the updated treatment options for COVID-19 and to provide detailed literature on the use of hydroxychloroquine, azithromycin, and lopinavir/ritonavir therapy in pregnancy and breastfeeding.

Use of Hydroxychloroquine in Pregnancy and Breastfeeding

The results of different studies and case reports about hydroxychloroquine are that the use of this drug during pregnancy does not increase the risk of congenital anomalies (7-9). Based on some experimental studies and case reports that hydroxychloroquine use during pregnancy may cause problems in vision and hearing functions in born babies, large-scale studies have been conducted on these defects (10). Children who were exposed to hydroxychloroquine in their mother's womb were followed up and no visual or hearing problems were found in their examinations (11,12). A 2011 systematic review concluded that there is no evidence that the use of chloroquine or hydroxychloroquine during pregnancy causes ocular toxicity (13).

In another study in which clinical studies conducted between 1980 and 2007 were compiled, it was reported that the use of hydroxychloroquine in pregnant women with autoimmune disease was not associated with congenital defects, miscarriage, stillbirth or preterm birth (14). Another meta-analysis published in 2015 reached similar conclusions; however, some increase in the risk of spontaneous abortion has been reported. The significant increase in the risk of miscarriage was thought to be due to the mother's autoimmune disease rather than hydroxychloroquine (15). The literature suggests that hydroxychloroquine should not be discontinued during and after pregnancy to prevent exacerbation of autoimmune diseases. In the European League Against Rheumatism (EULAR) report published on the use of antirheumatic drugs during pregnancy in 2016, it was stated that hydroxychloroquine treatment does not increase the risk of congenital malformations according to the available evidence; It has been recommended to continue using hydroxychloroquine in symptomatic patients during pregnancy (16).

Hydroxychloroquine is also recommended for malaria prophylaxis in pregnant women who have to travel to endemic areas. Since it is thought that malaria, which progresses badly

Table 1. COVID-19 Adult Patient Treatment Options *

Name of the drug	Daily dose/administration	Duration of medication (day)
Treatment in uncomplicated possible/definite diagnosed COVID-19 cases		
Hydroxychloroquine 200 mg tablet -/+ Azithromycin	2x200 mg tablet, oral First day, 500 mg tablet, oral Following 4 days 250mg/day	5 day 5 day
Treatment in possible/definite diagnosed COVID-19 cases with mild pneumonia (those without severe pneumonia)		
Hydroxychloroquine 200 mg tablet -/+ Azithromycin	2x400 mg loading dose, followed 2x200 mg, oral First day, 500 mg tablet, oral Following 4 days 250mg/day	5 day 5 day
Treatment in possible/definite diagnosed COVID-19 cases with with severe pneumonia		
Hydroxychloroquine 200 mg tablet AND/OR Favipiravir 200 mg tablet -/+ Azithromycin	2x400 mg loading dose, followed 2x200 mg, oral 2x1600 mg loading 2x600 mg maintenance First day, 500 mg tablet, oral Following 4 days 250mg/day	5 day 5 day 5 day
Treatment in patients whose clinical condition is aggravated or whose pneumonia symptoms progress while receiving hydroxychloroquine treatment		
Favipiravir 200 mg tablet (hydroxychloroquine treatment should be completed to 10 days and discontinued)	2x1600 mg loading 2x600 mg maintenance	5 day
Treatment in pregnant women with covid-19 definite diagnosis		
Hydroxychloroquine 200 mg tablet or Lopinovir 200 mg/ritonavir 50 mg tablet	2x200 mg tablet, oral 2x2 tablet, oral	5 day 10-14 day

*<https://covid19bilgi.saglik.gov.tr/depo/tedavi/COVID19-EriskinHastaTedavisi.pdf>, COVID-19: Coronavirus disease-19

due to the decrease in cellular responses during pregnancy, will harm pregnancy much more, the use of hydroxychloroquine in mandatory situations has been accepted as safe (17).

Babies exposed to hydroxychloroquine during breastfeeding receive only a very small amount of the drug that passes into breast milk (18-20). It has been reported that babies of mothers who take hydroxychloroquine in doses of 200-400 mg per day may be exposed to 0.06-0.2 mg/kg drug with breast milk (21). No drug-related adverse effects in terms of growth, vision and hearing functions were found in babies whose development was followed up to the age of one (22-24). Hydroxychloroquine is considered to be acceptable for use during breastfeeding.

It has also been reported that the infants of mothers who took hydroxychloroquine once a week due to malaria prophylaxis, the amount of the drug in the milk that would not harm the baby, but did not protect the baby against malaria (25). Therefore, when malaria prophylaxis is required, breastfed babies should also take hydroxychloroquine at recommended doses.

Lopinavir/Ritonavir Use During Pregnancy and Breastfeeding

Exposure to protease inhibitors during pregnancy is not thought to cause an increased risk of congenital anomalies. Although adverse pregnancy outcomes were reported in the studies, they were observed in fewer and mostly premature babies.

In a study comparing the concentrations of protease inhibitors in maternal and cord blood, it was reported that these drugs did not exceed the placenta at term (26). In 2009, it was found that lopinavir was not in measurable concentrations in cord blood in samples taken from 26 human immunodeficiency virus (HIV)-infected pregnant women (27). As a result of the fact that some drug solutions contain propylene glycol and premature babies cannot eliminate this substance, kidney and respiratory problems have occurred in some premature babies. In a study reported from France in 2011, it was observed that adrenal dysfunction developed in babies of HIV-infected mothers who took lopinavir-ritonavir at birth and for an average of 30 days (28). All term babies born at term are asymptomatic; however, it was reported

that three of the preterm babies showed signs of dangerous adrenal insufficiency such as hyponatremia and hyperkalemia and cardiogenic shock developed in one premature baby. All adverse findings resolved after cessation of lopinavir-ritonavir exposure. Researchers also stated that these findings in premature babies may have occurred due to propylene glycol toxicity (28).

According to thousands of pregnancy data collected until 2019, the rate of congenital malformation in pregnant women who received lopinavir for HIV treatment is around 2.1%, which is similar to the general population (29). No increase in the risk of congenital defects was observed in pregnancies using lopinavir, 1333 of which were in the first trimester and 2371 in the second trimester (30). According to UK and Ireland national data, 134 babies with congenital defects were born out of 4864 pregnancies using lopinavir; the congenital anomaly rate is 2.9% (31). The defects reported by the researchers, who stated that there is no difference in anomaly rates between those who started the drug in the first trimester and afterwards, include limb deficiencies, heart defects, musculoskeletal defects, chromosomal abnormalities and urinary system defects. However, the rate of congenital anomalies reported in this study is not higher than the expected rate in the general population. Another study investigating the effects of lopinavir in different periods during pregnancy concluded that first trimester drug exposure may be associated with preterm delivery compared to late use (32).

Data on lopinavir and ritonavir treatment have been obtained from pregnant women and mothers with HIV infection. Accordingly, breastfeeding in HIV-infected mothers in many developed countries is restricted by the thought that the infection can be transmitted to the baby through milk. The World Health Organization (WHO) recommends that antiretroviral therapy be continued in a way that minimizes the risk of transmission of infection from mother to baby in countries where adequate and acceptable nutrition opportunities are not available instead of breast milk; However, there is no lopinavir-ritonavir among the treatment options recommended by WHO (33). Therefore, observational data on the use of lopinavir and ritonavir in lactation are very limited.

Lopinavir passes into breast milk in small amounts (34). In a study conducted with HIV-positive women, the average amount in breast milk was found to be 4263 mcg/L (35). In this study, 9 HIV-positive pregnant women received 3 doses of lopinavir (200 mg), ritonavir (150 mg), zidovudine (300 mg), lamivudine (50 mg) before cesarean section, 3 hours apart of each, and milk samples were collected at a mean postpartum 25th hour. Mean ritonavir levels measured in breast milk in the same study were 240 mcg/L. According to the results of an observational study conducted in breastfed infants, no adverse effects were observed at 1, 3 and 6 months in babies whose mothers received lopinavir (400 mg) and ritonavir (100 mg) twice daily as part of the HIV infection treatment (36).

Use of Azithromycin in Pregnancy and Breastfeeding

Based on experimental animal studies and human reports, the use of azithromycin during pregnancy is not expected to increase the

risk of birth defects. In 21 human placentas where transplacental transmission was evaluated, it was reported that less than 3% of the maternal azithromycin dose passed to the fetal compartment (37).

In case reports and retrospective studies reporting the results of more than a thousand pregnant women who received azithromycin for the treatment of chlamydia infection, no risk of pregnancy complications and congenital defects was reported (38-40). According to the data of the Israel Teratogenicity Information Service published in 2012, no increase in the risk of major congenital malformation or cardiovascular defect was detected in 156 pregnant women exposed to azithromycin, 119 of which were in the first trimester (41). In a study examining 1459 children whose mothers used azithromycin during their pregnancy, no increase was identified in terms of congenital defects (42). In a study investigating the relationship between the use of antibiotics during pregnancy and spontaneous abortion in 2017, it was reported that azithromycin use may be associated with abortions (43).

Since azithromycin passes into milk in small amounts, it is not expected to have adverse effects in breastfed babies. Measurement and standardization of azithromycin levels in breast milk is difficult due to its slow clearance and accumulation. It has been reported that after 500 mg of oral azithromycin intake per day, breast milk concentrations increased to 1.3 mg/L 1 hour after the first dose and 2.8 mg/L 30 hours after the third dose (44). The amount that the baby can receive through breast milk has been calculated as approximately 0.5 mg/day.

If the mother is using azithromycin during the breastfeeding period, it should be monitored whether there are possible gastrointestinal findings such as candidiasis, vomiting, and diarrhea. Although there are studies reporting the risk of infantile hypertrophic pyloric stenosis in babies of mothers who used macrolides in the first two weeks of breastfeeding, the relation of this situation with drug use is highly doubtful (45,46). In a study conducted on babies whose mothers used macrolide and breastmilk, no relationship was found between pyloric stenosis and macrolide use (47). In this study, it was reported that the use of azithromycin during breastfeeding was present in 10 out of 55 mothers, and a comparison was made with the use of amoxicillin in terms of adverse effects. Accordingly, the rate of adverse reactions in infants exposed to macrolide was 12.7%, while this rate was similar to the adverse reaction rate seen in infants exposed to amoxicillin through breast milk. Reactions observed in infants include rash, diarrhea, decreased appetite, and tendency to sleep. It was reported that no adverse effects were observed in babies breastfed by eight mothers who were given 500 mg intravenous azithromycin at 15, 30 and 60 minutes prior to cesarean section (48). In two meta-analyses reported in 2019, it was concluded that there was no relationship between macrolide use during breastfeeding and infantile hypertrophic pyloric stenosis (49,50).

Result

COVID-19 treatment options during pregnancy and breastfeeding should be carefully evaluated in terms of possible

risks and the patient should be informed. Following this evaluation and information, some medications administered to other adult individuals can also be used in the treatment of the pregnant patient in cases where medication is necessary. A risk assessment that is satisfactory for both the follow-up clinician and the patient, with detailed literature information, can also reduce anxiety related to the disease and possible drug use. The use of hydroxychloroquine and azithromycin during pregnancy and lactation is not expected to increase the risk of birth defects or cause adverse effects in the newborn. Although our information about lopinavir/ritonavir treatment belongs to pregnant women with HIV infection, these drugs can be used both during pregnancy and breastfeeding in situations that threaten maternal health. There is always a need for large-scale epidemiological studies to evaluate the effects of drugs used in the treatment of COVID-19 during pregnancy and lactation. Although COVID-19 is a disease full of unknowns for today, it is the duty of health professionals to provide treatment options to pregnant and breastfeeding mothers with an approach that takes into account both maternal health and baby's health in the light of current information.

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