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REVIEW ARTICLE / DERLEME MAKALE

VACCINATION AGAINST COVID 19 INFECTION DURING PREGNANCY AND LACTATION: A BRIEF REVIEW

GEBELİK VE LAKTASYON DÖNEMİNDE COVID 19 ENFEKSİYONUNA KARŞI AŞILAMA: KISA BİR DEĞERLENDİRME

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ABSTRACT

Objective: *Vaccination plays a crucial role in the protection against the Covid 19 infection. However, pregnant and lactating women are excluded from clinical trials of vaccines due to the unknown effects of the vaccine on the expectant mother, fetus, and infant. Pregnancy and the following lactation periods are long processes with unique physiological, psychological, and pathological characteristics, in which many practices are discussed for the mother and the baby. Based on the limited data available on the mechanisms of action of vaccine types, Covid 19 vaccines cannot possibly cause any risk to pregnant women and nursing mothers. On the other hand, there is currently insufficient data on the safety of Covid 19 vaccines in pregnant and lactating women.*
Result and Discussion: *Evidence-based and personalized information about vaccines is needed to support pregnant and breastfeeding women's decision-making about vaccines. Vaccination should be recommended to all pregnant and lactating women after they have been sufficiently informed about the advantage and risks of Covid 19 vaccines and their consent has been obtained. This brief review was conducted to discuss vaccination against Covid 19 infection during pregnancy and the lactation period based on scientific data and literature.*
Keywords: *Covid 19 infection, lactation, pregnancy, vaccination*

ÖZ

Amaç: *Aşılama, Covid 19 enfeksiyonuna karşı korunmada hayati rol oynamaktadır. Bununla*

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birlikte, gebe ve emziren kadınlar aşının anne adayı, fetüs ve bebek üzerindeki bilinmeyen etkileri nedeniyle aşıların klinik denemelerinin dışında tutulmaktadır. Gebelik ve onu takip eden laktasyon dönemleri, anne ve bebek için pek çok uygulamanın tartışıldığı, kendine has fizyolojik, psikolojik ve patolojik özellikleri olan uzun bir süreçtir. Aşı türlerinin etki mekanizmalarına ilişkin mevcut sınırlı verilere dayanarak, Covid 19 aşılarının hamile kadınlar ve emziren anneler için herhangi bir risk oluşturması muhtemel değildir. Öte yandan, şu anda hamile ve emziren kadınlarda Covid 19 aşılarının güvenliğine ilişkin yeterli veri bulunmamaktadır.

Sonuç ve Tartışma: *Hamile ve emziren kadınların aşılar hakkında karar vermesini desteklemek için aşılar hakkında kanıta dayalı ve kişiselleştirilmiş bilgilere ihtiyaç vardır. Tüm gebe ve emziren kadınlara Covid 19 aşılarının yararları ve riskleri hakkında yeterince bilgi verildikten ve onamları alındıktan sonra aşı önerilmelidir. Bu bağlamda bu kısa derleme gebelik ve laktasyon döneminde Covid 19 enfeksiyonuna karşı aşılamanın bilimsel verilere ve literatüre dayalı olarak tartışılması amacıyla yapılmıştır.*

Anahtar Kelimeler: *Aşılama, Covid 19 enfeksiyonu, gebelik, laktasyon*

INTRODUCTION

The World Health Organization (WHO) China Country Office reported cases of pneumonia of unknown etiology in Wuhan, Hubei Province, China, on 31 December 2019. On January 7, 2020, the agent was determined to be a new coronavirus strain never before identified in humans [1,2,3]. Covid 19, which significantly affects the respiratory system and spreads rapidly, quickly swept the world and was declared a pandemic by WHO on March 11, 2020 [4]. Fever and dry cough are the most common findings of Covid 19, but also severe malaise, nasal congestion, myalgia, headache, sore throat, dyspnea, and taste and smell disorders. Recently, gastrointestinal symptoms such as diarrhea have been reported [5]. It has been observed that comorbidities such as cardiovascular disease, chronic lung disease, asthma, diabetes, and hypertension, together with Covid 19, may enhance the risk of the disease occurring and exacerbate the clinical status [6].

This study, which aims to provide comprehensive information on vaccination against Covid 19 infection during pregnancy and lactation is a brief review. In such studies, the information in the relevant literature is researched, classified analyzed, and compared. The primary outcome is to examine the effect on mortality. The review was based on a literature search in the following databases for publications up to January 2023, Pub Med; Web of Science, ScienceDirect, Google Scholar, and ResearchGate. Keywords used for the search were; Covid 19 infection, lactation, pregnancy, and vaccination. All results of the search were manually scanned for relevant information and their references were also searched for additional publications that might be relevant. Relevant national and international publications, recommendations, and guides published in the specified date range are also included in the study.

Covid 19 Infection During Pregnancy

Pregnancy, while not being comorbidity, is a long process with its own physiological, psychological and pathological characteristics. Hormonal changes at this time increase susceptibility to infection in pregnant women compared with non-pregnant women. The high mortality rates from SARS-CoV and MERS-CoV viruses in pregnant women were reported in the past [7]. Therefore, the risk of Covid 19 may be also higher during pregnancy. However, the Turkish Maternal-Fetal Medicine and Perinatology Society stated that no raised sensitivity for Covid 19 was reported in pregnant women compared to others [8]. Due to insufficient data, guidelines were quickly issued to ensure the management of the process for pregnant women who belong to the risk groups. These guides were revised according to the progression of cases and in light of new findings [9]. This phase seeks to develop strategies for the impact of Covid 19 on the expectant mother and fetus. Treatment planning in pregnant women, possible vaccine options, and vaccination protocol concerning the measures taken for pregnant women in the previous SARS and MERS epidemics [10].

CDC (Centers for Disease Control and Prevention) and ACIP (Advisory Committee on Immunization Practices), in cooperation with ACOG (American College of Obstetricians and Gynecologists) and AAP (American Academy of Pediatrics), have published a guideline that pregnant

women should be included in Covid 19 vaccinations in December 2020 [11]. As stated in this guideline, Covid 19 carries the risk of causing severe health problems for the mother and fetus during pregnancy. The mortality rate due to Covid 19 in pregnant women ranges from 0.4 to 2%. This rate is 70% higher than in non-pregnant women. On the other hand, pregnant women hospitalized with Covid 19 are more likely to stay in the intensive care unit (ICU) than women who are not pregnant but have infections [12]. According to research by Wong et al., about 50% of pregnant women with SARS were followed in the ICU, 33% required mechanical ventilation, and the mortality rate was up to 25% [13]. Pregnant women with Covid 19 are at higher risk for preterm delivery than those without Covid 19. They are also considered at higher risk for other adverse pregnancy events. The incidence of preterm birth in the third trimester is increased approximately threefold, possibly (likely) due to the possibility of vertical transmission and medical interventions for maternal conditions [14].

The approach to disease prevention, assessment, diagnosis, and treatment is similar to that of non-pregnant side effectsiduals in pregnant women with suspected Covid 19. It is offered that pregnant women with Covid 19 disease or in a suspicious condition be cared for in an isolated negative pressure room and continue at home if the illness is mild or if the clinic is not appropriate [15]. The option of untreated follow-up in pregnant women with uncomplicated Covid 19 infection is primarily evaluated. Treatment is considered when risk factors or a severe prognosis are present in pregnant women with a possible diagnosis. Regarding the recommended treatment options for antiviral treatment for Covid 19 in pregnant women, it is foreseen to decide according to the patient's condition, drug's pregnancy category, and risk-benefit ratio. For example, while lopinavir and ritonavir, which are drugs used in the first days of the pandemic but not currently used in the treatment of Covid, are recommended during pregnancy, favipiravir is contraindicated [16].

Because of the presence of ACE 2 (Angiotensin-converting enzyme) receptors in the placenta, it is hypothesized that there is a theoretical possibility of infection of the placenta with Covid 19 and, thus, the transmission of the disease to the fetus. On the other hand, no virus was found in amniotic fluid, cord blood, placental tissues, and throat swabs taken from newborns in studies, and based on these available data, it has been reported that there is no possibility of transplacental transmission of Covid 19 disease in the advanced gestational week or that it is practically negligible [17]. The literature does not know whether and how the infection affects the embryo and the fetus.

Covid 19 Infection During Lactation

The lactation period is defined as the period that begins with the secretion of milk after birth. The health of the nursing mother is essential for the health and development of the baby during the lactation period, which is a sensitive period for the health of both mother and child. UNICEF recommends that even HIV (Human Immunodeficiency Virus) positive mothers continue to breastfeed their babies for up to two years [18].

According to the ABM (Academy of Breastfeeding Medicine) statement and WHO recommendations, the general trend in coronavirus infection is to continue breastfeeding even if the mother is infected [19]. Since the intake of breast milk has been shown to have no adverse effect on the course of the disease, breastfeeding is recommended even in SARS and MERS infections that have already been experienced. It has been reported as a precaution that the risk of infection in the baby is reduced due to the mother paying attention to hand-chest hygiene and breastfeeding with a medical mask [20].

The treatment options recommended in the guidelines for Covid 19 in nursing mothers should be decided based on the risk-benefit ratio according to the patient's condition. While lopinavir and ritonavir are recommended, favipiravir is contraindicated, as in pregnancy [16]. According to WHO, the sick mother should start breastfeeding as soon as she feels well. If the baby is younger than six months, the mother and baby should not be separated, skin-to-skin contact should be ensured as soon as possible, and only breast milk should be given for the first six months. Breastfeeding should continue with safe and healthy complementary feeding when the baby is older than six months [21]. The active Covid 19 disease virus has not been detected to be transmitted to the infant through breast milk and breastfeeding [22].

RESULT AND DISCUSSION

Vaccines Against Covid 19 Infection

-Inactivated Vaccines: Inactivated vaccines contain the entire pathogen killed by chemical or physical methods. Therefore, the agent can't replicate and cause infection [23]. The immune system is stimulated by decomposing and neutralizing the virus and then delivering it to the body. They are considered safer in the first stage since they include the killed/ inactivated virus, but their production is more complicated and slower than other vaccine types [24]. Sinopharm, Sinovac's Coronavac vaccine, which contains inactivated SARS-CoV-2 and an alum adjuvant, and Türkiye's Turkovac vaccine was developed using this method.

-Viral Vector (Adenovirus) Vaccines: They cannot cause disease in humans because they are weakened while the microorganisms in the vaccines are alive; the attenuated virus (vector) carries the desired antigen (S protein) gene in its genome. When the virus infects the cells, it carries the foreign gene into the cell. After transcription and translation in the cell, the gene produces the desired antigen, lifting it to the cell surface and stimulating the immune system. It is quickly produced in cell cultures and can be easily purified without destroying the structure of the antigen [23,24]. Sputnik-V, Johnson & Johnson's Janssen, and Oxford/AstraZeneca vaccines fall into this group. The Janssen adenovirus vaccine has been modified to prevent replication. Therefore, viremia during pregnancy is not expected, and the vaccine is not expected to reach the fetus [25].

-Messenger RNA (mRNA) Vaccines: The vaccine contains highly purified single-stranded mRNA obtained by amplifying the relevant RNA sequence encoding the spike (S) protein of SARS-CoV-2 in vitro in a cell-free medium. Once in the cell, the RNA functions as an mRNA and reprograms the cell to produce the foreign protein usually produced by pathogens (e.g., viruses) or cancer cells. These protein molecules then activate the body's adaptive immune response so that the body learns to destroy pathogens or cancer cells inside the protein [23,24,26]. This group includes BioNTech/Pfizer and Moderna vaccines. Because of the short half-life of the mRNA vaccine, it is unlikely to pass to the fetus during pregnancy or to the baby during breastfeeding. If the mRNA vaccine is excreted into breast milk, it will not be functionally absorbed due to its degradation during digestion. The protein expressed by the mRNA remains in the body for several days, similar to conventional protein-based vaccines. Because the expressed protein probably remains associated with the cell, it is unlikely to pass via breast milk to the fetus during pregnancy or lactation [27]. Table 1 lists Covid 19 vaccines by their mechanism of action, the number of doses administered and dates of emergency use.

Table 1. Covid 19 vaccines by the mechanism of effect, number of doses administered, and date of emergency use approval

Country	Vaccine	Number of doses	Mechanism of effect	Emergency use approval by FDA	Emergency use approval by WHO
Sinovac, China	Coronavac	2	Inactivated Vaccine	---	1 June 2021
Pfizer/BioNTech, USA, Germany	BNT162b2	2	Messenger RNA (mRNA) Vaccine	11 December 2020	31 December 2020
Moderna, USA	mRNA-1273	2	Messenger RNA (mRNA) Vaccine	18 December 2020	30 April 2021
Johnson&Jonhson, USA	Ad26COVs1	1	Viral Vector (Adenovirus) Vaccine	27 February 2021	12 March 2021
AstraZeneca, UK	ChAdOx1	2	Viral Vector (Adenovirus) Vaccine	---	16 February 2020
Gamaleya Res Inst, Russia	Sputnik V	2	Viral Vector (Adenovirus) Vaccine	---	---
Turkovac, Turkey	ERUCOV-VAC	2	Inactivated Vaccine	---	---

CDC notes that the only absolute contraindication to vaccination is having an allergy to vaccine components [28]. Table 2 lists Covid 19 vaccines by their mechanism of action and contraindication status.

Table 2. Covid 19 vaccines by the mechanism of action and their contraindication status

Vaccine name	Type	Contraindication
Pfizer/BioNTech	Messenger RNA (mRNA) Vaccine	Polyethylene glycol allergy
Moderna	Messenger RNA (mRNA) Vaccine	Polyethylene glycol allergy
Johnson&Jonhson	Viral Vector (Adenovirus) Vaccine	Polysorbate allergy
AstraZeneca	Viral Vector (Adenovirus) Vaccine	Polysorbate allergy

Vaccines Against Covid 19 Infection in Pregnancy and Lactation

The main target of any disincentive prenatal intervention is to minimize risk to the first mother and then the fetus while optimizing health benefits. Thus, the primary indication for administering Covid 19 vaccination is for maternal protection. The purpose of immunization during pregnancy is to protect both the pregnant woman and the fetus and newborn from infection. Since the maternal antibodies are transferred from mother to child during pregnancy by the transplacental route and after birth with the mother's milk, there is protection against infection in the early phase of the child's life [29]. Influenza vaccine administered in the third trimester has been reported to reduce febrile respiratory infections by 36% in the first six months of infant life and a very high 63% reduction in the incidence of laboratory-confirmed influenza in infants born to vaccinated mothers [30].

ACIP states that inactive viral/bacterial and toxoid vaccines do not pose a risk to the fetus during pregnancy. Still, caution should be used when administering live attenuated viral and bacterial vaccines during pregnancy [23]. A woman receiving a live vaccine is not recommended to become pregnant within the next four weeks. Most vaccine manufacturers list this period as three months on the product's brief product information sheet. If a live vaccine is inadvertently given to a pregnant woman or if pregnancy occurs within four weeks of vaccination, the person should be counseled about the vaccine's possible effects on the fetus. Still, abortion is not recommended in such a case [31].

The mother, who has been sufficiently immunized during pregnancy, protects herself and the fetus in the womb with antibodies of the type IG G (immunoglobulin G) passed on to the baby via the placenta. Again, the antibodies delivered from breast milk to the baby after birth via breastfeeding are critical for immunity to disease in the neonatal period. In the 2008 study by Gottfredsson et al., the mortality rate for pregnant women in 1918 cases with influenza was 37%, while this rate was 2-6% for others [32].

Although many studies have been conducted and many ongoing studies of emergency-approved vaccines developed for Covid 19, pregnant and lactating women are often excepted from studies for many reasons, including associated physiologic changes, fetal/infant protection, diagnosis, and treatment limitations. However, it should be noted that no vaccine falls into category A, which is considered safe for use during pregnancy. The bivalent HPV vaccine is in pregnancy category B, the anthrax vaccine is in pregnancy category D, and all other vaccines (including H1N1 and seasonal influenza) are in pregnancy category C. It is recommended to apply vaccination in the second trimester to prevent congenital disabilities that may occur for other reasons from being attributed to vaccination [33].

Considering the guidelines of CDC, ACIP, and AMP mentioned in the second part and the more dramatic course of Covid 19 infection in pregnant women, vaccination of pregnant women who are healthcare workers in the high-risk pregnancy classification who work in markets, restaurants, shopping malls, who have to work at a distance of fewer than 1.5 meters from other employees, who smoke and who are overweight, have diabetes, heart disease, asthma, and hypertension are recommended [11].

Based on the mechanisms of the Covid 19 vaccine types, they are considered unlikely to cause a risk to pregnant women [34]. However, there is currently too little data on the safety of Covid 19 vaccines in pregnant women and the general population. The studies examining the safety and efficacy of Covid

19 vaccines in pregnant women are currently planned and ongoing. There are preliminary data from animal studies that received the mRNA Covid 19 vaccine before or during pregnancy that there are no safety concerns in pregnant animals or their offspring. In addition, no side effects have been reported after vaccination with mRNA vaccines in pregnant women other than in non-pregnant women [14].

The first study in pregnant women began in February 2021 (ClinicalTrials.gov identifier NCT04754594). This is a continuing phase II/III randomized, placebo-controlled, observer-blind study in 700 healthy pregnant women vaccinated at four weeks. The study assessed the safety, tolerability, and immunogenicity of two doses of the Pfizer/Biotech vaccine administered 21 days apart versus a placebo [35,45].

Table 3 compares the V-Safe project's preliminary found side effects during pregnancy in pregnant women who have and have not been vaccinated against Covid 19.

Table 3. Comparison of pregnant women with and without mRNA Covid 19 vaccine in terms of side effects during pregnancy [27]

Side Effects	Covid-19 Vaccinated Pregnant Women (%)	Non-Covid-19 Vaccinated Pregnant Women (%)
Gestational diabetes	10	7-14
Preeclampsia and gestational hypertension	15	10-15
Eclampsia	0	0.27
Intrauterine growth restriction	4	3-7
Abortus	15	26
Stillbirth	1	0.6
Premature birth	10	0.1
Neonatal death	0	0.38

Considering to the CDC, from January 2020 to July 2021, approximately 102 thousand pregnant women with COVID-19 were in the United States. 448 (0.44%) patients stayed in an ICU, and 114 (0.11%) patients passed away [35].

Additionally, in a study of about 400,000 women with COVID-19, they were possibly admitted to an ICU, received invasive ventilation and extracorporeal membrane oxygenation (ECMO), and had a 70.0% raised risk of death [36]. As of September 2021, more than 160 thousand pregnant women had been vaccinated with the COVID-19 vaccine and were registered with the COVID-19 vaccine safety monitoring system (V-SAFE). However, adverse events have not been identified through V-SAFE. A study conducted in Israel analyzed data collected from approximately 15 thousand vaccinated and unvaccinated pregnant women. This study showed that vaccinated pregnant women have a substantially lower risk of SARS-CoV-2 than those not vaccinated and Pfizer's vaccines were safe [37].

A large registry-based study of births in Sweden and Norway (28506 vaccinated; 129015 unvaccinated) found no significantly increased risk of adverse pregnancy outcomes including preterm birth, stillbirth, small for gestational age, or NICU admission in people vaccinated against SARS-CoV-2 during pregnancy [38].

Breast milk is optimal for babies because it protects against infections, promotes optimal growth and development, decreases morbidity and mortality rates, is economical, and offers many other benefits [39]. The need to feed infants only breast milk for the first six months is emphasized at every opportunity [40]. Breastfeeding individuals were excluded in accelerated clinical trials for COVID-19 vaccines, which can be used under emergency use authorization from health authorities [15].

Professional associations and government health authorities should therefore recommend offering COVID-19 vaccines to breastfeeding women, as the potential benefits of maternal vaccination while breastfeeding outweigh the risks [41].

Statement of Key Findings

There are preliminary data from animal studies that received the mRNA Covid 19 vaccine before or during pregnancy that there are no safety concerns in pregnant animals or their offspring [14].

COVID-19 vaccines are not considered a risk to nursing mothers or their infants because of how vaccines work in the body. For this reason, it is recommended that nursing mothers may also receive the COVID-19 vaccine. Reports have demonstrated that breastfeeding individuals vaccinated with COVID-19 mRNA have antibodies in their breast milk that may help protect their babies [42-44].

Strengths and Limitations

This study is important in terms of summarizing and guiding the results of Covid-19 vaccines in pregnant and lactating mothers. However, the results cannot be generalized because pregnant and lactating women are not included in drug and vaccine studies and the number of studies is limited.
Covid 19 vaccine data on pregnancy and lactation are limited, as pregnant and lactating women are excluded from vaccine trials. This is not because of any particular safety concern but rather a matter of precaution, as in the problems of many other drugs. However, preclinical studies in animals that received the Covid 19 vaccine did not raise any safety concerns [14]. Evidence continues to build showing that Covid 19 vaccination before and during pregnancy is safe, effective, and beneficial to both the pregnant person and the baby.

There is no harm, at least theoretically and within the context of limited clinical data, in administering all vaccine types during pregnancy and lactation [14]. All over the world, health authorities such as ACOG, RCOG (Royal College of Obstetricians and Gynaecologists), EBCOG (European Board & College of Obstetrics and Gynaecology), The Joint Committee on Vaccination and Immunisation (JCVI) and Turkish Ministry of Health recommend access to COVID-19 vaccines, especially for pregnancy at high risk [46,47]. Thus, Covid 19 vaccination is not only suggested but strongly recommended for pregnant and breastfeeding populations to protect mothers and newborns.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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