# Coronavirus Disease 2019 and messenger RNA Vaccination in Pregnant Women.

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Introduction

Since its appearance in December of 2019, the SARS-CoV-2 infection has been associated with greater severity in patients with pre-existing pathologies. With the progression of the disease and adequate studies in pregnant women, it has been shown that this group of the population is associated with a higher risk and severity of the disease[1]. About 10% of pregnant women evolve severely, there is a higher risk of admission to the intensive care unit (ICU), the need for mechanical ventilation, maternal deaths, a higher risk of pre-eclampsia, premature births, and neonatal complications[2-4]. Vaccines based on an mRNA platform have become one of the safest and most widely used alternatives for combatting SARS-CoV-2 [5] infections.

Pregnant women with SARS-CoV-2

Pregnant women with COVID-19 are 3-5 times more likely to enter the ICU compared to non-pregnant women of reproductive age or pregnant women without the disease. In addition, there is a fatality percentage between 0.6 to 1.6%, which is highly significant [2,3]. Another finding that worsens the prognosis is the association between COVID-19 and pre-eclampsia. This association has been observed in a longitudinal study [3] and in a systematic review[4]. Pregnant women infected with SARS-CoV-2 have a significant 62% greater likelihood of developing pre-eclampsia than those without infection, including a higher risk of presenting the worst conditions of pre-eclampsia in its severe form, HELLP syndrome and eclampsia, according to the findings of a systematic review[4].

As pregnant women are at high risk when infected with SARS-CoV-2, said prognosis worsens, as it is associated with pre-eclampsia/eclampsia. They are two diseases with poor maternal and perinatal prognosis.

Neonatal complications, prematurity, and NICU stay are higher in those born to mothers with COVID-19 [1,3]. In addition to these findings, the frequency of cesarean sections is significantly higher in pregnant women with severe COVID-19. Therefore, neonatal results seem to be influenced more by the diagnosis of disease severity than the presence of the maternal infection itself.

Vaccination before pregnancy and in the first weeks of pregnancy

Messenger RNA vaccines are not live, attenuated, inactivated virus vaccines, nor do they use an adjuvant. These vaccines do not enter the nucleus and do not alter human DNA. As a result, mRNA vaccines cannot cause any genetic changes. Animal studies performed with the Moderna vaccine, evaluating perinatal and postnatal toxicity, show no alterations to embryonic, fetal or postnatal development after use of this type

of vaccine. Pregnant women were not included in the original studies where the usefulness of these vaccines was confirmed. Therefore, there are no randomized studies that show benefits (or complications) in pregnant women.

After the acceptance of the emergency use of the COVID-19 vaccine, several studies have been completed that show results associated with pregnancy. A report in the UK shows us that in the vaccinated women who were part of the original randomized studies, the number of unplanned pregnancies was the same in both groups (vaccine or placebo); furthermore, there were no differences in loss percentages in the first trimester of pregnancy [6].

More recently, a preprint [5] vaccination report from the United States shows us the results of 2,456 pregnant women and the risk of spontaneous abortion between 6 and 19 weeks when these women were vaccinated in the pre-conception period or before the first 20 weeks of pregnancy. This study does not show a higher incidence of spontaneous abortions in the population vaccinated with mRNA vaccines, compared to the reference standard.

Vaccination according to trimester of pregnancy

There are no randomized controlled studies proving the benefit of SARS-CoV-2 vaccines in pregnant women, however, there are several reports on its benefits and safety regardless of the trimester of pregnancy in which it has been used. A large cohort [7]shows us that of 3,958 vaccinated pregnant women, 28.6% were vaccinated in the first trimester of pregnancy and 43.3% in the second trimester. According to the findings of this study in the United States[7] and another in Israel [8], mass vaccination of the population occurs in all trimesters of pregnancy and the follow-up study of the population that has finished their pregnancy shows that there was no evidence of an increase in: abortions, malformations, fetal or neonatal death, premature birth, or restricted growth. In addition, there is a series of cases that shows that vaccination in the third trimester does not cause placental disorders[9].

Evidence of protection

Two large retrospective cohorts have evaluated the effect of mRNA vaccines in vaccinated pregnant women. The study carried out in the USA[7] with 3,958 pregnant women shows us that the possibility of infection 14 days after the first dose is 0.3%. Furthermore, the study carried out in 7,530 vaccinated pregnant women in Israel [8] compared to 7,530 unvaccinated (paired) women shows that between 11 and 28 days after the first dose, there is a significant decrease in infection when compared to the unvaccinated group. This difference becomes greater with the increase of the number of days post vaccination until a follow-up of 70 days.

Another important finding with maternal vaccination is the possible fetal and neonatal protection. Breast milk was tested in a cohort of 84 vaccinated mothers with at least two doses of mRNA vaccine[10]. This study found a robust secretion of specific IgG and IgA antibodies against SARS-CoV-2 in breast milk for 6 weeks after vaccination. These results suggest the potential protective effect against SARS-CoV-2 in infants of vaccinated or infected breastfeeding mothers.

On the other hand, the transplacental transfer of IgG antibodies has been evaluated in mothers who have received mRNA vaccine in the third trimester [11]. The studies show that if 16-21 days have passed since the first dose by the time of birth, there will already be a large amount of IgG antibodies present in the umbilical cord and the greatest amount of passive immunity will be obtained 3-4 weeks after the first dose of mRNA vaccine administered to the mother. By that time, the amount of antibodies in the umbilical cord are similar to those existing in maternal blood [11].

Other studies [12] have performed analyzes on both pregnant and lactating women and their results show that maternal antibodies generated by vaccines are transported to the child through umbilical cord blood and breast milk.

Summary

Pregnant women represent a group at high risk of infection by SARS-CoV-2. There are greater levels of admission to ICU, more death, more pre-eclampsia and prematurity,

Vaccines with the mRNA platform have been shown to be effective and safe in pregnant women and there is no evidence of fetal or neonatal damage in any trimester of pregnancy.

Vaccination against COVID-19 in pregnant women has been delayed in the world due to the non-inclusion in the original randomized studies; despite the absence of valid scientific elements demanding their exclusion. This experience should be used in the future and especially with this type of vaccine.

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