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# Does COVID-19 vaccination still have a role in maternal and perinatal outcomes during the Omicron era? A multicentre observational study

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**ABSTRACT**

**Objective.** COVID-19 vaccination has a reduced efficiency against the Omicron variant. The aim of this study was to assess the clinical impact of COVID-19 vaccination on maternal and perinatal outcomes during the Omicron wave.

**Materials and Methods.** This was an observational multicentre study, pregnant women who gave birth while infected by SARS-CoV-2 during the Omicron waves were included.

Patients with incomplete vaccination and recurrent infections were excluded. Patients were divided into 2 groups: the Vaccinated group included pregnant women with completed vaccination (≥ 3 doses of mRNA vaccine or 2 doses ≤ 6 months) and the Non-vaccinated group included pregnant women who had no COVID-19 vaccination. Data about obstetrical and foetal outcomes in both groups were compared.

**Results.** In total, 59 vaccinated and 49 unvaccinated patients were included. The incidence of patients requiring oxygen support was reduced from 36.7% to 1.7% with $p < 0.001$. The mode of delivery was comparable in both groups. The need for referral to an intensive care unit was reduced from 22.4% to 1.7% with $p \leq 0.001$. The length of hospitalization was reduced from 6.8 ± 5 to 2.8 ± 2 days, with $p \leq 0.001$. The prematurity rate was comparable in both groups, but the need for neonatal intensive care admission was reduced from 22.4% to 4.1% with $p = 0.019$.

**Conclusions.** The COVID-19 vaccination seems to be efficient during the Omicron waves. Obstetrical and neonatal outcomes were improved with complete vaccination. Pregnant women should be advised to have a complete vaccination status.

## INTRODUCTION

The 2019 novel coronavirus disease (COVID-19) is caused by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), which is a highly contagious and transmissible virus in humans. Rapid increases in case numbers and several epidemiological waves were observed worldwide with over 641 million cases confirmed and nearly 6.6 million deaths globally [1]. Furthermore, since its emergence, SARS-CoV-2 hasn't stopped mutating [2]. Several variants appeared and caused different epidemiologic waves [3]. The Omicron variant (B.1.1.529), becoming the dominant SARS-CoV-2 virus circulating in the world, appears to cause less severe acute illness than previous variants [4, 5], at least in vaccinated people [6]. During pregnancy, the severity of COVID-19 was reduced

during the Omicron wave in comparison with the Delta wave with lower rates of pneumonia requiring oxygen support [3]. In our population, maternal mortality among non-vaccinated pregnant women requiring hospital admission was reduced from 14.2% during the delta wave to 2.2% during the Omicron wave [3]. It has been reported that during pregnancy, vaccination improves maternal and perinatal outcomes by reducing the severity of COVID-19 [7]. However, Omicron demonstrated increased transmissibility due to its unprecedented ability to evade vaccine and infection-based, "natural" immunity [8, 9]. So, is there still a role for COVID-19 vaccines among pregnant women with the Omicron variant characterized by reduced efficiency of vaccines and reduced virulence of the virus? Studies evaluating the clinical effectiveness of vaccines in pregnancy against the Omicron variant are urgently needed because there is a lack of data on the subject [5]. The aim of this study was to assess the clinical impact of COVID-19 vaccination on maternal and perinatal outcomes during the Omicron wave.

## MATERIALS AND METHODS

### *Study design*

After obtaining patients' oral consent and local ethics committee approval, a multicentre observational study was conducted to assess the impact of COVID-19 vaccination on maternal and perinatal outcomes during the Omicron wave.

### *Study setting*

This study was carried out at four level 2 or level 3 maternity hospitals in southern Tunisia from the 15th of November 2021 to the 15th of October 2022. In this period, there were two waves of COVID-19 with the Omicron variant mainly (**Figure 1**). Four hospitals participated in this study: the Hedi Chaker University Hospital in Sfax, the Habib Bourguiba University Hospital in Medenine, the COVID-19 national military hospital in Sfax, and the regional hospital of Tataouine.

### *Study population with selection criteria*

Women with singleton completed pregnancies (> 24 WG) admitted to delivery while infected by SARS-CoV-2 during the Omicron waves and having had a recent (less than 5 days) positive reverse transcriptase-polymerase chain reaction (RT-PCR) test result were included.
We did not include patients aged less than 18 years, as well as individuals declining to consent or not being able to consent.
We did not include pregnant women who were hospitalized for COVID-19 but had negative rt-PCR at the moment of birth. We did not include cases of foetal loss (foetal death < 14 WG) and late miscarriage (14-24 WG). Patients with incomplete vaccination (only 1 dose of Pfizer-BioNTech COVID-19 vaccine or when the second dose of vaccination is older than 6 months) and patients with recurrent COVID-19 infections were excluded.

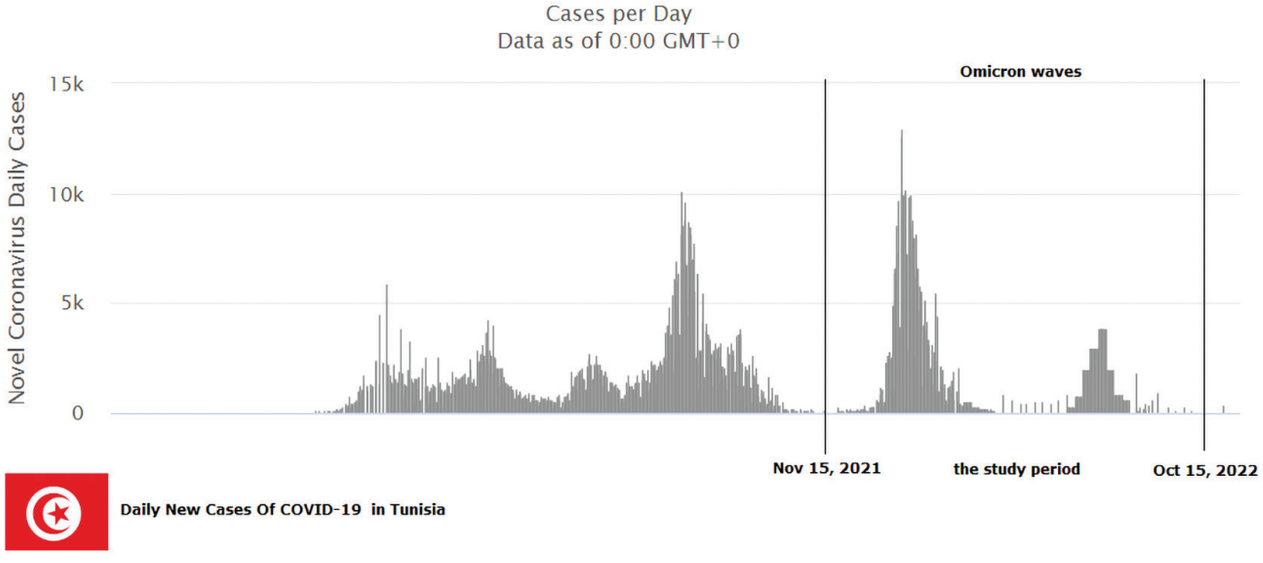


**Figure 1.** *The period of the Omicron waves in Tunisia.*

### *Data collection*

We collected data about demographic parameters like age, body mass index (BMI), parity, term of pregnancy, previous co-morbidities, and vaccination status. Clinical and biological features such as clinical signs, the severity of COVID-19 syndrome, the need for $O_2$ (6 L/min, 6-15 L/min, and >15 L/min, or advanced oxygen support), the incidence of preeclampsia and anaemia, and cytolysis were also evaluated at hospital admission. The mode of delivery and the maternal outcomes after delivery investigated were the incidence of clinical deterioration, which was defined by an increased need for oxygen supplementation after delivery, or referral to ICU, and maternal complications (ARDS, postpartum haemorrhage, thromboembolic events, septic shock, and pregnancy-related complications including retro-placental haematoma, HELLP syndrome, and acute fatty liver of pregnancy). For severe COVID-19 requiring advanced oxygen support or intensive care before delivery, clinical deterioration is defined by the incidence of a severe complication or death. The main neonatal outcomes assessed were neonatal intensive care unit (NICU) admission rates, rates of prematurity, and SARS-CoV-2 perinatal transmission. The length of hospital stay, the need for ICU referral, the need for advanced resuscitation (advanced oxygen support with CPAP or intubation, and/or the need for catecholamine), and the incidence of maternal complications or death were assessed as well.

### *Study size*

The sample size determination was based on data from preliminary results of the 53 first patients enrolled in this study (30 vaccinated and 23 unvaccinated patients). The incidence of severe COVID-19 requiring intensive care unit referral was 3.3 % in the Vaccinated group and 26 % in the Non-vaccinated group. So, we determined that a study sample of 49 patients in each group is required for 90% confidence level and 5% margin of error.

### *Bias*

All patients enrolled in this study had the same management protocol. We verified that the clinical and obstetrical management of COVID-19 in the different hospitals participating in this study adheres to the INAES (Instance nationale de l'évaluation et de l'accréditation en santé) guidelines for COVID-19 patients [10]. Patients with incomplete vaccination or with COVID-19 reinfection were excluded to address selection bias.

### *Groups definition*

To assess the impact of the COVID-19 vaccination among pregnant women, who gave birth while primo-infected by COVID-19 during the Omicron waves, on the maternal and perinatal outcomes, patients were divided into two groups according to their vaccination status.
The Vaccinated group included patients who had completed vaccination by receiving 3 doses of Pfizer-BioNTech COVID-19 vaccine or 2 doses on condition that the second dose was received within the previous 6 months. The Non-vaccinated group (control group) included non-vaccinated primo-infected pregnant women.

### *Statistical analysis*

Statistical analyses were achieved using the SPSS 23.0 (SPSS, Chicago, IL, USA) statistical package. Continuous variables were presented as means value ±standard deviation.
We distinguished two groups according to the vaccination status during Omicron waves among primo-infected pregnant women. The comparison between groups was achieved by Student's t-test and $Chi^2$ test for continuous variables and categorical variables, respectively. The Fisher exact test was used when the $Chi^2$ test was not applicable. The Mann-Whitney U test was used for non-parametric continuous variables. The significance threshold was set at $p < 0.05$.

### *Ethical approval*

The approval of the Hedi Chaker University Hospital Local Ethics Committee was obtained before beginning the study.

## RESULTS

In this study, we included 108 pregnant women with COVID-19 who were admitted to the hospital

for delivery during the Omicron wave. Fifty-nine patients were vaccinated, and 49 were not vaccinated. Twenty-six patients were excluded because of incomplete vaccination against COVID-19 and/or recurrent SARS-CoV-2 infection. The booster dose of the vaccine (3rd dose) was received in 41 patients (69.4%). No vaccine-related adverse effects were noted.

Demographic parameters concerning age, body mass index, parity, term of pregnancy, and co-morbidities were comparable in both groups (**Table 1**).

The vaccination reduced the severity of COVID-19 (**Table 2**). Asymptomatic forms were seen in 45.7% of the Vaccinated group *versus* 20.4% of the Non-vaccinated group ($p = 0.005$). The vaccination reduced the incidence of dyspnoea from 38% to 2.2% ($p = 0.003$) and the need for oxygen from 36.7% to 1.7% ($p < 0.001$).

The mode of delivery was comparable in both groups (**Table 3**). Clinical deterioration after delivery was seen in 11.8% of the Vaccinated group *versus* 28.5% in the Non-vaccinated group ($p = 0.004$). The incidence of maternal complications (particularly acute respiratory distress syndrome – ARDS), referral to the intensive care unit, and advanced respiratory and/or hemodynamic resuscitation were lower in the Vaccinated group (**Table 3**). The length of hospitalization was reduced from 6.8 ± 5 days in the Non-vaccinated

**Table 1.** *Demographic parameters.*

| | Vaccinated group n = 59 | Non-vaccinated group n = 49 | P-value |
|---|---|---|---|
| Age (year) | 32.3 ± 5.1 | 31.6 ± 5.6 | 0.493 |
| >35 (n, %) | 11 (18.6%) | 16 (32.6%) | 0.074 |
| BMI (kg/m$^2$) | 29.1 ± 3.9 | 28.6 ± 3.1 | 0.749 |
| > 30 kg/m$^2$ | 20 (33.8%) | 19 (38.7%) | 0.372 |
| Parity: primiparous or multiparous | 12/47 | 7//42 | 0.286 |
| With comorbidities (N, %) | 9 (15.2%) | 2 (4.1%) | 0.053 |
| Hypertensive disorders | 1 | 0 | - |
| Diabetes | 4 | 1 | 0.284 |
| Respiratory disease | 4 | 1 | 0.221 |
| Term of pregnancy | 36.3 ± 3.2 | 36.6 ± 2.9 | 0.674 |

**Table 2.** *Maternal data at hospital admission.*

| | Vaccinated group n = 59 | Non-vaccinated group n = 49 | P-value |
|---|---|---|---|
| Asymptomatic (%) | 27 (45.7%) | 10 (20.4%) | **0.005** |
| Cough | 25 (42.3%) | 29 (59.1%) | 0.061 |
| Fever | 24 (40.6%) | 19 (38.7%) | 0.499 |
| Headache or asthenia | 10 (16.9%) | 28 (57.1%) | **0.001** |
| Dyspnoea | 1 (1.7%) | 9 (18.3%) | **0.003** |
| Digestive signs (nausea, vomiting, diarrhoea...) | 2 (3.3%) | 8 (36.7%) | **0.023** |
| Others: sore throat or rhinorrhoea, anosmia and ageusia | 1 (1.7%) | 5 (10.2%) | 0.066 |
| Pre-eclampsia | 8 (13.5%) | 12 (24.4%) | 0.114 |
| Anaemia < 10g/dL | 4 (6.7%) | 11 (22.4%) | **0.019** |
| Cytolysis (> 3×) | 3 (5.0%) | 7 (14.2%) | 0.095 |
| Thrombopenia < 50,000 | 0 | 1 (2%) | 0.454 |
| Radiological signs > 20% (yes/no) | 1/0 | 4/5 | 0.129 |
| Need for $O_2$ at hospital admission | 1 (1.7%) | 18 (36.7%) | **<0.001** |
| $O_2$ needed < 6L/min | 0 | 13 | |
| $O_2$ needed 6-15L/min | 1 | 2 | **<0.001** |
| $O_2$ needed > 15 L/min | 0 | 3 | |

**Table 3.** *Maternal outcomes after delivery.*

| | Vaccinated group n = 59 | Non-vaccinated group n = 49 | P-value |
|---|---|---|---|
| Mode of delivery | | | |
| Caesarean delivery | 30 (50.8%) | 29 (59.2%) | 0.251 |
| Vaginal delivery | 29 (49.2%) | 20 (40.8%) | |
| Indications for caesarean delivery | | | |
| Foetal distress | 6 | 7 | |
| Obstetrical indications | 23 | 13 | |
| Severe preeclampsia | 1 | 2 | **0.002** |
| Maternal life-saving | 0 | 7 | |
| Maternal outcomes after delivery | | | |
| Clinical deterioration after delivery (%) | 7 (11.8%) | 14 (28.5%) | **0.004** |
| Increased need for $O_2$ after delivery (yes/no) | 7 (11.8%) | 15 (30.6%) | **0.015** |
| $O_2$ needed < 6 L/min | 7 | 12 | |
| $O_2$ needed 6-15 L/min | 0 | 1 | 0.128 |
| $O_2$ needed > 15 L/min or opti-flow | 1 | 8 | |
| Postpartum referral to ICU | 1 (1.7%) | 11 (22.4%) | **0.001** |
| Complications (yes/no) | 5 (8.4%) | 16 (32.6%) | **0.002** |
| ARDS | 0 | 10 | **0.003** |
| Postpartum haemorrhage | 2 | 5 | - |
| Thromboembolic events | 1 | 2 | - |
| Septic shock | 1 | 0 | - |
| Pregnancy related complication | 1 | 1 | - |
| Need for advanced resuscitation | 1 | 6 | **0.033** |
| Length of hospital stay (days) | 2.8 ± 2.8 | 6.8 ± 5.7 | **< 0.001** |
| Maternal death | 1 | 3 | 0.242 |

group to 2.8 ± 2 days in the Vaccinated group (p < 0.001). Maternal death was seen in 3 Non-vaccinated patients and one vaccinated patient (p = 0.242). All deaths were for severe COVID-19.

Perinatal outcomes concerning the rates of prematurity, vertical transmission, and stillbirth were comparable in both groups (**Table 4**). However, NICU admissions were reduced from 22.4% in the Non-vaccinated group to 4.1 % in the Vaccinated group (p = 0.019).

## DISCUSSION

After the doubts raised on the effectiveness of COVID-19 vaccines on the Omicron variant, characterized by a modified spike protein structure and reduced neutralizing activity of antibodies against this protein, there was a need to assess the clinical impact of complete vaccination during the Omicron waves, particularly among pregnant women. This study emphasizes the role of COVID-19 vaccination

**Table 4.** *Perinatal outcomes.*

| | Vaccinated group n = 59 | Non-vaccinated group n = 49 | P-value |
|---|---|---|---|
| Severe prematurity: delivery < 28 WG | 1 (1.7%) | 0 | 0.546 |
| Premature delivery: 28-34 WG | 11 (18.6%) | 12 (24.4%) | 0.307 |
| Vertical transmission | 0 | 2 (4.1%) | 0.204 |
| Breastfeeding | 45 (76.2%) | 32 (65.3%) | 0.149 |
| Admission in neonatal ICU | 4 (6.7%) | 11 (22.4%) | **0.019** |
| Neonatal deaths and stillbirth | 0 | 2 (4.1%) | 0.204 |

on full-term infected pregnant women during the Omicron waves. We showed that vaccination reduced the severity of the disease with lower rates of dyspnoea and oxygen support requirements and improved maternal and foetal morbidity.

Even if several previous studies estimate that the Omicron variant gives less severe forms [3-5] and announces the end of the pandemic [11-13], our study showed that COVID-19 persists and the risk of severe and complicated forms caused by this variant should never be underestimated [14], especially during pregnancy [15-17]. This study also showed the efficiency of the RNA vaccine against the Omicron variant.

In previous COVID-19 waves, the most common symptoms of COVID-19 infection were fever and cough, which over 80% of hospitalized patients complain about [18]. The incidence of pneumonia can reach 90% in symptomatic patients [18]. This may explain the high rate of hospital admissions and intensive care admissions, especially in case of either preexisting chronic medical conditions in pregnancy or obstetrical disorders occurring in pregnancy [19]. The role of vaccination was shown previously during previous COVID-19 waves as it improved maternal and foetal outcomes by reducing the severity of COVID-19 [8]. Vaccination has been shown to reduce the incidence of pneumonia and ARDS [8, 20], which can cause life-threatening hypoxemia and necessitate advanced resuscitation and, in some cases, caesarean delivery for foetal distress or maternal life-saving [8]. This may explain why vaccination allowed lower rates of caesarean deliveries and better maternal and foetal outcomes [8, 21]. However, SARS-CoV-2 Omicron (B.1.529) and its subvariants (BA.1, BA.2, *etc.*), which have been dominating COVID-19 infections worldwide since November 2021 [22], are associated with a lower risk of severe forms and appear to have a lower hypoxemia rate when compared to previous SARS-CoV-2 variants [23, 24]. On the other hand, recent studies have raised doubts about the coverage and effectiveness of existing COVID-19 vaccines against the Omicron variant [25]. It was reported that two doses of the vaccine provide limited protection against symptomatic disease, and a booster dose increases protection for 5 to 9 weeks before waning over time [25]. This may be explained by a rapid decline in vaccine-boosted neutralizing antibodies against the SARS-CoV-2 Omicron variant [26]. The doubts about the vaccine efficiency against the Omicron variant were confirmed by other studies demonstrating reduced neutralizing activity of antibodies elicited by the RNA vaccine against the Omicron variant [27, 28]. However, other studies showed that broadly neutralizing antibodies can overcome SARS-CoV-2 Omicron antigenic shift as a fraction of broadly neutralizing sarbecovirus monoclonal antibodies neutralized Omicron through recognition of antigenic sites outside the receptor-binding motif [29].

Despite the reduced neutralization of the antibodies, Omicron spike recognition and Fc receptor binding continue to attenuate the COVID-19 severity in pregnant women [30], especially after booster doses [31]. Nevertheless, the clinical impact of vaccination on maternal and perinatal outcomes during the omicron period seems to be difficult to assess, as both vaccination and the omicron variant give less severe and complicated forms [32]. This may explain why there is still little clinical data on this subject.

In our study, vaccinated patients were better protected than non-vaccinated patients and had better maternal and foetal outcomes indicating the importance of vaccination against COVID-19 in the Omicron era. Our findings were comparable with those of recent studies indicating the importance of vaccination against COVID-19 in pregnancy during the Omicron era [33-35]. Fully vaccinated pregnant women infected with SARS-CoV-2 during the Omicron wave had a milder illness and were less likely to require oxygen supplementation and intensive care compared with the unvaccinated. However, according to our study, the incidence of maternal death was comparable in both groups. This may be explained by the reduced incidence of maternal mortality during the Omicron waves. To determine the impact of vaccination on maternal mortality during the Omicron waves, larger samples and further studies may be required.

In our study, we included infected patients admitted for delivery, which allowed us to assess the perinatal data and investigate the role of maternal vaccination on newborns. Previous studies evaluated the neutralization efficiency against the SARS-CoV-2 Omicron variant in cord blood sera after antenatal BNT162b2 maternal vaccination and emphasized the role of the booster dose [36]. Others detected maternal antibodies elicited by COVID-19 vaccination in amniotic fluid, which can give more perinatal protection at birth [37] and can explain the lower rates of NICU admissions [38].

Indeed, the duration of this passive protection in newborns and infants is still unknown. A Norwegian population-based cohort study suggests that newborns of mothers who were vaccinated during pregnancy seem to be protected till the first 4 months of life [39].

Our study gave us feedback on the efficacy of vaccines against COVID-19 on maternal and perinatal morbidity during the Omicron waves. It seems that complete vaccination is efficient even during the Omicron wave as it allowed less severe disease which can improve maternal and perinatal outcomes. The main limitation of this study was that the viral RNA sequencing data, which can allow the diagnosis of the variant determining the infection, was not available for all patients. The period of Omicron waves in our country was used to study the impact of vaccination on the Omicron variant. The second limit is that the exclusion of patients having had prior SARS-CoV-2 infection is not possible in cases of asymptomatic or unknown or undocumented SARS-CoV-2 infections, which can be a common situation in our population.

The main clinical implication of our findings is that they encourage obstetricians to continue advising vaccination in order to improve maternal and perinatal outcomes. We should mention that complete vaccination is mandatory and that booster doses may be beneficial.

## CONCLUSIONS

In this study, the vaccination allowed the reduction of COVID-19 severity as it increased the rate of asymptomatic forms and reduced the incidence of patients requiring oxygen support. This resulted in improved maternal and foetal outcomes with lower rates of maternal complications and clinical deterioration after delivery and newborns referral to the neonatal intensive care unit.

These findings emphasize the message to unvaccinated pregnant and maternity health care providers that there is still an important role for vaccination against the Omicron variant. As the world is entering a new era of COVID-pandemic, booster vaccinations seems to be beneficial against severe COVID-19, particularly during pregnancy. It seems that the vaccination can improve perinatal outcomes by reducing the severity of the disease among mothers while also providing passive protection to newborns.

## COMPLIANCE WITH ETHICAL STANDARDS

### *Authors contribution*

A.J.: Conceptualization, investigation, methodology, writing – review & editing. M.K.: Writing – original draft. M.K.: Data curation, formal analysis, investigation. M.D., H.S.: Writing – review & editing. K.C., K.K.: Supervision, validation, visualization.

### *Funding*

None.

### *Study registration*

N/A.

### *Disclosure of interests*

The authors declare that they have no conflict of interests.

### *Ethical approval*

It was obtained from the HCUH (Local Ethics Committee).

### *Informed consent*

It was obtained from all patients included in the study.

### *Data sharing*

Data are available under reasonable request to the corresponding author due to privacy/ethical restrictions.

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