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The impact of COVID-19 booster vaccination in the current pregnancy during the Omicron waves on maternal and perinatal outcomes: a multicentre observational study

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ABSTRACT

Objective. The aim of this study is to investigate the impact of COVID-19 booster vaccination received during the current pregnancy on maternal and perinatal outcomes.

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 were divided into 2 groups: the "Booster vaccination" group included pregnant women who had completed vaccination and had received an additional dose of vaccine during pregnancy; the "Non-booster vaccination" group included pregnant women who had completed primary vaccination without booster shots. Data about obstetrical and neonatal outcomes in both groups were compared.

Results. In total, 59 patients were included: 41 received booster shots during the current pregnancy, and 18 did not. Asymptomatic forms were seen in 58.5% of the "Booster vaccination" group *versus* 16.6% of the "Non-booster vaccination" group with $p = 0.003$. The need for caesarean delivery was reduced from 72.2% to 41.4% with $p = 0.028$. The length of hospitalization was reduced from 4.67 ± 4 days in the "Non-booster vaccination" group to 1.98 ± 0.93 days in the "Booster vaccination" group with $p = 0.001$. The booster vaccination allowed reduced rates of prematurity with $p = 0.011$ and neonatal intensive care admissions with $p = 0.007$.

Conclusions. The COVID-19 booster vaccination seems to be beneficial during the Omicron waves. It improved obstetrical and neonatal outcomes. So, pregnant women could be advised to get a booster dose of the COVID-19 vaccine when they get pregnant.

INTRODUCTION

Pregnant women are not more susceptible to SARS-CoV-2 infection, but they may face a more serious COVID-19, because of their unique physiological and immunological status [1]. Nowadays, vaccination against COVID-19 is very common and has shown its safety and efficiency against the virus [2]. It has reduced the severity of the disease and improved maternal and perinatal outcomes

[2]. However, the new omicron variant of SARS-CoV-2, which is dominating all over the world, is characterized by a modified spike protein structure which can lead to an increased risk of immune evasion with the reduced neutralizing activity of antibodies against this protein [3, 4]. Recent doubts about the vaccines' efficiency against this variant were evoked [5], but other clinical studies showed that complete vaccination still plays a role in the improvement of outcomes [6]. In the general population, recent studies reported that primary COVID-19 vaccination efficacy was up to 90% within 6 months, decreasing rapidly to 34-80% after this period [7]. So, the reduced efficacy of vaccines may be related to the new variant but also to the time from the last vaccination which emphasizes that COVID-19 vaccine booster doses are required for restoring vaccine efficacy and limiting virus circulation [7, 8]. However, pregnant women remain hesitant to get booster shots of vaccine and there are still little data on the interest of booster vaccination during pregnancy in improving maternal and foetal protection against this widely spread variant [9]. Studies investigating the role of booster vaccination during pregnancy and its impact on the prognosis of the patients are intriguing, especially when specific to the last Omicron period.
The aim of this study is to investigate the impact of COVID-19 booster vaccinations received during the current pregnancy among pregnant women on the severity of the disease and maternal and perinatal outcomes.

MATERIALS AND METHODS

Study design

After obtaining patients' oral consent and local Ethics Committee approval, we conducted this multicentre observational study to assess the impact of COVID-19 booster 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, two waves of COVID-19 occurred in our country, and the Omicron variant was the dominant variant. 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 in Tataouine.

Study population with selection criteria

Women with complete vaccination status and having singleton completed pregnancies (> 24 WG) admitted to delivery while infected by SARS-CoV-2 during the Omicron waves and having had a recent (in the last 5 days before delivery) positive reverse transcriptase-polymerase chain reaction (RT-PCR) test result were included. Completed vaccination was considered when the patient had received 3 doses or more of mRNA vaccine, or only 2 doses on condition that the second dose was received within the last 6 months.
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). Non-vaccinated women as well as 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. Patients who had their booster dose before they get pregnant without a second booster during pregnancy were also excluded.

Data collection

We collected data about:

- Demographic parameters: age, body mass index (BMI), parity, term of pregnancy, previous co-morbidities, and vaccination status.
- Clinical and biological features at hospital admission: clinical signs and 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, anaemia, and cytolysis, as well as radiographic findings.
- The mode of delivery: vaginal or caesarean section delivery.
- The main indications of caesarean section delivery were: foetal distress (foetal heart rate deceleration during labour), obstetrical indications

(labour dystocia, suspected foetal macrosomia, foetal malpresentation…), severe or complicated preeclampsia and maternal life-saving (severe hypoxia or septic shock indicating the foetal extraction).
- The maternal outcomes after delivery: a clinical deterioration was defined by an increased need for O_2 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 was defined by the incidence of a severe complication or maternal death.
- Neonatal outcomes assessed were: neonatal intensive care unit (NICU) admission rates, rates of prematurity, and SARS-CoV-2 perinatal transmission. We defined extreme prematurity (less than 28 weeks), severe prematurity (28 to 32 weeks), and moderate to late prematurity (32 to 37 weeks).
- Maternal follow-up and prognosis: 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 (such as ARDS, postpartum haemorrhage, thromboembolic events, septic shock, and pregnancy-related complication) or maternal death.

Study size

The sample size determination was based on data from the preliminary results of the 32 first patients enrolled in this study (22 with booster vaccination and 10 primarily vaccinated patients). The incidence of asymptomatic COVID-19 was 10% in the vaccination group and 59.09% in the "Booster vaccination" group. So, we determined that a study sample of 18 patients in each group is required for a 90% confidence level and a 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. The timing and mode of delivery were determined primarily on the basis of obstetrical indications.

Groups definition

To assess the impact of the COVID-19 booster vaccination among pregnant women who gave birth while primo-infected by COVID-19 during the Omicron waves, patients were divided into two groups:
1. the "Booster vaccination" group included patients who had completed primary vaccination and had received a booster dose of vaccine during pregnancy. This group includes patients who received two doses of Pfizer-BioNTech COVID-19 vaccine prior to pregnancy and a third dose (booster dose) while pregnant, as well as all patients who received three doses prior to pregnancy and a second booster dose (4^{th} dose) of vaccine while pregnant.
2. the "Non-booster vaccination" group (control group) included patients who had completed primary vaccination but had not received a booster dose of vaccine during pregnancy. This group included patients who received only 2 doses, with the second dose received within the last 6 months at the moment of delivery.

Statistical analysis

Statistical analyses were performed 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 the 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. A binary logistic regression analysis was done to investigate the impact of booster vaccination on maternal and neonatal outcomes. Odds ratios, and a confidence

interval of 95% (OR, 95%CI) were reported. 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 59 pregnant women who gave birth while infected by SARS-CoV-2 during the Omicron wave. Forty-one patients had received a booster vaccination during the current pregnancy, and 18 women had completed their primary vaccination but had not received a booster dose of vaccine. Twenty-six patients were excluded due to incomplete vaccination against COVID-19 and/or recurrent SARS-CoV-2 infection. No patient had experienced any side effects related to the booster dose. Demographic parameters concerning age, body mass index, parity, term of pregnancy, and co-morbidities were comparable in both groups (**Table 1**). The booster vaccination during the current pregnancy reduced the severity of COVID-19 (**Table 2**). Asymptomatic forms were seen in 58.5% of the "Booster vaccination" group *versus* 16.6% of the "Non-booster vaccination" group ($p = 0.003$). The need for caesarean delivery was seen in 17 patients in the "Booster vaccination" group (41.4%) *versus* 13 patients in the "Non-booster vaccination" group (72.2%) with $p = 0.028$. We noted no

Table 1. *Demographic parameters.*

	Booster group n = 41	Non-booster group n = 18	P-value
Age (year)	31.49 ± 4.5	34.1 ± 5.6	0.059
> 35 (n, %)	6 (14.6%)	5 (27.7%)	0.201
BMI (kg/m²)	28.6 ± 3	30.2 ± 4	0.075
> 30	11 (26.8%)	9 (50%)	0.077
Parity	9/32	3/15	0.466
Primiparous/multiparous			
With comorbidities (n, %)	4 (9.7%)	5 (27.7%)	0.087
Hypertensive disorders	1	0	
Diabetes	2	2	0.147
Respiratory disease	1	3	
Term of pregnancy (weeks of gestation)	36.8 ± 2.7	35.1 ± 3.6	0.061

Table 2. *Maternal data at hospital admission.*

	Booster group n = 41	Non-booster group n = 18	P-value	OR (95%CI)
Asymptomatic (%)	24 (58.5%)	3 (16.6%)	**0.003**	OR 5.5 (1.5-19.8)
Cough	15 (36.5%)	10 (55.5%)	0.142	
Fever	12 (29.2%)	12 (66.6%)	**0.008**	OR 0.2 (0.06-0.67)
Headache or asthenia	6 (14.6%)	4 (22.2%)	0.357	
Dyspnoea	0	1 (5.5%)	0.305	
Digestive signs (nausea, vomiting, diarrhoea...)	1 (2.4%)	1 (5.5%)	0.521	
Others: sore throat or rhinorrhoea, anosmia and ageusia	1 (2.4%)	0	0.695	
Pre-eclampsia	5 (12.2%)	3 (16.6%)	0.464	
Anaemia < 10g/dL	3 (7.3%)	1 (5.5%)	0.644	
Cytolysis (> 3×)	2 (4.8%)	1 (5.5%)	0.672	
Thrombopenia < 50,000	0	0	-	
Radiological signs > 20% (yes/no)	0	1 (5.5%)	0.305	
Need for O_2 at hospital admission	0	1 (5.5%)	0.305	
O_2 needed < 6 L/min	0	0		
O_2 needed 6-15 L/min	0	1		
O_2 needed > 15 L/min	0	0		

significant difference concerning the indications of caesarean delivery (**Table 3**). The booster vaccination allowed a reduced incidence of clinical deterioration after delivery from 33.3% to 2.4% with p = 0.002. The incidence of maternal complications was also lower (**Table 3**). The length of hospitalization was reduced from 4.67 ± 4 days in the "Non-booster vaccination" group to 1.98 ± 0.93 days in the "Booster vaccination" group (p = 0.001). Maternal death was seen in one patient in the "Non-booster vaccination" group (p = 0.305). This death was related to a severe form of COVID-19.

The booster vaccination reduced prematurity rates from 61.1% to 12.1% with p = 0.011 (**Table 4**). Furthermore, the need for NICU admissions was seen in 4 neonates (22.2%) in the "Non-booster vaccination" group *versus* no patient in the "Booster vaccination" group (p = 0.007).

DISCUSSION

This study emphasizes the role and importance of COVID-19 vaccine booster shots received in the

Table 3. *Maternal outcomes after delivery.*

	Booster group n = 41	Non-booster group n = 18	P-value	OR (95%CI)
Mode of delivery				
Caesarean delivery	17 (41.4%)	13 (72.2%)	**0.028**	OR 0.272 (0.082-0.908)
Vaginal delivery	24 (58.6%)	5 (27.7%)		
Indications for caesarean delivery				
Foetal distress	3 (17.6%)	3 (23%)	0.232	
Obstetrical indications	14 (82.3%)	9 (69%)	0.074	
Severe preeclampsia	0	1 (7.7%)	0.305	
Maternal life-saving	0	0	-	
Maternal outcomes after delivery				
Clinical deterioration after delivery	1 (2.4%)	6 (33.3%)	**0.02**	OR 0.05 (0.005-0.45)
Increased need for O_2 after delivery	1 (2.4%)	6 (33.3%)	**0.02**	OR 0.05 (0.005-0.45)
O_2 needed < 6 L/min	1	5	**0.038**	
O_2 needed 6-15 L/min	0	0	-	
O_2 needed > 15 L/min or Optiflow	0	1	0.305	
Postpartum referral to ICU	0	1	0.305	
Complications (yes/no)	0	5	**0.002**	
ARDS	0	0	-	
Postpartum haemorrhage	0	2		
Thromboembolic events	0	1	0.305	
Septic shock	0	1	0.305	
Pregnancy related complication	0	1	0.305	
Need for advanced resuscitation	0	1	0.305	
Length of hospital stay (days)	1.98 ± 0.93	4.67 ± 4	**0.001**	
Length of hospitalization ≤ 5 days	40 (97.5%)	12 (66.6%)	**0.0001**	OR 20 (2.1-189)
Maternal death	0	1 (7.7%)	0.305	

Table 4. *Perinatal outcomes.*

	Booster group n = 41	Non-booster group n = 18	P-value	OR (95%CI)
Extreme prematurity: delivery < 28 WG	0	1 (5.5%)	0.305	
Severe prematurity (28 to 32 WG)	4 (9.7%)	7 (38.8%)	**0.04**	OR 0.278 (0.07-1.07)
Moderate to late prematurity (32 to 37 WG)	1 (2.4%)	1 (5.5%)	0.586	
Prematurity (≤ 37 WG)	5 (12.1%)	11 (61.1%)	**0.011**	OR 0.19 (0.06-0.91)
Vertical transmission	0	0	-	
Breastfeeding	34 (82.9%)	11 (61.1%)	**0.072**	OR 3.0 (0.88-10.7)
Admission in neonatal ICU	0	4 (22.2%)	**0.007**	
Neonatal deaths and stillbirth	0	0	-	

current pregnancy on maternal and perinatal outcomes during the COVID-19 Omicron waves. The booster vaccination resulted in higher rates of asymptomatic forms of the disease and more vaginal deliveries with fewer rates of complications and clinical deterioration after delivery. Furthermore, neonatal outcomes were improved with a lower rate of prematurity and less need for a neonatal intensive care unit. The main strength of this study is that it shows the benefits of booster shots of the vaccine received during pregnancy in enhancing maternal and neonatal protection against the Omicron variant, which is now dominating the world, when compared to mothers who did not get their booster dose. This study may be useful in convincing hesitant mothers to get their booster dose because they were pregnant and in enhancing the acceptance rate of the SARS-CoV-2 vaccine among pregnant women [11]. In the general population, Barda and colleagues reported the effectiveness of booster mRNA vaccines in a large population study from Israel [12]. A booster dose administered at least 5 months after the second dose significantly reduced the rate of new COVID-19 infections, hospital admissions, and severe infections [12]. In pregnancy, the American College of Obstetricians and Gynaecologists recommended booster doses for pregnant and post-partum women on the basis of their increased risk of COVID-19-related complications [13]. Despite its safety, mothers are hesitant [14], and data on the durability of the immune response in pregnant women and the impact on maternal and perinatal outcomes are scarce [15], particularly with the new and recent SARS-CoV-2 variants [3, 6]. Several studies in the literature demonstrated the safety of the BNT162b2 second- and third-dose vaccines in pregnancy in terms of early adverse events and immunogenicity, as well as the absence of early obstetric complications [16-18]. However, the immune response during pregnancy was reported to be lower than in non-pregnant women. In a previous study, the blood serology for SARS-CoV-2-specific antibodies before the third dose of the vaccination did not differ significantly between the pregnant and non-pregnant groups. However, the SARS-CoV-2 IgG serum level 33 days after the third dose was significantly lower among pregnant women compared with nonpregnant women [18]. This same study confirms that the booster dose was effective as it generated a stronger humoral immune response in pregnant women compared with the second dose [18], including against Omicron [19]. This may explain the improved maternal outcomes owing to the booster vaccination during pregnancy [20].

In addition, the available data suggest that a COVID-19 booster dose during pregnancy induces a robust antibody response in pregnant women and increases maternal antibodies [21]. This may be implicated in reducing the severity of the disease, especially when the mother catches the virus in the peripartum period. In our study, the booster vaccination resulted in more asymptomatic forms and better general conditions. However, we didn't find significant difference in the incidence of dyspnoea or oxygen requirements. This seems to be particular to the Omicron variant, which causes less respiratory injury, particularly in vaccinated patients. Our results were comparable with those in the literature [16, 21]. Moreover, the maternal outcomes are conditioned by the severity of the disease [22]. Severe forms of COVID-19, characterized by an inadequate inflammatory response, can cause maternal respiratory distress, thromboembolic events, and multiple organ failure. These severe cases can impact the mode of delivery and the prognosis of the patients [23]. In our study, the booster vaccination allowed fewer caesarean deliveries and a better prognosis after delivery with reduced rates of complications and a shorter hospital stay [24].

The maternal immune response was associated with the transmission of SARS-CoV-2 antibodies to the foetus [16, 25]. It was also reported that third-trimester booster doses were associated with the highest maternal and umbilical cord antibody levels [26]. The vaccination of lactating women is associated with high levels of SARS-CoV-2 antibodies in the breast milk as well [27]. This may explain the improved neonatal outcomes in our study, particularly the lower rates of prematurity and the need for hospitalization in NICU. According to a previous study [28], the effectiveness of maternal vaccination against hospitalization for COVID-19, among infants aged less than 6 months, was 52% overall, 80% during the delta period, and 38% during the omicron period. The effectiveness was increased to 69% when maternal vaccination occurred during pregnancy, particularly after 20 weeks of gestation [29]. In our observational study, the booster shot of vaccine given during the current pregnancy has reduced the incidence of prematurity, known to be the most common adverse pregnancy outcome [30]. These findings can be

explained by improved maternal conditions with reduced severity of the disease [31]. Several risk factors for adverse perinatal outcomes in foetuses with maternal COVID-19 infection have been reported in the literature, including early gestational age at infection, maternal ventilatory support, and low birthweight [32].

However, these improved neonatal outcomes seem to be particular to the booster vaccination because a previous study including 24,288 singleton live births showed that the risks of preterm birth and small birth weight were similar between newborns prenatally exposed and unexposed to maternal vaccination with only two doses [29].

The improved neonatal outcomes may encourage mothers to get their booster dose of vaccine during pregnancy. For this reason, it is important to implement an informative campaign to make mothers aware of the impact of booster vaccination on maternal and foetal wellbeing, which seems to strengthen the mother's adherence to recommendations [33].

Our findings showed the protective role of booster doses of vaccine during pregnancy. This can provide positive psychological support for vaccinated mothers and may relieve the psychological distress previously observed during the COVID-19 pandemic among mothers and maternity healthcare providers [34]. In fact, the perception of the risk of contamination and its consequences was correlated with the feeling of work exhaustion among obstetric healthcare providers [35]. We think that boosting the immunity of mothers, which can lead to less severe forms and reduce the workload and the feeling of work exhaustion. Furthermore, in the postpartum period, several cases of puerperal psychosis were observed during the COVID-19 pandemic, which seems to be related to maternal anxiety about themselves and their newborns and being obsessed by possible perinatal complications [36, 37]. So, the mothers' awareness of the degree of protection when vaccinated with a booster dose may help. Furthermore, long COVID is an increasingly recognized complication of COVID-19 infection. It is due to a multisystem disorder that presents significant diagnostic challenges because of its various symptoms such as fatigue, pain, memory and attention troubles, and even menstrual cycle troubles [38].

Although vaccination and oligo elements supplementation [39] may contribute to a reduction in the population health burden of long COVID and should be encouraged during pregnancy [40], other studies reported menstrual irregularities after COVID-19 vaccination [41].

The main limitation of this study was that the viral RNA sequencing data allowing the diagnosis of the variant was not available. So, the unproven SARS-CoV-2 variant limits the ability to be sure that all cases were affected by the omicron one. The inclusion criteria of full-term infected women allowed for bias to be addressed and the impact of booster vaccination on maternal and neonatal outcomes to be investigated but resulted in a small sample size for this study. On the other hand, sample size calculation seems biased by the lower rates of asymptomatic women in the booster vaccination group, thus leading to a small final sample size. The other limit is that the exclusion of patients who had recurrent COVID-19 infections during the previous waves is sometimes not possible in cases of asymptomatic, unknown or undocumented SARS-CoV-2 infections. Furthermore, we didn't investigate the role of prenatal booster vaccination on long COVID syndrome and particularly its impact on female reproductive functions [38, 41] and mental health [36].

CONCLUSIONS

The COVID-19 booster vaccination during pregnancy seems to be beneficial during the Omicron period. It improved obstetrical and neonatal outcomes. It reduced the severity of the maternal disease by increasing the rate of asymptomatic forms and protected against clinical deterioration, increased oxygen support after delivery, and prematurity. It also reduced the duration and risk of long hospital stay. We suggest that physicians and maternity healthcare providers should encourage the COVID-19 booster vaccination during the current pregnancy and convince mothers about its benefits to prevent maternal, foetal, and neonatal adverse outcomes.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

M.K.: Writing – original draft. A.J.: Conceptualization, investigation, methodology, writing – review & editing. Y.E.: Data curation, formal analysis, in-

vestigation. M.D.: Data curation, investigation. A.B.: Data collection. K.C., K.K.: Supervision, validation, visualization.

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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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