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ORIGINAL ARTICLE

Maternal and perinatal outcomes in the COVID-19 Omicron wave in comparison with the Delta wave: a multicenter observational study.

Short title: Omicron wave versus Delta wave in pregnancy

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Abstract

Objective. The aim of the study was to compare maternal and neonatal outcomes of the COVID-19 in Omicron and Delta wave.

Materials and Methods. In this prospective observational multicenter study, we included unvaccinated patients who were hospitalized to deliver and who gave birth while infected. Patients who gave birth from May 15, 2021 to November 15, 2021 were allocated to the Delta group and those who gave birth from November 15, 2021 to the 1st of June 2022 were included in the Omicron group.

The maternal and fetal outcomes were compared between the two groups. The significance level was set at $p < 0.05$.

Results. We included 84 patients in the Delta group and 45 patients in the Omicron group. We noted more asymptomatic COVID-19 ($p = 0.001$), less dyspnea ($p = 0.021$), and less need for oxygen ($p = 0.008$) in the Omicron group. Cesarean section delivery was seen in 62 patients from the Delta group, and vaginal delivery was seen in 20 patients from the Omicron group with $p = 0.029$. Even if the incidence of complications and clinical deterioration after delivery were comparable in both groups, the length of hospital stay and the number of deaths were significantly higher in the Delta group with $p = 0.038$ and $p = 0.024$, respectively. The fetal outcomes were comparable.

Conclusions. SARS-CoV-2 infection during the Omicron wave had a lower requirement for oxygen support and improved maternal outcomes in comparison with the Delta wave.

Key words: COVID-19 waves; SARS-CoV2 variants; pregnancy; maternal outcomes; fetal outcomes.

Introduction:

Pregnant women are vulnerable to viral infections such as COVID-19 infection [1]. Heavy morbidity and high rates of mortality [2] may be due to immunological and physiological changes during pregnancy [3], particularly when infection occurs in the peripartum period with unvaccinated patients [4]. Since the beginning of the pandemic, several waves with different SARS-CoV2 variants have created a tsunami of COVID-19 worldwide [5]. The omicron variant of SARS-CoV-2 (B.1.1.529) spread rapidly across the world, out-competing the previous variants such as the Delta variant (B.1.617.2) [6]. Omicron, first detected in November 2021, appears to cause less severe acute illness than previous variants, at least in vaccinated populations [6]. The role of vaccination in reducing the COVID-19 severity should be considered. To date, scientists think that this omicron wave indicates the end of the pandemic even if COVID-19 persists [7]. However, we must exercise caution regarding the impact of this new variant in specific and high-risk patients, such as pregnant women. The impact of this new variant on maternal and fetal outcomes is not yet well known.

The aim of the study was to compare maternal and perinatal outcomes of the Omicron COVID-19 wave with the Delta wave among unvaccinated pregnant women, infected at delivery.

Materials and Methods

After obtaining patients' oral consent and local ethics committee approval, a multicenter observational cohort study was conducted to compare the maternal and neonatal outcomes of the Omicron COVID-19 wave with the Delta wave among unvaccinated pregnant women. This study was conducted in four (level 2 or level 3) maternity hospitals from 3 regions in the south of Tunisia (Sfax, Medenine, and Tataouine) from May 15, 2021, to the 1st of June 2022.

We included only unvaccinated patients who were hospitalized for delivery and gave birth while infected with COVID-19. The patients included had a positive reverse transcriptase–polymerase chain reaction (RT-PCR nasopharyngeal swab) test result for severe acute respiratory syndrome coronavirus 2 within the 5 days preceding delivery. We excluded cases of fetal loss defined as spontaneous antepartum fetal death < 14 weeks of gestation (WG) and cases of late miscarriage 14–24 WG. Vaccinated patients and those whose management did not adhere to the standard protocol were also excluded. We also excluded patients with recurrent SARS-CoV2 infections.

The variables were:

• Demographic parameters considered were: age, body mass index (BMI), term of pregnancy, parity, and previous co-morbidities.

• Clinical and biological features of the COVID-19 infection before delivery and the need for oxygen supplementation define the severity of the infection.

• Maternal adverse outcomes after delivery include increased need for oxygen supplementation after delivery, referral to the intensive care unit (ICU), maternal complications, and maternal deaths.

Clinical deterioration was defined by an increased need for O2 supplementation after delivery, or referral to ICU, and maternal complications (acute respiratory distress syndrome: ARDS, postpartum hemorrhage, thromboembolic events, septic shock, and pregnancy-related complications including retro-placental hematoma; hemolysis, elevated liver enzymes, and low platelets Syndrome: 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. We looked at the length of hospital stay and the incidence of maternal deaths.

• Neonatal outcomes considered were neonatal ICU (NICU) admission, prematurity, vertical transmission, and stillbirth or neonatal deaths.

All patients enrolled in this study were not vaccinated and had the same management protocol. All maternity hospitals participating in this study adhere to the INAES (Instance Nationale d'Evaluation et d'Accréditation en Santé) guidelines [8].

To compare maternal and perinatal outcomes between Omicron and Delta waves among pregnant women who tested positive at the moment of birth, patients were divided into 2 groups with reference to the epidemiologic situation and COVID-19 waves that occurred in Tunisia (figure 1):

• Delta Group: patients who gave birth during the delta wave, lasting from May 15, 2021, to November 15, 2021.

• Omicron Group: patients who gave birth during the Omicron waves, lasting from November 15, 2021, to the 1st of June 2022.

The COVID-19 waves were called Delta and Omicron because, in these periods, the predominant variants circulating in our country were respectively the Delta variant (B.1.617.2) and the Omicron variant (B.1.1.529) [9].

Then, statistical analyses were conducted using the SPSS 23.0 (SPSS, Chicago, IL, USA) statistical package. We distinguished two groups according to the COVID-19 wave among positive pregnant women. The comparison between groups was achieved by Student's t-test and Chi2 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 level was set at $p<0.05$.

Results:

Of the 189 patients participating in the study, 129 deliveries were included: 84 deliveries in the Delta wave and 45 deliveries in the Omicron wave. Sixty patients were excluded: three for fetal loss (<14 WG), four because of late miscarriage (14-24 WG), and 53 because of completed or uncompleted vaccination. No patient was excluded because of recurrent SARS-CoV2 infection. All fetal losses and late miscarriages occurred in the Delta wave, and all vaccinated patients were admitted in the Omicron wave. The 129 patients included were recruited mainly from 3 regions in the south of Tunisia: Sfax (N=102), Medenine (N=19), and Tataouine (N=8).

Demographic parameters (age, BMI, comorbidities, parity, and term of pregnancy) were comparable in both groups (table 1). Asymptomatic COVID-19 was seen in 22% and 3.5% of patients in the Omicron wave and Delta wave, with p=0.001. In the Omicron group, we noted lower rates of cough (p=0.032), fever (p=0.001), and dyspnea (p=0.021). The other clinical features (asthenia, digestive troubles, otorhinolaryngological symptoms, preeclampsia, anemia, and cytolysis) were comparable in both groups (table 2).

The Delta group had a higher rate of patients requiring oxygen supplementation before delivery (47 patients: 55.9%) than the Omicron group (15 patients: 33.3%), with p = 0.008. However, the oxygen flow administered (in patients who needed oxygen supplementation) and the need for ICU admission were comparable in both groups (table 2). The incidence of vaginal delivery was higher in the Omicron group (55.5%) in comparison with the Delta group (26.1%) with p=0.029. Cesarean section was performed mainly for fetal distress in the Delta group (51.6%) and for obstetrical reasons in the Omicron group (59%); p = 0.001 (table 3). After delivery, the incidence of clinical deterioration, an increased need for oxygen, maternal complications, and referral to the ICU were comparable in both groups. Furthermore, the Delta group had a significantly longer hospital stay and a higher number of deaths (table3). Fetal and neonatal outcomes regarding prematurity, vertical transmission, neonatal critical care unit admission, and stillbirth or neonatal deaths were comparable in both groups (table 4).

Discussion:

This study showed that the COVID-19 severity in unvaccinated pregnant women was reduced during the Omicron wave. We noted more asymptomatic and minor forms, which influenced the mode of delivery and the indications of cesarean deliveries and reduced postpartum morbidity and mortality.

The main strength of this study is that it provides data related to maternal and perinatal outcomes associated with COVID-19 during the Delta and the Omicron waves among unvaccinated women from the south of Tunisia. To date, there is little data on the severity of infection by the emergent Omicron variant in unvaccinated pregnant women compared with previous variants. Our study showed that even if the Omicron variant is less dangerous than the Delta, unvaccinated parturients may need oxygen support and sometimes ICU admissions. This emphasizes the importance of vaccination [4].

The main limitation of the study was that variant sequencing data was not available for all patients. So, the time of infection was used to indicate the predominant variant. The second limit is that the patients were not recruited simultaneously (the Omicron wave came after), which can affect the management of the patients because health workers (anesthesiologists, obstetricians, midwives, and nurses) have gained more experience from previous waves [10].

The Omicron variant, first identified in Botswana in November 2021, is rapidly becoming the dominant circulating variant. It has a significant growth in contagion over the Delta, leading to rapid spread with higher incidence levels [11]. In our study, the number of patients admitted during the omicron wave was lower than that of patients admitted during the delta wave. This may be explained by the exclusion of vaccinated patients. We excluded vaccinated pregnant women because previous studies showed the effectiveness of the BNT162b2 vaccine against severe COVID-19 requiring hospital admission [12].

COVID-19 has been mild in comparison to the Delta since the emergence and spread of the omicron variant [11]. Several studies in the general population [13, 14], and in pregnant women [15, 16] evoked lower severity with a significant decrease in deaths [17]. These findings were comparable with our results, as we noted more asymptomatic patients and less need for oxygen supplementation. However, we should mention that the omicron variant appeared after the globalization of the vaccine, and even if the majority of studies comparing delta with omicron selected unvaccinated patients, the indirect effect of vaccination in the general population should be discussed. It was reported that mRNA-based COVID-19 vaccines are associated with a reduction in SARS-CoV-2 infections requiring hospital admission, not only among vaccinated individuals but also among unvaccinated adults [18]. In our population, pregnant women were hesitant about vaccination. However, the general population has been widely and completely vaccinated since September 2021 [19]. The COVID-19 severity can impact the mode of delivery and the maternal and fetal outcomes as a consequence. Maternal hypoxemia due to COVID-19 pneumonia, ARDS, and villous infraction (thrombotic lesions in the placenta) [20], often seen in the Delta wave, can lead to emergent cesarean section delivery for fetal distress or maternal life-saving [21]. However, vaginal delivery can be accepted only in patients who have no need or low flow of oxygen [22]. This may be the explanation for our obstetrical results (mode of delivery and indications for cesarean delivery) [23].

Even if enhanced recovery strategies after cesarean section reduce the risks of postpartum complications and improve maternal outcomes [24], the physiological stress induced by surgery is known to increase the rate of complications in infected pregnant women. This might explain the higher length of hospital stay after delivery in the delta group, in which cesarean delivery was the main mode of delivery.

In our study, fetal outcomes were comparable in both groups. However, prematurity (<34 WG) was higher in the delta wave. These results are compatible with those of previous studies [16]

which reported that preterm birth was significantly increased during the Delta wave (15.4%) compared with the pre-Delta period (4.9%) and omicron wave (2.8%). The incidence of prematurity in the delta wave in our region seems to be comparable with previous waves [25]. Nevertheless, maternal oxygen support, which seems to be increased with the delta variant, was reported as a risk factor for adverse fetal outcomes [26]. This may argue in favor of a higher incidence of adverse perinatal outcomes in fetuses with maternal COVID-19 infection in the Delta wave [27]. It was also reported that early gestational age at infection is one of the main determinants of adverse fetal outcomes [26]. However, in our study, we included only infected parturients at delivery. In the literature, some habits known to be involved in adverse fetal outcomes were not investigated in our study, like coffee drinking [28], alcohol intake [29], and sleep deprivation [30], It was also reported that maternal vascular malperfusion, including decidual arteriopathy, was significantly more frequent after SARS-CoV-2 infection, with the highest rates in the Delta era [27]. This may explain the poor fetal outcomes that could be associated with the Delta variant.

Recent and novel evidence suggests that the cytokine storm underlies the activation of the coagulation system which may lead to villous infarction and decidual arteriopathy with thrombosis [31]. MicroRNAs (miRNAs), small non-coding RNAs, serve as gene expression regulators and are involved in balancing the pro/anticoagulant and pro-/anti-inflammatory factors maintaining homeostasis [32]. The miRNAs can also reduce the viral load by degradation of viral RNA and reducing the expression of ACE2 receptors, besides mitigating the deleterious consequences of the exaggerated secretion of cytokines [33]. The miRNAs are expressed in the placenta and are involved in regulating trophoblast differentiation, migration, invasion, proliferation, apoptosis, vasculogenesis, angiogenesis, and cellular metabolism [34]. As a result, changes in the expression of selective miRNAs in COVID-19 may play an important role in both placental-induced diseases, such as intrauterine growth restriction [35]. However, the impact of SARS CoV2 variants (Delta variant and Omicron variant) on placental miRNA dysregulation is not yet well known and further studies are needed.

Conclusion

SARS-CoV-2 infection during the Delta wave was associated with clinical signs of severity, increased need for oxygen support, and higher maternal mortality compared with infection during the Omicron wave. Obstetrical outcomes may be influenced by COVID-19 severity. This may explain the improved maternal and perinatal outcomes during the Omicron wave. However, underestimating the risks of the Omicron variant is inexcusable and may adversely affect the vaccination rate among pregnant women, who are at an increased risk of adverse maternal and perinatal events related to COVID-19 severity.

- **Authors' contribution:**

- A.J : Conceptualization, Investigation, Methodology, review & editing
- M.K: original draft, Writing
- O.B: Data curation, Formal Analysis and Investigation
- Y.E: article revision
- O.D: Investigation

- K.C: Supervision, Validation, Visualization
- K.K: Supervision, Validation, Visualization

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- **Enhancing the quality and Transparency Of health Research:** this manuscript is conforming to the EQUATOR network guidelines.

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Table 1: Demographic parameters

	Delta Group N= 84	Omicron Group N= 45	P value
Age	30.5 ± 4.7	31.4 ± 5.7	0.309
Age >35 years	21 (25%)	15 (33.3%)	0.211
BMI	28.6 ± 3.6	28.6 ± 3.1	0.966
BMI>30 kg/m^2	31 (36.9%)	18 (40%)	0.437
With comorbidities	10 (11.9%)	2 (4.4%)	0.086
Term of pregnancy (WG)	35.6 ± 3.8	36.6 ± 3.0	0.130
Multiparity (>2)	59 (70.2%)	39 (86.6%)	0.051

Table 2: COVID-19 severity before delivery

	Delta Group N= 84	Omicron Group N= 45	P value
Asymptomatic	3 (3.5%)	10 (22.2%)	**0.001**
couph	64 (76.1%)	27 (60%)	**0.032**
fever	58 (69%)	17 (37.7%)	**0.001**
Headacke and asthenia	51 (60.7%)	25 (55.5%)	0.314
Dyspnea	31 (36.9%)	7 (15.5%)	**0.021**
Digestive signs	18 (21.4%)	6 (13.3%)	0.208
Sore throat, rhinorrhoea, anosmia and ageusia)	9 (10.7%)	2 (4.4%)	0.194
preeclampsia	18 (21.4%)	12 (26.6%)	0.375
anemia	11 (13%)	11 (24.4%)	0.133
cytolysis	11 (13%)	7 (15.5%)	0.419
Thrombopenia (<50000)	0 (0%)	1 (2.2%)	0.176
CT-Scan > 50% (yes/no)	7/5	3/0	0.266
Need for O2 before delivery	47 (55.9%)	15 (33.3%)	**0.008**
O2<6 L/min	37 (82.2%)	13 (86.6%)	0.233
O2 : 6-15 L/min	7 (14.9%)	0	
O2 > 15 L/min, optiflow or CPAP	3 (6.4%)	2 (13.4%)	
ICU before delivery	2 (2.3%)	3 (6.6%)	0.230

Table 3: Maternal outcomes after delivery.

	Delta Group N=84	Omicron Group N= 45	P value
Mode of delivery (cesarean/ vaginal)	62/22	25/20	**0.029**
Indications of cesarean delivery			
Foetal distress	32 (51.6%)	2 (8%)	
Obstetrical indications	18 (29%)	13 (59%)	**0.001**
Severe preeclampsia	2 (3.2%)	1 (4%)	
Maternal life-saving	9 (14.5%)	5 (11.1%)	
Other circumstances	1(1.6%)	5 (11.1%)	
Clinical deterioration (%)	37 (44%)	14 (31.1%)	0.106
Increased need for O2 after delivery	32 (38%)	13 (28.8%)	0.198
Postpartum referral to ICU	24 (28.5%)	9 (20%)	0.198
Complications (yes/no)	34 (40.4%)	15 (33.3%)	0.168
ARDS	16	8	
Postpartum hemorrhage	4	5	
Thromboembolic events	1	2	0.065
Septic shock	4	0	
Pregnancy related complication	9	0	
Length of hospital stay (days)	8.6 ±6.5	6.3 ± 4.4	**0.038**
Maternal deaths	12 (14.2%)	1 (2.2%)	**0.024**

Table 4: Neonatal outcomes

	Delta Group N=84	Omicron Group N= 45	P value
Severe prematurity : Delivery < 28 WG	4 (4.7%)	0	0.175
Premature delivery : 28-34 WG	26 (30.9%)	10 (22.2%)	0.199
Prematurity < 34 WG	30 (35.7%)	10 (22.2%)	0.084
Vertical transmission	3 (3.5%)	1 (2.2%)	0.565
Admission in neonatal ICU	24 (28.5%)	10 (22.2%)	0.287
Neonatal deaths and stillbirth	7 (8.3%)	2 (4.4%)	0.333