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COVID-19 Severity Among Non-Vaccinated Pregnant Women During the Delta Wave in Tunisia: A Retrospective Monocentric Study

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ABSTRACT

Introduction: Pregnant women are vulnerable to SARS-CoV2 infection, particularly with the Delta variant. The aim of our study is to describe the COVID-19 syndrome among non-vaccinated pregnant women during the delta wave and to investigate risk factors for severe forms.

Methods: In this study, we included all non-vaccinated pregnant women who tested positive for COVID-19 and who required hospital admission at any stage of gestation during the Delta wave in the maternity of Sfax, Tunisia. Patients were divided into 2 groups according to the mode of delivery in case of completed pregnancies and according to the severity of the disease. Severe COVID-19 is considered when the pregnant woman requires advanced oxygen support or intensive care unit referral. We performed univariate and multivariate logistic regression models to investigate the predictors of severe maternal outcomes among infected pregnant women. The significance level was set top ≤ 0.05.

Results: one hundred patients were included. Severe adverse outcomes were observed in 23 patients (group1). The mortality rate during the Delta wave was 6%. The mode of delivery had not influenced the maternal and perinatal outcomes. Age >35 years old [OR 3.16, 95% CI 1.13- 8.84], BMI>30 kg/m2 [OR 2.63, 95% CI 1.0 -6.95], preeclampsia [OR 4.0, CI 95% 1.04- 15.32], dyspnea [OR 7.55, 95% CI 2.62- 21.7], cytolysis [OR 4.6, 95% CI 1.48- 14.2], and lung injury in CT Scan > 50% [OR9.6, 95%CI 1.48-62.1] were significantly associated with an increased risk of severe maternal outcomes.

Conclusions: During the delta wave in Tunisia, non-vaccinated pregnant women seem to be at higher risk of severe maternal outcomes and maternal deaths. The main risk factors for severe outcomes were age 35, obesity, preeclampsia, cytolysis, and severe lung damage in the CT scan.

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Introduction

Since the emergence of the SARS COV2 virus in 2019 in China, many variants have been seen [1]. This may explain why COVID-19 appears with a large spectrum of clinical presentations and a non-negligible occurrence of life-threatening and fatal complications, particularly with the Delta variant, which seems to be the most harmful [2]. COVID-19 generally manifests with fever, cough or gastro-intestinal troubles, but sometimes it can lead to severe outcomes with pneumonia or ARDS (acute respiratory distress syndrome), renal failure, thrombo-embolic events and multiple organ dysfunctions, mostly in patients with comorbidities or with immunodeficiency disorders [3]. Pregnant women are vulnerable to viral infections and are at higher risk of complications and mortality because of immunological and physiological changes during pregnancy, particularly when they are not vaccinated [4-6]. The aim of this study was to describe the maternal and fetal outcomes during the Delta wave and to investigate the main risk factors for severe maternal outcomes among non-vaccinated pregnant women during the Delta wave.

Methods

Study Design and Setting

This is a retrospective case-control study. It was conducted after obtaining the local ethics committee approval and patients informed oral consent. We collected data from pregnant women who were hospitalized in the COVID 19 Unit of the Gynecology and Obstetrics department of the Hedi Chaker University Hospital in Sfax, Tunisia, from March 19, 2021 to November 15, 2021 (the period of the delta wave in Tunisia: figure1).

Participants

In this study, we included all non-vaccinated pregnant women suffering from COVID-19, confirmed with rt-PCR for

nasopharyngeal swab and who needed hospitalization (moderate to severe forms or asymptomatic patients who were hospitalized for obstetrical reasons) at any stage of gestation, except those < 18 years of age as well as individuals declining to consent or not able to consent for themselves. We did not include parturients hospitalized for COVID 19 with negative rt-PCR even if their chest CT scan was evocative. We did not include pregnant women who did not require hospitalization (asymptomatic or minor forms with no obstetrical reason for hospital admission). We excluded vaccinated patients.

Variables and Data Measurements

In this study, we collected data about:

- Demographic parameters: age, weight, size, body mass index, term of pregnancy, and comorbidities.
- Clinical features: clinical signs of COVID-19 and the delay between the appearance of symptoms and hospitalization.
- Radiographic and biological findings
- Obstetric and anesthesia outcomes: For completed pregnancies (pregnancy ending in either fetal loss > 14 WG or livebirth), obstetrical outcomes (pregnancy outcome, gestation age at delivery, mode of delivery) and perinatal outcomes (neonatal death, stillbirth, admission to the neonatal ICU (NICU) and birthweight) were assessed. We considered fetal loss as a spontaneous antepartum fetal death > 14 WG, a late miscarriage 14–24 WG, and a stillbirth fetal demise > 24 WG. Suspected perinatal SARS-CoV-2 transmission was defined as a positive RT-PCR result performed at birth for all newborns.
-Follow-up and prognosis: we assessed maternal and fetal complications, length of stay in COVID19 unit or ICU, and final issue (recovery, survival with post-COVID syndrome, or death).

Bias: Standardized COVID 19 Management

All patients enrolled in this study had the same management protocol. In our department, clinical management of COVID-19 adheres to the INAES (Instance nationale de l'évaluation et de l'accréditation en santé) guidelines for COVID-19 patients [7]. For obstetric management, the timing and mode of delivery in all participating hospitals were based on obstetrical indications.

Quantitative Variables: Case and Control Definition

In our study, patients were divided into 2 groups according to the severity of the COVID-19 form:

Group 1: included patients who needed advanced oxygen support (high flow cannula, non-invasive ventilation through CPAP or mechanical ventilation) or were referred to the intensive care unit (ICU) and maternal death cases. (23 patients).

Group 2: (control group) included pregnant women with either mild adverse outcomes, defined as maternal hospitalization requiring oxygen supplementation, or no adverse outcomes, defined as outpatient management or hospitalization not requiring oxygen supplementation. (77 patients). Pregnant women with severe adverse outcomes (cases/group 1) were compared to pregnant women with mild or no adverse outcomes (controls/group 2). The effect of maternal characteristics known to be risk factors for SARS-CoV-2 severe adverse outcomes in the general population (maternal age, obesity defined as a BMI > 30 kg/m2 and co-morbidities), as well as pregnancy-related risk factors such as preeclampsia, gestational age at infection, and hospitalization delay, were tested.

For completed pregnancies, we also compared the maternal and perinatal outcomes of the patients according to the mode of delivery.

Statistical Analysis

All 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 mode of delivery and then according to the severity of maternal outcomes 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.

Univariate logistic regression analysis was used to determine crude odds ratio with the 95% approximate confidence intervals as estimators of severe forms of COVID 19 in pregnancy. To assess the predictors of severe maternal outcomes, we performed a multivariate logistic regression model. The significance threshold was set at $p<0.05$.

Results

In this study, we included 100 patients: 23 patients had a severe form of COVID-19 (group 1) and 77 others had mild adverse outcomes (group 2). Therefore, the incidence of severe maternal adverse outcomes was 23% and the mortality rate was 6%.

COVID-19 In Pregnancy During the Delta Wave

In this study, we included 100 pregnant women with COVID-19. The maternal age ranged from 19 to 41. Thirty patients were aged more than 35 years. The gestation period at COVID-19 diagnosis ranged from 11 weeks (based on the last menstrual period) to 41 weeks. The majority of patients were in the third trimester of gestation (90%). Twenty-six patients had significant co-morbidities, and only two patients had chronic pulmonary disease (well controlled asthma). Obesity (BMI>30 kg/m2) was seen in 71 patients, and 63 women were multiparous. Preeclampsia was seen in 10% of our study population.

All patients were symptomatic. The main symptoms were cough (76%), fever (68%), headache, and asthenia (64%). Dyspnea (36%) and digestive symptoms like diarrhea and vomiting (19%) are also frequent. However, sore throats (3%), rhinorrhea, anosmia, and ageusia (6%) were less frequent. Biological blood analyses showed an inflammatory syndrome with elevated CRP (100%), lymphopenia (62%), anemia with Hb<9g/dL (22%), and cytolysis (16%). In this study, a chest CT scan was done for 27 parturients and showed 1 case of pulmonary embolism and 10 cases with severe forms (lung injury >50%).

The Maternal and Perinatal Outcomes According to The Mode of Delivery: (Table 1)

Seventy-six patients were infected at delivery. Cesarean section delivery was indicated for 56 parturients, and vaginal delivery was accepted in only 20 patients.

The main indications for cesarean section delivery were obstetrical indications (41.0%), fetal distress (33.9%), maternal lifesaving (14.2%), and severe preeclampsia (10.7%). There were no significant differences in the maternal or fetal outcomes between the two modes of delivery (Table 1). However, cesarean delivery was more frequent in patients requiring high oxygen flow (> 6 L/min).

Table 1: Mode of delivery and maternal outcomes

Mode of delivery	Cesarean section N= 56	Vaginal delivery N=20	P value
Age (years)	29.9 +/- 5	31.1 +/- 3	0.220
BMI (Kg/m^2)	29.5 +/- 3.1	28.8 +/- 2.9	0.542
Multiparity	39 (70%)	17 (85%)	0.181
Gestations weeks at delivery Patients <28 GW	36.3 +/- 3 25 (42.8 %)	35.2 +/- 5 10 (50%)	0.170 0.680
Indications	Obstetrical indication: 23 Fetal distress : 19 Severe Preeclampsia : 6 including 2 Hellp Syndrome Maternal life saving: 8		-
O2 > 6 L/min required before delivery	40 (71.4 %)	9 (40%)	0.034
Anesthesia technique Spinal anesthesia General anesthesia Epidural anesthesia No anesthesia	 49 (87.5%) 7 (12.5 %) 0 0	 0 0 0 20 (100%)	-
Maternal Complications after delivery	Uterine atony : 2 Respiratory distress : 3 including 1 case of Pulmonary embolism	Cardiac arrest (amniotic embolism) : 1	-
fetal coutcomes Apgar Score< 7 Birth weight (Kg) Stillbirth	 4 (7.4%) 3.12 3 (5.3%)	 0 2.54 2 (10%)	 0.569 0.091 0.293
Increased O2 after delivery	+5 (8.9%)	+2 (10%)	0.825
Referral to ICU	13 (23.3%)	2 (10%)	0.328
Duration of hospitalization (days)	6.3 +/- 3.4	5.35 +/- 3.7	0.280
Deaths	5 (8.9%)	1 (5%)	0.785

BMI : body mass index ; O2 : oxygen; ICU: intensive care unit

The Maternal and Perinatal Complications

Severe COVID-19 was seen in 23 patients. Acute respiratory distress syndrome remains the main complication (13 patients). Seven patients required CPAP and six required intubation. Preeclampsia occurred in 19 patients. Ten of them had severe and complicated preeclampsia, with two cases of HELLP syndrome and one case of eclampsia. Bacterial infection with septic shock (2 patients), sudden cardiac arrest after amniotic embolism (1 patient), and pulmonary embolism (1 patient) were less frequent complications.

The main fetal complications were premature birth (35 newborns), intrauterine growth retardation (26 cases), fetal distress (19 cases), lower birth weight (14 cases), and intrauterine fetal demise (5 cases). In our study, we had no neonatal deaths and no cases of vertical transmission. Complete recovery after COVID-19 in pregnancy was noted in 88 patients. Six patients suffered from post-Covid syndrome, with five cases of lung fibrosis and chronic respiratory insufficiency and one case of neurological deficiency due to a cardiac arrest during vaginal delivery complicated by amniotic embolism. The maternal mortality rate was 6%. Maternal deaths were caused by severe ARDS (2 cases), septic shock after bacterial infection (2 cases), one case of acute fatty liver of pregnancy, and one case of acute massive pulmonary embolism.

Predictors of Severe Covid-19 In Pregnancy: (Table 2)

Table 2: Risk factors for severe COVID 19 in pregnancy

Maternal outcomes	Pregnant women with COVID 19.		OR [95% CI]	aOR [95% CI]	P value
	Group 1	Group 2			
	N=23(%)	N =77 (%)			
Age >35 yo	9 (39.1%)	13 (16.8%)	3.16 [1.13- 8.84]	1.64 [0.16-16.2]	0.024
Multiparity> 1	8 (34%)	18 (23%)	1.13 [0.39-3.25]		0.688
Prgestational comorbidities Without With	 20 (86.9%) 3 (13.0%)	 64 (83.1%) 13 (16.8%)	 1.25 [0.39-3.93]		 0.764
BMI > 30 kg/m2	15 (65.2%)	32 (41.5%)	2.63 [1.0 -6.95]	1.66 [0.10-25.2]	0.022
Timing of exposure >24 Weeks gestation	19 (82%)	71 (92%)	1.12 [0.2-6.0]		0.315
Pre-eclampsia	5 (21.7%)	5 (6.4%)	4.0 [1.04- 15.32]		0.032
Gestational diabetes	2 (8.6%)	7 (9.0%)	0.95 [0.18-4.93]		0.954
Delay between signs and hospitalization (days)	5 +/- 4	2.4 +/- 1	1.39 [1.17- 1.66]	1.556 [0.97-2.48]	0.008
Dyspnea	17 (73.9%)	21 (27.2%)	7.55 [2.62- 21.7]	1.827 [0.19-17.2]	0.05
Anemia (Hb< 9 g/dl)	1 (4.3%)	3 (3.8%)	1.12 [0.11-11.3]		0.923
Cytolysis (> 3 ×)	8 (34.7%)	8 (10.3%)	4.6 [1.48- 14.2]	1.187 [0.48-29.5]	0.005
Lymphopenia	15 (65%)	47 (61%)	1.19 [0.45- 3.16]		0.717
Lung injury in Chest Scan > 50%	8 (34.7%)	2 (2.5%)	9.6 [1.48-62.1]	7.28 [0.61-86.4]	0.001

In a univariate analysis, age >35 years old [OR 3.16, 95% CI 1.13-8.84], BMI>30 kg/m2 [OR 2.63, 95% CI 1.0 -6.95], preeclampsia during current pregnancy [OR 4.0, CI 95% 1.04- 15.32], dyspnea [OR 7.55, 95% CI 2.62- 21.7], cytolysis [OR4.6, 95% CI 1.48-14.2]and lung injury in CT Scan > 50% [OR 9.6 , 95% CI 1.48-62.1] were significantly associated with an increased risk of severe maternal outcomes (Table 2).

A multivariate analysis adjusting for risk factors of COVID-19 severity, gestational risk factors of severe maternal outcomes, and accounting for missing values through multiple imputation showed that age [aOR1.64, 95%CI 0.16-16.2], BMI > 30 kg/m2 [aOR 1.64, 95% CI 0.10-25.2], the delay between signs and hospital admission [aOR 1.556, 95% CI 0.97-2.48], Dyspnea [aOR 1.827, 95%CI 0.19-17.2] and lung injury in chest CT scan > 50% [aOR 7.28 95%CI 0.61-86.4] were significantly associated with an increased risk of severe maternal outcomes (Table 2).

Discussion

This retrospective study emphasizes the severity of COVID-19 caused by the Delta variant of SARS-CoV2 in pregnancy, particularly in non-vaccinated populations. We experienced high rates of severe maternal outcomes and maternal mortality [8,9]. The main risk factors for severe COVID-19 were age over 35 years, obesity, preeclampsia, cytolysis, and severe lung damage in the CT scan. However, the mode of delivery did not influence the maternal and perinatal outcomes.

The clinical implication of this study is that it shows the vulnerability of pregnant women to the delta variant and emphasizes the role of vaccination in pregnant women to reduce the severity of the disease. Moreover, by investigating risk factors for severe forms that may require ICU referral, physicians may be able to anticipate actions. However, our study had several limitations. Indeed, we included only pregnant women requiring hospital admission, and we had no idea about minor forms treated at home, which may increase the mortality and morbidity rates. The role of vaccination on the Delta variant was not studied because it was not yet very common in the general population and particularly among pregnant women. In addition, in this period of the study, the Delta variant of SARS Cov2 was the major pathogen circulating in our region, but we do not have viral mARN sequencing for all patients included.

In our study, the incidence of severe COVID-19 was about 23 % and the mortality rate was 6%. This was higher than in previous studies and may explain the vulnerability of pregnant women to the delta variant [2,5]. In fact, the modulations of the maternal immune system in pregnancy may cause alterations of cellular modulated immune responses that can affect the response to viruses, and particularly to SARS-Cov2 [10]. The elevated basal metabolism in pregnancy may exacerbate hypoxemia, especially with the Delta variant, which gives severe COVID-19 pneumonia. In addition, pregnancy is a hypercoagulable state, this may exacerbate the risk of thromboembolic events commonly seen with COVID-19 and may be due to the cytokine storm, and the elevated concentrations of interleukin-6 implicated in coagulation and endothelial dysfunction [4,11].

Clinical features of COVID-19 in pregnancy during the Delta wave in our study were comparable with previous studies in the literature [5]. However, we noted an association with severe preeclampsia and cytolysis. This may be explained by possible micro thrombi in the placenta causing placental ischemia and COVID-19 preeclampsia-like [12,13]. It was reported that pre-eclampsia-like syndrome is induced by severe forms of COVID-19, which may be more frequent with the Delta variant [14,15].

In this study, we noted a high rate of cesarean section delivery (73.6% of deliveries). These results were comparable with those in the literature [16]. We think that severe maternal outcomes can

influence the mode of delivery [17]. The incidence of hypoxemia can lead to fetal distress requiring urgent cesarean delivery, in addition to severe preeclampsia and bad maternal conditions that can require cesarean delivery for maternal lifesaving. As well, the cesarean section may worsen the prognosis of the patients. Clinical deterioration, defined as an increased need for oxygen and/or the occurrence of complications, may occur more frequently after cesarean delivery than after vaginal delivery [18]. Even with enhanced recovery programs, the morbidity related to cesarean delivery is always higher [19]. To date, there is no evidence to support that the cesarean section is better than vaginal delivery in preventing possible vertical transmission [20]. The majority of cesarean section deliveries were done under spinal anesthesia, even in patients requiring oxygen support. We suggest that spinal anesthesia can be safe for COVID-19 infected pregnant women, even in patients with pneumonia [5, 21]. However, general anesthesia remains risky in obstetric patients because of difficult airway management and the risk of contamination of healthcare workers [22,23].

In this study, age >35, BMI>30 mg/m2, preeclampsia, the delay between signs and hospitalization, dyspnea, cytolysis, and lung injury> 50% were identified as risk factors for severe COVID 19 during pregnancy. However, the majority of our patients had no history of pulmonary comorbidities. In previous studies, pulmonary comorbidities and other pre-existing comorbidities (hypertension and diabetes) were the main risk factors in pregnant women and the general population [24,25]. A recent meta-analysis showed that increased maternal age, high body mass index, and pre-eclampsia were associated with severe COVID-19 in pregnancy, which was comparable to our findings [26]. The gestational age at diagnosis > 35 weeks of gestation was also reported as a risk factor [27].

Moreover, we noted that the delay between the beginning of symptoms and hospitalization was a risk factor for severity. This reflects the difficulty of accessing hospitals in developing countries during the COVID-19 waves. A previous study in Brazil, showed that black ethnicity, living in a peri-urban area, without any access to Family Health Strategy, or living more than 100 km from the hospital, were associated with an increased risk of adverse outcomes [28]. It was also reported that liver abnormalities with cytolysis biomarkers in patients with COVID-19 might be caused by the cytokine storm, hepatic ischemia, reperfusion dysfunction, or drug toxicity [29,30]. In pregnancy, it may be confounded with HELLP syndrome when associated with preeclampsia.

Even if the CT scan is not very common in pregnant women, it may be used in cases of severe respiratory distress, especially when pulmonary embolism is suspected. A pulmonary injury of >50% was a predictor for severe adverse outcomes. The role of the CT scan in assessing pulmonary injury and predicting severe forms has previously been reported [31].

Finally, we should mention that the latest variant (Omicron variant) is less harmful than the Delta, but it is becoming the dominant SARS-CoV-2 virus circulating in the world because of its very high contagiosity. However, recently, a new variant called deltamicron that recombined the genomes of these two variants has appeared [32].

Conclusion

The Delta variant of the SARS-CoV2 virus remains a dangerous pathogen in pregnant women, particularly those with increased age, obesity, difficult access to the hospital, and preeclampsia, who seem to be at higher risk of severe complications of SARS-CoV-2 infection. Nevertheless, patients with dyspnea, liver cytolysis, or pulmonary injury of more than 50% on the CT scan are at high risk of severe adverse outcomes, and these signs may worsen the prognosis of the patients. Obstetrical and neonatal outcomes appear to be influenced by the severity of maternal disease.

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Authors' contributions

M.K: original draft, writing
A.J: Conceptualization, Investigation, Methodology, review & editing
Y.M: statistical analysis and investigation
F.H, Y.E, and A.A: data collection
KK: Supervising, Validation, Visualization

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