

Risk Assessment of COVID-19 on Pregnant Women and Pregnancy Outcomes

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ABSTRACT

Background: Pregnant females represent a large category that deserves a meticulous consideration during any pandemics especially COVID-19.

Objectives: To assess maternal and fetal outcomes for 3rd trimester pregnant women during COVID-19 pandemic.

Patients and Methods: This cohort study was conducted on 85 COVID-19 pregnant women and 85 non-infected pregnant women (control) collected over 1.5 years period, they were followed up till delivery and hospital discharge.

Result: Maternal outcome of COVID-19 cases showed that 80% required blood transfusion vs 14.1% in control group (relative risk (RR)=5.7, 95% confidence interval (CI): 3.3-9.7), 40% needed intensive care unit admission vs 7.1% (RR=5.7, 95% CI: 2.5-12.8), 29.4% needed mechanical ventilation vs 1.2% (RR=25.0, 95% CI: 3.5-180.4), 47.1% had complications vs 7.1% (RR=6.7, 95% CI: 2.9-14.9), maternal mortality was 15.3% vs 1.2% (RR= 13, 95% CI: 1.7-97.2). Neonatal complications represented 41.2% vs 21.2% (RR=1.9, 95% CI: 1.2-3.2) and neonatal mortality was 14.1% vs 5.9% (RR= 2.4, 95% CI: 0.9-6.5). Gestational age, Oxygen saturation (SpO₂) on admission and SpO₂ during hospital stay were significantly lower among complicated cases (33.9±3.0 weeks, 78.5±13.5 % and 93.5±4.7 %, respectively). Multivariate logistic regression showed that gestational age (P=0.002, odds ratio (OR)=0.725, 95% CI=0.551-0.956) and SpO₂ on admission (%) (P=0.001, OR=0.851, 95% CI=0.773-0.936) were independent predictors for COVID-19 complications among pregnant females.

Conclusion: COVID-19 infection is associated with unfavorable maternal and neonatal consequences in 3rd trimester pregnant females, so comprehensive follow up of both infected mothers and their neonates is highly recommended.

Keywords: Pregnancy with COVID-19, Mortality, Maternal outcomes, Fetal outcomes.

INTRODUCTION

In late December 2019, an outbreak of novel coronavirus disease 2019 (COVID-19) caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, Hubei Province, China, and soon spread all over China and overseas [1].

On the 11th of March 2020, the World Health Organization (WHO) announced COVID-19 as a pandemic infectious disease. Egypt announced the detection of the first COVID-19 case on the 14th of February 2020 [2].

The outbreak of COVID-19 spread quickly and extensively all through the world within the early 2020s, disproportionately impacting the elderly, Black and Brown communities, and pregnant women [3].

Coronavirus family members responsible for severe acute respiratory syndrome (SARS-CoV-1) and Middle East respiratory syndrome (MERS-CoV) have been accompanied with severe complications during pregnancy and unfavorable pregnancy outcomes. On the other hand, SARS-CoV-2 belongs to the human coronavirus family, so it shows a pandemic trend to involve many pregnant women [4,5]. Pregnant women are more susceptible for severe illness from all respiratory

infections specially influenza than other general population. This is due to immunologic alterations and physiological (cardiopulmonary) adaptive changes (e.g., increased heart rate, reduced pulmonary residual capacity, etc.) that contribute to increased risk of hypoxemia and disease severity [6,7].

In addition to the impact of COVID-19 infection during pregnancy on maternal outcome, there are concerns related to the vertical transmission route and potential effect on fetal and neonatal outcome. So that pregnant women constitute a vulnerable group that requires special attention regarding prevention and management [8].

On the 26th of June 2020, Egyptian Ministry of Health advised women to postpone pregnancy as the virus could cause blood clotting and consequently could affect the placenta, which feeds the baby. In addition to that; the virus could cause other symptoms to the pregnant woman [9].

Yu *et al.* [10] reported that maternal and neonatal outcomes of late infected pregnant females appeared very good, while WAPM [7] and Li *et al.* [11] showed that maternal outcomes included maternal mortality, admission to ICU, requiring mechanical ventilation, etc.

and neonatal outcomes included preterm birth, admitted to NICU and neonatal deaths.

Based on the debates regarding maternal and neonatal outcomes of pregnant females with COVID-19 in Egypt; the risk of COVID-19 on this category of population needed to be assessed, so this study aimed to assess maternal and neonatal outcomes of 3rd trimester pregnant females with COVID-19.

PATIENTS AND METHODS

This multi-center cohort prospective study was conducted over 170 pregnant women in 3rd trimester (85 pregnant women with COVID-19 (cases) and 85 age matched healthy pregnant women (control group)) admitted to Obstetrics and Gynecology Departments in El-Bagour General Isolation Hospital, Shebin El-Kom Teaching Hospital and Menoufia University Hospital, Menoufia Governorate, Egypt during the period from 1st March 2021 to 31th August 2022. Sample size was calculated using GPower 3.1 program based on data reported by **DeBolt *et al.*** ^[12] that the COVID-19 laboratory-confirmed pregnant women had experienced higher rate of primary outcome (composite morbidity of death, a need for intubation, and other complications) when compared with control group (34.2% vs 14.9%; $P=0.03$). Calculated sample was 154 pregnant women (increased to 170 pregnant women for 10% drop-out rate) with confidence interval 95% and study power 80%.

Pregnant women with maternal age <17 or >40 years old, with twins, having pre-eclampsia or chronic diseases were excluded from the study. All pregnant women were followed up since their hospital admission till their hospital discharge after delivery. Their neonates were followed up since their time of birth till their discharge from hospital.

All pregnant women were subjected to complete personal, obstetric and present history, clinical data as oxygen saturation (SPO₂) and oxygen status during hospital admission and hospital stay.

Primary maternal outcome was assessment of mode of delivery, premature rupture of membrane (PROM), need of blood transfusion, ICU admission, need of mechanical ventilation, maternal complications and final maternal outcome.

Secondary neonatal outcome was assessment of fetal weight, time of birth, presence of congenital anomalies, polymerase chain reaction (PCR) for neonates to evaluate COVID-19 transmission from mother to fetus, admission to neonatal intensive care unit (NICU), neonatal complications and final neonatal outcome.

Ethical Approval:

Ethical approvals were obtained from Medical Ethics Committee of Menoufia Faculty of Medicine with IRP number (2/2021 COM 14). Another approval from Director of the Isolation Hospital in El-Bagour and an ethical approval from Cent. Direct. For Research and Health Development, Training and Research Sector of Ministry of Health and Population were obtained. The participants were simply informed about the purpose of this study and the steps that would be carried out. Oral consent was obtained from every participant. The study was conducted out according to Helsinki Declaration.

Statistical analysis

The IBM compatible personal computer with Statistical Package for the Social Sciences (SPSS) version 26 was used for data analysis. Quantitative data were expressed as mean± SD (standard deviation) with Student's t-test (t) and Mann-Whitney's test (U) as tests of significance, while qualitative data were expressed as number (%) with Chi-square test (χ^2) and Fisher's exact test (FE) to study association between these variables. Two-tailed P-value of < 0.05 was considered statistically significant. Relative risk (RR), which equals incidence among exposed (COVID-19 pregnant females) divided by incidence among non-exposed (control), was calculated. A logistic regression model was performed to assess the effect of different predictors on occurrence of COVID-19 complications (outcome).

RESULTS

The current study was conducted over 2 groups; Group 1 (85 pregnant women with COVID-19 (Cases)) and Group 2 (85 age matched healthy pregnant women (control)). Gestational age and previous caesarian section (CS) showed highly significant difference between both groups. Gestational age was lower in cases (**Table 1**).

Table 1: History

	Cases (n= 85)	Control (n= 85)	Test of significance	P-value
Age (years)	30.0±4.4	28.8±4.1	t= 1.89	0.061
Gestational age (weeks)	35.3±2.9	37.5±1.8	t= 5.72	<0.001**
Gravidity	3.1±2.0	2.7±1.3	U= 0.77	0.442
Parity	1.8±1.3	1.5±1.1	U= 1.24	0.216
Previous CS: Yes	57 (67.1)	23 (27.1)	$\chi^2=27.29$	<0.001**
No	28 (32.9)	62 (72.9)		

Quantitative data were expressed as Mean± SD (standard deviation), Qualitative data were expressed as number (%), t: student t test, U: Mann-Whitney test, χ^2 : Chi square test, **Highly significant, CS: caesarian section

Regarding clinical data of COVID-19 cases; SpO₂ on admission was 86.5±12.5 %, while SpO₂ during hospital stay was 95.5±3.8 %. Seventy-five cases (88.2%) were presented with pneumonia. **Figure 1** shows that majority of COVID-19 cases were on room air during hospital admission (39 cases (45.9%)), while during hospital stay majority of cases (23 cases (27.1%)) were on nasal cannula.

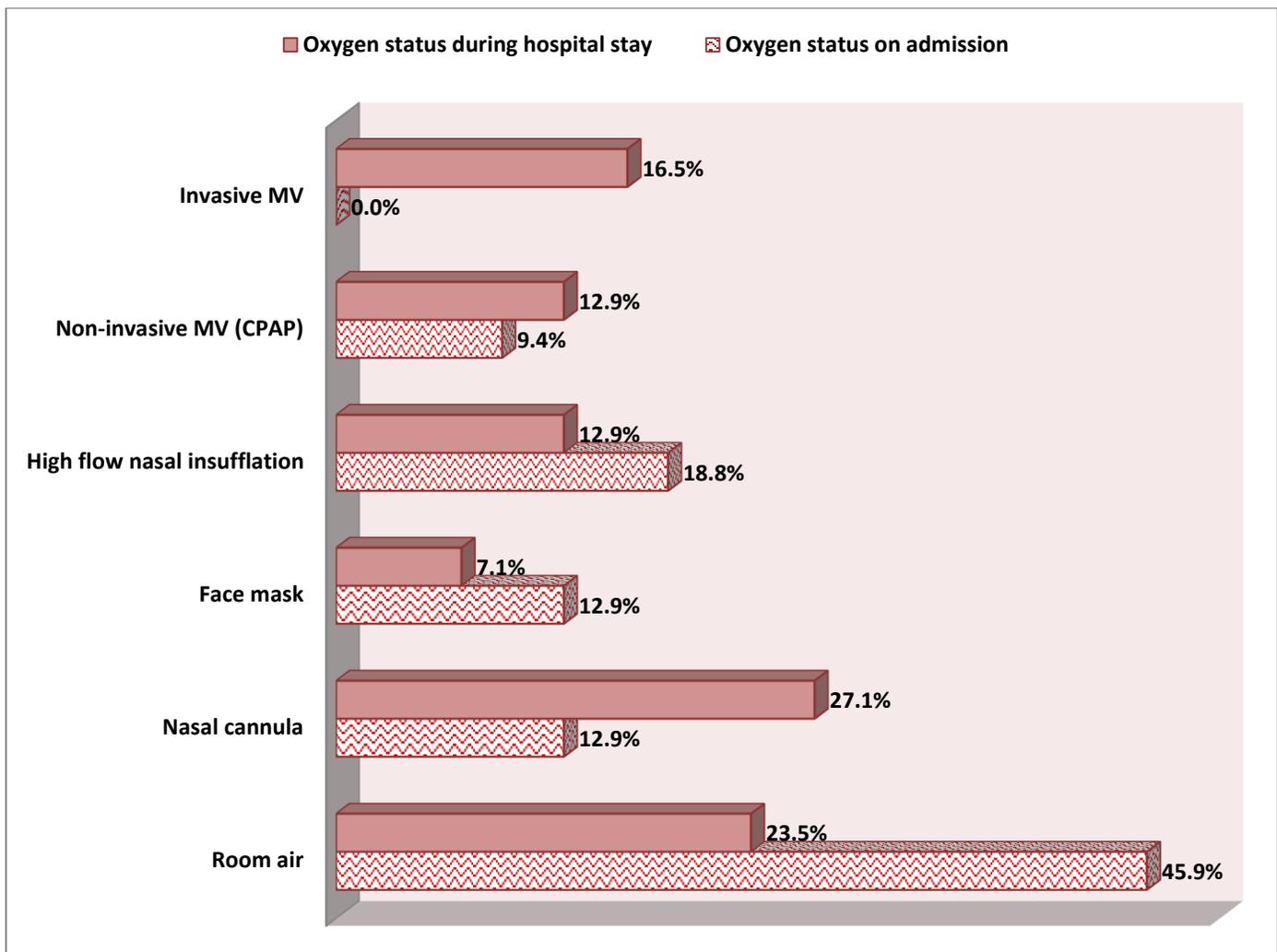


Figure 1: Oxygen status of COVID-19 cases

Mode of delivery, blood transfusion, intensive care unit (ICU) admission, mechanical ventilation, maternal complications, maternal mortality, length of hospital stay (LOS) and final maternal outcome showed highly significant difference between cases and controls. All COVID-19 cases gave birth through CS, 80% needed blood transfusion vs 14.1%, 40% needed ICU admission vs 7.1%, 29.4% needed mechanical ventilation vs 1.2%, 47.1% (40 cases) had complications vs 7.1%, 63.5% (54 cases) were cured completely and discharged, while 15.3% died (**Table 2**).

Table 2: Risk assessment of COVID-19 on maternal outcome

Maternal outcome	Cases (n= 85)	Control (n= 85)	χ^2	P-value RR (95% CI)
Mode of delivery:				
CS	85 (100.0)	34 (40.0)	72.86	<0.001**
NVD	-	51 (60.0)		
PROM:				0.161
Yes	26 (30.6)	18 (21.2)	1.96	RR= 1.4
No	59 (69.4)	67 (78.8)		(0.9-2.4)
Blood transfusion:				<0.001**
Yes	68 (80.0)	12 (14.1)	74.04	RR= 5.7
No	17 (20.0)	73 (85.9)		(3.3-9.7)
ICU admission:				<0.001**
Yes	34 (40.0)	6 (7.1)	25.63	RR= 5.7
No	51 (60.0)	79 (92.9)		(2.5-12.8)
Length of ICU stay (days)	8.3±6.3	3.5±1.4	U= 2.35	0.019*
Mechanical ventilation:				<0.001**
Yes	25 (29.4)	1 (1.2)	26.15	RR= 25.0
No	60 (70.6)	84 (98.8)		(3.5-180.4)
Venous thrombosis: No	85 (100.0)	85 (100.0)	0	1
Maternal complications				<0.001**
Yes	40 (47.1)	6 (7.1)	34.45	RR= 6.7
No	45 (52.9)	79 (92.9)		(2.9-14.9)
Maternal mortality:				<0.001**
Yes	13 (15.3)	1 (1.2)	11.21	RR= 13
No	72 (84.7)	84 (98.8)		(1.7-97.2)
Maternal outcome:				<0.001**
Complete cure and discharge	54 (63.5)	80 (94.1)		Reference
Improvement and home isolation	16 (18.8)	-	37.33	RR -
Referral	2 (2.4)	-		RR -
Discharge on-demand	-	4 (4.7)		RR -
Death	13 (15.3)	1 (1.2)		RR 15.7 (2.1-117.1)
LOS (days)	12.4±7.4	1.5±1.4	U=11.1 2	<0.001**

CS: caesarian section, NVD: normal vaginal delivery, PROM: premature rupture of membranes, ICU: Intensive care unit, mechanical ventilation includes invasive and non-invasive MV, LOS: length of hospital stay, U: Mann-Whitney test, χ^2 : Chi square test, RR: relative risk, CI: confidence interval.

There was significant difference between the studied groups regarding fetal weight, time of birth and neonatal complications. Neonatal complications rate among COVID-19 cases was 41.2% (35 cases) vs 21.2% and neonatal mortality was 14.1% (12 cases) vs 5.9% (**Table 3**).

Table 3: Risk assessment of COVID-19 on neonatal outcome

Neonatal outcome	Cases (n= 85)	Control (n= 85)	χ^2	P-value RR (95% CI)
Fetal weight (gm)	2532.0±506.2	2892.0±512.6	t= 4.61	<0.001**
Low birth weight:				0.018*
Yes	32 (37.6)	18 (21.2)	5.55	RR= 1.8
No	53 (62.4)	67 (78.8)		(1.1-2.9)
Time of birth:				<0.001**
Pre-term	46 (54.1)	23 (27.1)	12.90	RR= 2
Full-term	39 (45.9)	62 (72.9)		(1.3-2.9)
Congenital anomalies:				^{FE} 1.000
Yes	3 (3.5)	4 (4.7)	0.15	RR= 0.8
No	82 (96.5)	81 (95.3)		(0.2-3.3)
PCR of neonate:				
Positive	1 (1.2)	-	-	-
Negative	76 (89.4)	-		
Not done	8 (9.4)	85 (100.0)		
Admission to NICU:				0.496
Yes	26 (30.6)	22 (25.9)	0.46	RR= 1.2
No	59 (69.4)	63 (74.1)		(0.7-1.9)
Neonatal complications				0.005*
Yes	35 (41.2)	18 (21.2)	7.92	RR= 1.9
No	50 (58.8)	67 (78.8)		(1.2-3.2)
Neonatal mortality				0.074
Yes	12 (14.1)	5 (5.9)	3.20	RR= 2.4
No	73 (85.9)	80 (94.1)		(0.9-6.5)
Final neonatal outcome:				0.251
Improvement and discharge	66 (77.6)	73 (85.9)	4.01	Reference
Referral	7 (8.2)	7 (8.2)		RR=1.1(0.4-2.9)
Neonatal mortality:				
• IUFD	8 (9.4)	2 (2.4)		RR=4.1(0.9-18.5)
• Death after delivery	4 (4.7)	3 (3.5)		RR=1.4(0.3-6.2)

IUFD: intra-uterine fetal death, NICU: neonatal intensive care unit, t: student t test, χ^2 : Chi square test, FE: Fischer's Exact test, RR: relative risk, CI: confidence interval.

Furthermore, complicated cases of COVID-19 (40 cases) showed highly significant difference between them and non-complicated ones regarding gestational age, SpO₂ on admission and SpO₂ during hospital stay. All these variables were lower in complicated cases. Other parameters are shown in **table 4**.

Table 4: Comparison between complicated and non-complicated COVID-19 cases regarding history and oxygen status

	Complicated cases (n= 40)		Non-complicated cases (n= 45)		t	P-value
Age	29.3±3.9		30.7±4.7		1.56	0.124
Gestational age (weeks)	33.9±3.0		36.6±2.1		4.85	<0.001**
SpO ₂ on admission (%)	78.5±13.5		93.7±5.0		6.71	<0.001**
SpO ₂ during hospital stay	93.5±4.7		97.2±1.1		4.92	<0.001**
	N	%	N	%	χ ²	P-value
Pneumonia: Yes	38	95.0	37	82.2	3.33	FE0.095
No	2	5.0	8	17.8		
Oxygen status on admission:					22.76	<0.001**
Room air	8	20.0	31	68.9		
Nasal cannula	6	15.0	5	11.1		
Face mask	7	17.5	4	8.9		
High flow nasal insufflation	12	30.0	4	8.9		
Non-invasive MV (CPAP)	7	17.5	1	2.2		
Oxygen status during hospital stay:					44.36	<0.001**
Room air	2	5.0	18	40.0		
Nasal cannula	7	17.5	16	35.6		
Face mask	-	-	6	13.3		
High flow nasal insufflation	7	17.5	4	8.9		
Non-invasive MV (CPAP) Invasive MV	10 14	25.0 35.0	1 -	2.2 -		

SPO₂: Oxygen saturation, t: student t test, χ²: Chi square test, FE: Fischer’s Exact test, **Highly significant (P<0.001).

Regarding maternal outcome among complicated cases; need of blood transfusion, ICU admission, need of mechanical ventilation, maternal mortality and LOS were significantly higher than non-complicated cases (Table 5).

Table 5: Maternal outcome of complicated and non-complicated COVID-19 cases

Maternal outcome	Complicated cases (n= 40)		Non-complicated cases (n= 45)		χ ²	P-value
	No	%	No	%		
Blood transfusion:					7.38	0.007*
Yes	37	92.5	31	68.9		
No	3	7.5	14	31.1		
ICU admission:					50.37	<0.001**
Yes	32	80.0	2	4.4		
No	8	20.0	43	95.6		
Length of ICU stay (days):	8.3±6.5		8.0±0.0		U= 0.37	0.713
Mechanical ventilation:					34.05	<0.001**
Yes	24	60.0	1	2.2		
No	16	40.0	44	97.8		
Maternal mortality:					12.61	<0.001**
Yes	12	30.0	1	2.2		
No	28	70.0	44	97.8		
Maternal outcome:					15.99	0.001*
Complete cure and discharge	21	52.5	33	73.3		
Improvement and home isolation	5	12.5	11	24.4		
Referral	2	5.0	0	0.0		
Death	12	30.0	1	2.2		
LOS (days)	14.2±7.9		10.9±6.5		U= 2.19	0.029*

ICU: Intensive care unit, LOS: length of hospital stay, U: Mann-Whitney test, χ²: Chi square test, *Significant (P<0.05), **Highly significant (P<0.001).

Regarding neonatal outcome among complicated cases; low birth weight, pre-term, congenital anomalies, admission to NICU, neonatal complications and neonatal mortality were significantly higher than non-complicated cases (Table 6).

Table 6: Comparison between complicated and non-complicated COVID-19 cases regarding neonatal outcome

Neonatal outcome	Complicated cases (n= 40)		Non-complicated cases (n= 45)		Test of sig. (χ^2)	P-value
	No	%	No	%		
Fetal weight (gm):	2249.0±500.6		2783.5±360.0		t= 5.59	<0.001**
Low birth weight:						
Yes	26	65.0	6	13.3	24.08	<0.001**
No	14	35.0	39	86.7		
Time of birth:						
Pre-term	32	80.0	14	31.1	20.38	<0.001**
Full-term	8	20.0	31	68.9		
Congenital anomalies:						
Yes	3	7.5	-	-	3.50	FE0.100
No	37	92.5	45	100.0		
PCR of neonate:						
Positive	1	2.5	0	0.0	11.34	0.003*
Negative	31	77.5	45	100.0		
Not done	8	20.0	0	0.0		
Admission to NICU:						
Yes	23	57.5	3	6.7	25.78	<0.001**
No	17	42.5	42	93.3		
Neonatal complications						
Yes	29	72.5	6	13.3	30.61	<0.001**
No	11	27.5	39	86.7		
Neonatal mortality						
Yes	12	30.0	0	0.0	15.72	<0.001**
No	28	70.0	45	100.0		
Final neonatal outcome:						
Improvement and discharge	23	57.5	43	95.6	19.12	<0.001**
Referral	5	12.5	2	4.4		
Neonatal mortality:						
• IUFD	8	20.0	0	0.0		
• Death after delivery	4	10.0	0	0.0		

IUFD: intra-uterine fetal death, NICU: neonatal intensive care unit, t: student t test, χ^2 : Chi square test, FE: Fischer’s Exact test, *Significant (P<0.05), **Highly significant (P<0.001).

Gestational age, SpO₂ on admission (%) and creatinine were significant independent predictors for COVID-19 complications among pregnant females; each unit increase in gestational age (weeks) or SpO₂ on admission (%) decreases the odds (probability) of complications (holding other predictors constant) by (5-45%) or (7-23%) respectively (Table 7).

Table 7: Univariate and multivariate regression model for prediction of complicated COVID-19 cases

Independent variables	COVID-19 complications among pregnant females (outcome)					
	Univariate regression			Multivariate regression		
	B	P-value	OR (95% CI)	B	P-value	Adjusted OR (95% CI)
Gestational age	- 0.424	<0.001	0.654 (0.528-0.810)	- 0.321	0.002	0.725 (0.551-0.956)
SpO ₂ on admission (%)	- 0.218	<0.001	0.804 (0.735-0.879)	- 0.162	0.001	0.851 (0.773-0.936)
SpO ₂ during hospital stay	- 0.654	<0.001	0.520 (0.372-0.726)	- 0.225	0.257	0.799 (0.541-1.178)

SpO₂: Oxygen saturation, OR: Odds Ratio, CI: confidence interval.

DISCUSSION

This study demonstrates the relationship between COVID-19 infection and its related obstetric outcomes for pregnant women in 3rd trimester. Maternal outcome showed an increased rate of maternal complications (47.1%), mortality (15.3%) and ICU admission and mechanical ventilation. PROM, preterm labor and low birth weight were higher among cases. Additionally, neonatal outcome showed an increased rate of neonatal complications (41.2%), mortality (14.1%) and NICU admission. Gestational age, SpO₂ on admission and SpO₂ during hospital stay were significantly lower among complicated cases.

COVID-19 pregnant women in 3rd trimester reflected an increased incidence of maternal complications in line with **Salem et al.** [13] who reported that the 3rd trimester seemed to be the most vulnerable pregnancy period of infection and the risk of COVID-19 consequences exacerbation is greatest in this period. Also **DeBolt et al.** [12] reported that incidence of maternal complications was 34.2%. In contrast, other studies found that maternal morbidity was quite low [8,14,15].

Maternal mortality among COVID-19 pregnant women enrolled in our study was high similar to **St et al.** [16] who proved that 22 COVID-19 pregnant patients (44.9%) died, also **Villar et al.** [17] showed that maternal mortality was 22.3 times higher. These results don't fit with other studies that found mortality to be quite low [8, 14] or equal 0% [15].

These results demonstrated that all COVID-19 cases delivered through caesarean section (CS), various studies reported a higher-than-expected rate of CS [18-20], as the findings of **Smith et al.** [15] (80% CS) and **DeBolt et al.** [12] (72.7% CS). This could be explained by the fact that rate of previous history of CS is high, the benefit of decreasing stress of labor and keeping oxygen saturations above 94% in patients with severe COVID-19, other obstetric indications as improving the maternal condition and PROM that may result in and subsequent risks including maternal or neonatal infection [21]. Decision of

delivery by CS was following the standard obstetric guidelines. Other studies reported either unchanged CS rate compared to the pre-pandemic state [22] as **Dingom et al.** [23] reported 44.4% CS or even lower [24] as **Martinez-Perez et al.** [21] reported 22.4% CS.

Increased risk of intensive care unit (ICU) admission and need of mechanical ventilation is an important insight that should be taken into account as this risk is significantly high among cases and represents a bad indicator for COVID-19 progress and many cases needed mechanical ventilation for improving oxygen saturation to improve maternal and neonatal outcomes. **DeBolt et al.** [12] and **Villar et al.** [17] agreed with our findings that the risk of ICU admission was 5.04 and 5.2 times higher among cases, respectively, while **Smith et al.** [15] found only 4.3% of patients required ICU and ventilation.

Regarding PROM, preterm labor and low birth weight, various studies focused on increased risk of them [14,19,20,25]. PROM was 1.7 times higher among cases [21]. Preterm birth was 1.59 [17] and 2.12 [21] times higher among cases. Also, **Smith et al.** [15] noticed that 63.8%, 42.8% of cases had preterm births, low birth weight, respectively. **Wen** [25] reported that low birth weight was 1.13 folds higher among cases. PROM and preterm labor might be spontaneous; could be justified by activation of biochemical pathways and inflammatory mediators (play an important role in PROM and preterm labor), which is associated with SARS-CoV-2 infection, among these cytokines, circulating IL-6 that is closely linked to SARS-CoV-2 infection severity [26,27], or iatrogenic; with the goal of enhancing maternal oxygenation with delivery [18].

Our study proved that COVID-19 infection is associated with significant increase in neonatal complications, which contradict the claims of **Salem et al.** [13] and **Villar et al.** [17] who found no evidence of adverse perinatal outcomes increase.

Neonatal requirement for NICU admission was increased to 76.92% [15] and 4.62 times more than neonates of non-COVID-19 infected women [21], these findings are similar to ours.

Vertical transmission is possible based on one positive RT-PCR reported case in our study and **Smith et al.** study [15]. On the other hands, pooled prevalence of vertical transmission was found to be 10%, 95% CI: 4-17% [28]. However, based on the results of other studies, there was no evidence of vertical transmission and all neonates PCR tested negative [14, 23].

Finally, neonatal mortality was higher among cases, which is similar to **Sathian et al.** [28] (Pooled prevalence of neonatal mortality was 7%, 95% CI: 0-21%). While **Martinez-Perez et al.** [21] disagreed and reported (0%) neonatal mortality.

CONCLUSION

This multi-center prospective study demonstrated that COVID-19 infected pregnant women have unfavorable infection-related maternal and neonatal consequences, so comprehensive follow up of both infected mothers and their neonates is highly recommended.

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