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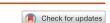
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ORIGINAL ARTICLE



Does the presence of symptoms affect pregnancy outcomes in third trimester in women with SARS-CoV-2

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ABSTRACT

Objective: Parturients with symptoms to COVID-19 have an increased risk for neonatal adverse outcomes and for any adverse outcome compared to the asymptomatic COVID-19 positive parturients and to the COVID-19-negative parturients. The purpose of this study was to determine the effect of COVID-19 on obstetric outcomes based on symptom status of parturients at or near term.

Methods: Retrospective cohort study of parturients diagnosed with COVID-19 between 26 March and 30 September 2020. Maternal and neonatal outcomes were assessed by comparing three groups of parturients: COVID-19 negative, asymptomatic COVID-19, and symptomatic COVID-19.

Results: A total of 2299 COVID-19-negative parturients and 172 patients with confirmed diagnosis of COVID-19 delivered during the study period. The median gestational age at the time of delivery was 39 (interquartile range 39–40) weeks. The most common symptom was cough (28/56, 50%). Gestational diabetes mellitus was significantly less common in COVID-19-negative than in COVID-19-positive patients. There was no significant increase in cesarean delivery in women who were COVID-19 positive and the incidence of preterm deliveries was not significantly different among the three groups. Of the 172 cases of COVID-19, only one parturient needed mechanical ventilation, and there were no maternal deaths in this group. There were no cases of severe neonatal asphyxia or neonatal death. Composite maternal adverse outcomes were not significantly different between the three groups. The aOR for composite neonatal adverse outcome and overall composite adverse outcome comparing COVID-19 positive to negative parturients was 2.1 (95% confidence interval [CI], 1.1–3.8; p=.02) and 1.6 (95% CI, 1.1–2.3; p=.02), respectively.

Conclusions: An increased risk for neonatal adverse outcomes and for any adverse outcome was found in the symptomatic COVID-19 group compared to the asymptomatic COVID-19-positive parturients and to the COVID-19-negative parturients.

ARTICLE HISTORY

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KEYWORDS

Pregnancy; coronavirus disease (COVID-19); symptomatic; asymptomatic; outcome

Introduction

In December 2019, severe acute respiratory syndrome coronavirus (SARS-CoV-2), a new strain of coronavirus, was first reported in Wuhan, Hubei, China [1]. The virus spread worldwide over the following months, and in March, 2020, the World Health Organization (WHO) declared the COVID-19 (coronavirus disease) outbreak a pandemic [2].

Pregnant women are known to be disproportionately affected by respiratory illnesses, which are frequently associated with increased infectious morbidity and high maternal mortality rates. Due to physiologic

maternal adaptations affecting the immune, coagulation, and cardiopulmonary systems, among others, there may be an increased risk of severe maternal illness following infection with respiratory viruses [3,4]. While most human coronavirus infections are mild, the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) epidemics during the past two decades have been morbid, with approximately one-quarter of infected parturients dying from these infections [5,6]. Beyond the impact on the gravid woman, there are concerns regarding the effect of maternal

respiratory dysfunction in COVID-19 on the fetus, and the direct effect of the virus on the fetus by vertical transmission. Available studies regarding the outcomes of women and their neonates after antepartum infection with COVID-19 in the third trimester of pregnancy report conflicting results. Multiple studies suggest minimal evidence of vertical transmission [7-9] or pregnancy complications, asides from increased preterm delivery (PTD) and cesarean delivery rates [10-12]. Meanwhile, recent data show increased maternal risk of severe disease including intensive care unit admission, use of invasive ventilation and extracorporeal membrane oxygenation (ECMO), and even death in symptomatic pregnant women compared to their non-pregnant counterparts [13]. Data on neonates of women infected during the first and second trimesters of pregnancy are still being assessed. Although data on COVID-19 continue to pour in, enhancing our understanding of this disease, pregnancy-specific information remains limited and unclear. A recent study of universal screening for COVID-19 in women admitted for delivery revealed that 10.4% were positive for SARS-CoV-2, and 78.6% were asymptomatic at presentation [11]. The importance of universal testing for all pregnant women admitted to the labor ward, in addition to those who present for triage evaluation of symptomatic complaints, has obvious benefits for determination of best practices to protect patients, their neonates, their families, and the care providers [11,12].

We present our experience of universal screening for COVID-19 during the study period in the pandemic and the effect of symptomatic versus asymptomatic COVID-19 status on maternal and neonatal outcomes.

Materials and methods

We conducted a single-center retrospective cohort study of parturients and their neonates who delivered between 26 March and 30 September 2020 at Mayanei Hayeshua Medical Center, a university-affiliated community hospital in Bnei Brak, Israel. During this period, women admitted to labor and delivery were universally tested for COVID-19 except those who were admitted with a recent positive test prior to their admission. Inclusion criteria were women aged 18–50 years with a singleton gestation who delivered during the study period. The study population was subdivided into three groups – those with a negative screening test (group 1), asymptomatic patients with a positive screening test (group 2), and symptomatic positive patients (group 3). Symptomatic

patients were parturients with any of the following: fever, cough, malaise, gastrointestinal symptoms, and/or anosmia and loss of taste. All neonates of COVID-19-positive mothers were tested for COVID-19 immediately after delivery, as well as at 24 and 48 h of life.

Data collection

We extracted maternal and neonatal data from electronic medical charts, delivery records, and computerized databases of the laboratory unit. Data included: maternal demographics, medical and obstetric history, and pregnancy, delivery, and neonatal outcomes.

The collected data included demographics, parity, obstetric history, hypertensive disorders (HTN), gestational diabetes (GDM), thromboembolic events which defined as DVT or PE, intrauterine growth restriction (IUGR), PTD prior to 37 weeks of gestation, preterm premature rupture of membranes (PPROM), placental abruption, meconium-stained amniotic fluid, postpartum hemorrhage (PPH) and chorioamnionitis), gestational age at infection, COVID-19 related symptoms, onset of symptoms to delivery, delivery outcomes (mode of delivery, Apgar score, cord arterial pH, and birth weight), and neonatal complications (transient tachypnea of the newborn or respiratory distress syndrome [TTN/RDS]), jaundice requiring phototherapy, sepsis, death). Laboratory results were extracted, including complete (CBC) and automated differential blood counts.

Composite neonatal adverse outcomes included RDS/TTN, 5-min Apgar score <7, cord arterial pH <7, very low birth weight (VLBW, birthweight <1500 g). Composite maternal adverse outcomes included PPH, thromboembolic events, PPROM, PTD, and urgent cesarean delivery. Combined composite adverse outcomes included any adverse maternal or neonatal outcome.

Sample collection

Respiratory specimens were collected using nasopharyngeal swabs and processed according to WHO guidelines [14]. All samples were processed at the Clinical Microbiology Laboratory of the Mayanei Hayeshua Medical Center. The presence of SARS-CoV-2 was detected by two separate commercial kits, following WHO guidelines for qRT-PCR.

In brief, amplification of SARS-CoV-2 open reading frame envelope (E), nucleocapsid protein (N) and RNA-dependent RNA polymerase (Rdrp) genes fragments, using Allplex 2019 n-COV (Seegene) and amplification

of ORF1ab gene using Real-Time Fluorescent RT-PCR Kit for Detecting SARS-CoV-2 (BGI). Internal control was performed for each gRT-PCR reaction.

Interpretation of test results was performed according to the commercial kit instructions provided. For the Seegene kit, a positive result was reported when three target genes (E, N and Rdrp) were detected and a weak positive reported when only one or two target genes were detected. Weak positive results were confirmed by re-testing. For BGI kit, a cycle threshold value (Ct-value) of less than 37 was defined as a positive test, and a Ctvalue of 40 or more was defined as a negative test. A medium load, a Ct-value of 37 to less than 40, was defined as a weak positive result and required confirmation by retesting.

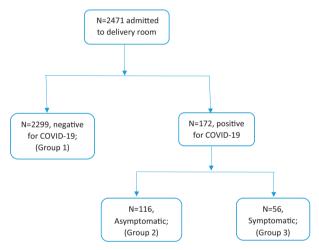


Figure 1. Flowchart of enrollment of women presenting to labor and delivery.

Statistical analysis

Normal distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test, probability plots and histograms. Since all variables were skewed. we used median and interquartile range (IQR) to describe them. Categorical variables were described by frequency percentage. Continuous variables were compared between groups using Mann-Whitney or Kruskal-Wallis tests. Pearson Chi-square and Fisher's exact tests were applied to compare categorical variables. Multivariable logistic regression was used to study the association between COVID-19 and the studied outcomes after controlling for potential confounders. All statistical tests were two-sided and p < .05 was considered to be statistically significant. All analyses were conducted using ICSS2020 statistical software (2020), NCSS, LLC, Kaysville, UT.

Results

A total of 2471 parturients with a singleton pregnancy delivered during the study period. Of these, 172 (7%) were positive for COVID-19. There were a total of 2299 COVID negative patients who served as controls (group 1). Of the positive patients (n = 172), 116 (5%) were asymptomatic (group 2) and 56 (2%) were either diagnosed on arrival with symptoms or arrived after having been recently diagnosed in the community (group 3) (Figure 1).

The two study groups (groups 2 and 3) were compared jointly as COVID-19 positive patients (Tables 1 and 2) and individually (Tables 3 and 4) to all healthy controls who screened negative.

Table 1. Demographics, baseline characteristics and outcomes of COVID-19-negative versus COVID-19-positive parturients.

Characteristics	COVID-19 negative ($n = 2299$)	COVID-19 positive ($n = 172$)	Total ($n = 2471$)	<i>p</i> -Value
Age (years), median (IQR)	29 (25–34)	29 (24–35)	29 (24–34)	.96
Gravida (no.), median (IQR)	4 (2–7)	4 (2–7)	4 (2-7)	.38
Parity (no.), median (IQR)	4 (2–6)	4 (2–7)	4 (2-6)	.29
Gestational age at infection (weeks), median (IQR)		39 (38–40)	39 (38-40)	
Onset of symptoms to delivery, (days), median (IQR)		7.5 (1–27)	7.5 (1–27)	
Leukocytes (*10 ³ /μl), median (IQR)	10.6 (8.9–12.2)	10.1 (7.8–11.6)	10.6 (8.8-12.1)	.06
Lymphocytes absolute count (*10 ³ /μl), median (IQR)	1.7 (1.3–2.1)	1.5 (1.1–1.8)	1.7 (1.3-2.1)	<.01
Platelets (*10³/μl), median (IQR)	182 (152–215)	174 (145–213)	181 (151-215)	.13
Gestational age at delivery (weeks), median (IQR)	39 (39–40)	39 (39–40)	39 (39-40)	.36
Pregnancy complications, N (%)				
Gestational diabetes mellitus	135(5.9)	17 (9.9)	152 (6.2)	.03
Hypertensive disorders	32 (1.4)	4 (2.3)	36 (1.5)	.31
IUGR	56 (2.4)	3 (1.7)	59 (2.4)	.79
Mode of delivery, N (%)				.55
Spontaneous vaginal delivery	1882 (81.2)	138 (80.2)	2020 (81.8)	
Instrumental delivery	182 (7.9)	11 (6.4)	193 (7.8)	
Elective CD	78 (3.4)	8 (4.6)	86 (3.5)	
Urgent CD	157 (6.8)	15 (8.7)	172 (6.9)	

IQR: interquartile range; CD: cesarean delivery.

Table 2. Demographics, baseline characteristics and outcomes of COVID-19-negative parturients compared with COVID-19-positive symptomatic and asymptomatic parturients.

		COVID-19-positive	COVID-19-positive	
Characteristics	COVID-19 negative ($n = 2299$)	Asymptomatic ($n = 116$)	Symptomatic ($n = 56$)	<i>p</i> -Value
Age (years), median (IQR)	29 (25–34)	29 (24–35)	28 (23-34)	.58
Gravida, median (IQR)	4 (2-7)	4 (2–8)	3 (2–6)	.09
Parity, median (IQR)	4 (2–6)	4 (2-7)	3 (2–5)	.06
Gestational age at infection (weeks), median (IQR)		39 (38–40)	38 (36–39)	.05
Onset of symptoms to delivery, (days), median (IQR)			7.5 (1–27)	
Leukocytes (*10 ³ /μl), median (IQR)	10.6 (8.9-12.2)	10.1 (7.8–11.8)	10.1 (7.6–11.2)	.66
Lymphocytes absolute count (*10 ³ /µl), median (IQR)	1.7 (1.3–2.1)	1.5 (1.1–1.8)	1.5 (1.2–1.8)	.51
Platelets (*10³/μl), median (IQR)	182 (152–215)	180 (148–219)	171 (138–202)	.31
Gestational age at delivery (weeks), median (IQR)	39 (39–40)	39 (39–40)	40 (39–40)	.98
Symptoms, N (%)				
Fever			12 (21.4)	
Cough			28 (50)	
Malaise			16 (28.6)	
Gastrointestinal			2 (3.6)	
Anosmia/loss of taste			18 (32.1)	
Pregnancy complications, N (%)				
Gestational diabetes mellitus	135(5.9)	11 (9.5)	6 (10.7)	.79
Hypertensive disorders	32 (1.4)	3 (2.6)	1 (1.8)	>.99
IUGR	56 (2.4)	3 (2.6)	0	.55
Mode of delivery, N (%)				.06
Spontaneous vaginal delivery	1882 (81.2)	94 (81)	44 (78.6)	
Instrumental delivery	182 (7.9)	8 (6.9)	3 (5.4)	
Elective CD	78 (3.4)	8 (6.9)	0	
Urgent CD	157 (6.8)	6 (5.2)	9 (16.1)	

IQR: interquartile range; CD: cesarean delivery.

Table 3. Maternal and neonatal outcomes of COVID-19-negative versus COVID-19-positive parturients.

Characteristics	COVID-19 negative ($n = 2299$)	COVID-19 positive ($n = 172$)	Total (n = 2471)	<i>P</i> -Value
Birthweight grams, median (IQR)	3360 (3065–3655)	3335 (3011–3589)	3360 (3065-3645)	.19
VLBW <1500 g, N (%)	15 (0.66)	2 (1.2)	17 (0.7)	.33
Apgar 5 min $<$ 7; N (%)	17 (0.7)	2 (1.2)	19 (0.8)	.38
Cord arterial pH, median (IQR)	7.29 (7.23–7.34)	7.29 (7.25–7.34)	7.3 (7.2–7.3)	.41
PPROM, N (%)	11 (0.5)	2 (1.2)	13 (0.5)	.23
Preterm birth <37 wk, N (%)	98 (4.3)	5 (2.9)	103 (4.2)	.39
Meconium-stained amniotic fluid, N (%)	309 (13.4)	19 (11.1)	328 (13.3)	.37
Placental abruption, N (%)	36 (1.6)	2 (1.2)	38 (1.5)	>.99
PPH, N (%)	41 (1.8)	7 (4.1)	48 (1.9)	.04
Maternal complications, N				
Mortality	0	0	0	
Mechanical ventilation	0	1	1	
ECMO	0	0	0	
Thromboembolic event	0	1	1	
Composite outcomes – maternal, N (%)	260 (11.3)	27 (15.7)	287 (11.6)	.08
Neonatal complications, N (%)				
RDS/TTN	66 (2.9)	10 (5.8)	76 (3.1)	.03
Neonatal jaundice	97 (4.2)	10 (5.8)	107 (4.3)	.32
Neonatal death	10 (0.4)	1 (0.6)	11 (0.5)	.55
Composite outcomes – neonatal, N (%)	81 (3.5)	12 (7)	93 (3.7)	.02
Composite outcomes – overall, N (%)	298 (13)	33 (19.2)	331 (13.4)	.02

ECMO: extracorporeal membrane oxygenation; IQR: interquartile range; thromboembolic event (DVT/PE).

Composite neonatal outcomes included RDS/TTN, 5-min Apgar score <7, cord arterial pH <7, very low birth weight (VLBW, birthweight <1500 g). Composite maternal outcomes included PPH, Deep thromboembolic events, PPROM, PTD, and urgent cesarean delivery. Overall composite outcomes included any adverse maternal or neonatal outcome.

There was no difference between the groups in maternal age, parity, gestational age at delivery, total white blood cell count, or platelet count. Total lymphocyte count was significantly lower in the COVID-19 positive groups (groups 2 and 3) compared to healthy controls (group 1). The incidence of GDM was higher in COVID-19-positive groups (groups 2 and 3) when compared to healthy controls (group 1) (Table 1), but not when comparing symptomatic to asymptomatic COVID-19 positive patients (group 2 versus group 3) (Table 2). No differences were seen in rates of hypertensive disorders of pregnancy, IUGR or mode of delivery (Tables 1-4).

The groups did not differ in birth weight, cord arterial pH, Apgar scores, incidence of VLBW, PPROM, PTD, meconium stained amniotic fluid, placental abruption, or maternal complications (Tables 3 and 4). All neonates of COVID-19-positive mothers were tested



Table 4. Maternal and neonatal outcome of COVID-19-negative parturients compared with COVID-19-positive symptomatic and asymptomatic parturients.

	COVID-19	COVID-19-positive	COVID-19-positive	
Characteristics	negative (<i>n</i> = 2299)	Asymptomatic ($n = 116$)	Symptomatic ($n = 56$)	<i>p</i> -Value
Birthweight g, median (IQR)	3360 (3065–3655)	3327 (2976–3584)	3365 (3066-3594)	.62
VLBW <1500 g, N (%)	15 (0.66)	1 (0.9)	1 (1.8)	.55
Apgar score (5 min) < 7 ; N (%)	17 (0.7)	2 (1.7)	0	.39
PH, median (IQR)	7.29 (7.23–7.34)	7.3 (7.2–7.4)	7.3 (7.2–7.3)	.06
PPROM, N (%)	11 (0.5)	1 (0.9)	1 (1.8)	.55
Preterm birth $<$ 37 wk, N (%)	98 (4.3)	4 (3.5)	1 (1.8)	>.99
Meconium-stained amniotic fluid, N (%)	309 (13.4)	12 (10.3)	7 (12.5)	.67
Placental abruption, N (%)	36 (1.6)	2 (1.7)	0	>.99
PPH, N (%)	41 (1.8)	6 (5.2)	1 (1.8)	.43
Maternal complications, N				
Mortality	0	0	0	
Mechanical ventilation	0	0	1	
ECMO	0	0	0	
Thromboembolic event	0	0	1	
Composite outcomes – maternal, N (%)	260 (11.3)	16 (13.8)	11 (19.6)	.32
Neonatal complications, N (%)				
RDS/TTN N	66 (2.9)	5 (4.3)	5 (8.9)	.29
Neonatal jaundice	97 (4.2)	8 (6.9)	2 (3.6)	.51
Neonatal death	10 (0.4)	1 (0.9)	0	>.99
Composite outcomes – neonatal N (%)	81 (3.5)	7 (6)	5 (8.9)	.04
Composite outcomes – overall N (%)	298 (13)	19 (16.4)	14 (25)	.02

ECMO: extracorporeal membrane oxygenation; IQR: interquartile range; thromboembolic event (DVT/PE). Composite neonatal outcomes (RDS/TTN), 5-min Apgar score <7, pH <7, very low birth weight (VLBW, birthweight <1500 g). Composite maternal outcomes included PPH, thromboembolic events, PPROM, PTD, and urgent cesarean delivery. Overall composite outcomes included any adverse maternal or neonatal outcome.

for SARS-CoV-2. Three neonates born vaginally tested positive at delivery followed by a negative test at 24 and 48 h of life, indicating that the positive tests were most likely due to maternal contamination.

A higher incidence of PPH and RDS/TTN was seen in COVID-19-positive patients (groups 2 and 3) than in healthy controls (group 1) (Table 3).

Composite maternal adverse outcomes showed a trend toward increasing incidence in the COVID-19positive women when compared to COVID-19-negative women (p = .08) (Table 3). Among the three groups, there appears to be a trend of increased incidence of composite maternal adverse outcomes from healthy (11.3%) to asymptomatic (13.8%) to symptomatic (19.6%) women (p = .32) (Table 4 and Figure 2).

There was a statistically significant difference in the composite neonatal adverse outcomes between COVID-19-negative and -positive patients (adjusted odds ratio [aOR] 2.1, 95% confidence interval [CI] 1.1–3.8, p = .02) (Table 5) as well as in subanalysis of the three groups (p = .04), with an incidence of 3.5% in healthy controls, 6.0% in asymptomatic patients and 8.9% in symptomatic patient (p = .04) (Table 4). While the difference in composite neonatal adverse outcomes was not different between healthy controls and asymptomatic COVID-19 patients (aOR 1.8, 95% CI 0.8–3.9, p = .16), symptomatic COVID-19 patients had worse outcomes compared with healthy controls (aOR 2.7, 95% CI 1.1–6.9, p = .04) (Table 5).

Overall composite adverse outcomes also revealed a statistically significant difference between COVID-19negative and -positive patients (aOR 1.6, 95% CI 1.1–2.3, p = .02) (Table 5) with an increasing incidence between healthy (13%), asymptomatic (16.4%), and symptomatic (25%) patients (Table 4 and Figure 2). As with neonatal composite outcomes, a comparison of healthy controls and symptomatic COVID-19 patients showed worse overall outcomes for the latter group (aOR 2.2, 95% CI 1.2-4.1, p = .01), while asymptomatic COVID-19 healthy controls and patients did not differ (aOR 1.3, 95% CI 0.8-2.2, p = .31) (Table 5).

Discussion

Universal screening revealed that 93% of women admitted to the labor ward during the study period were negative for COVID-19. Of the COVID-19-positive patients, 67% were asymptomatic. Most pregnancy and delivery outcomes were similar between COVID-19-positive and -negative parturients with no differences in terms of gestational HTN, gestational age at delivery, mode of delivery, birth weight, and Apgar scores. The rates of preterm PROM, preterm delivery, and IUGR were also similar, as were the rates of very low birthweight, meconium stained amniotic fluid and placental abruption in these patients. Interestingly, most of the patients who delivered at our center

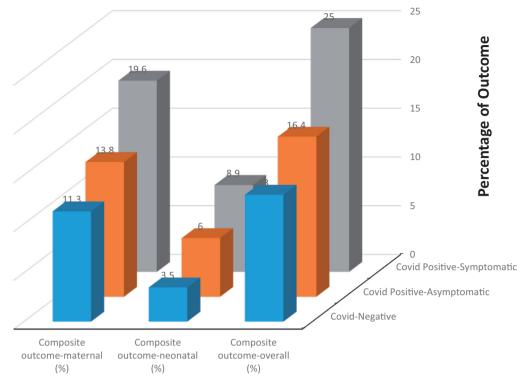


Figure 2. Rates of maternal, neonatal and overall composite adverse outcomes of COVID-19-negative parturients compared with COVID-19-positive symptomatic and asymptomatic parturients.

Table 5. Regression analysis for composite adverse outcomes.

	aOR	95% CI	<i>p</i> -Value
Composite adverse outcomes – maternal:			
COVID-19-positive versus negative	1.4	0.9-2.2	.09
COVID-19 negative	1		
COVID-19 asymptomatic	1.2	0.7-2.1	.43
COVID-19 symptomatic	1.9	0.9 - 3.7	.06
Composite adverse outcomes –neonatal:			
COVID-19-positive versus negative	2.1	1.1-3.8	.02
COVID-19 negative	1		
COVID-19 asymptomatic	1.8	0.8-3.9	.16
COVID-19 symptomatic	2.7	1.1-6.9	.04
Overall composite adverse outcomes:			
COVID-19-positive versus negative	1.6	1.1-2.3	.02
COVID-19 negative	1		
COVID-19 asymptomatic	1.3	0.8 - 2.2	.31
COVID-19 symptomatic	2.2	1.2-4.1	.01

aOR: adjusted odds ratio.

during the study period were at term gestation. As noted by Meyer et al., there was a reduction in the preterm birth rate during a similar period, postulated to be due to both changes in social behavior and medical practices during the pandemic [15].

Significant differences between the COVID-19-positive and healthy controls included higher rates of GDM, low lymphocyte counts, PPH, and neonatal respiratory complications (TTN/RDS). Subanalysis of the healthy, asymptomatic, and symptomatic groups did not show any statistically significant differences in these parameters. Only one patient developed severe respiratory illness requiring intensive care and

mechanical ventilation and was discharged from the hospital in good condition after 6 weeks. All others were discharged within several days.

The composite neonatal and overall adverse outcomes were significantly increased in COVID-19 cases. In addition, a trend toward progressively worse outcomes was observed between healthy controls, asymptomatic patients and symptomatic patients. Composite maternal adverse outcomes showed a non-statistically significant trend toward increased severity in the infected group.

One hundred and seventy-two out of 2471 (7.0%) patients admitted during the screening period were COVID-19 positive. Of these, over two thirds were asymptomatic. These numbers are similar to the findings of Prabhu et al. in New York City [11]. The rate of infection cannot be compared to the general population in our country, as universal screening has not been implemented. Most of the symptomatic patients had only mild symptoms with only one case of severe respiratory dysfunction requiring intensive care.

Parturients with COVID-19 were managed in similar fashion to healthy women with the mode of delivery dictated by obstetric indications as shown safe in previous studies [16,17]. This is contrary to many reports during the early phase of the pandemic, mainly from China, that showed an increased rate of cesarean deliveries [18]. Most birth outcomes were similar

among our COVID-19-positive and -negative patients. The similar rate of preterm delivery differed from results in early reports [19] and one of the reports from Israel [17].

At the time of the submitting of this manuscript, over 61 million cases of COVID-19 have been documented worldwide with over 1,400,000 deaths from the disease [20]. In Israel, over 333,000 cases have been documented with over 2800 deaths [21]. To date, approximately 661 deliveries of COVID-19-positive women have been documented out of a total of roughly 120,000 deliveries since the start of the outbreak in Israel [22].

Due to the high rate of infection in our local population, and to reduce the risk of cross infection within the labor and postnatal wards for patients and hospital staff alike, we introduced a policy of universal screening for COVID-19 for patients admitted to the labor and maternal fetal medicine wards. This enabled us to achieve a relatively large cohort of pregnant patients with COVID-19, many of whom were asymptomatic carriers of the virus. This highlights the need for universal screening to prevent spread of the virus amongst healthy patients and hospital staff, who then would go on to spread the virus further in the community. Furthermore, our findings reveal that, amongst our population, COVID-19 in the third trimester of pregnancy has clinical implications, albeit at lower rates than expected once asymptomatic patients are taken into account.

Since the outbreak of COVID-19, hundreds of studies have been published trying to elucidate the effect of infection on pregnant women and their offspring. More data are needed to better delineate the differences between pregnancy outcomes seen in certain poppotentially related to different viral characteristics (subtypes, viral load), patient epigenetics, or other factors. Additionally, the effects of maternal infection on the fetus both in terms of symptomatic maternal illness and vertical viral transmission remain to be further investigated. Our study focused on women in the third trimester with COVID-19 diagnosed in close proximity to delivery. Further studies are currently underway to better understand the effect of COVID-19 in the first and second trimesters.

Our study was performed in a single center in a high prevalence area of COVID-19. As such, universal screening in our unit captured a relatively high number of COVID-19-positive patients allowing us a better perspective of the full clinical spectrum of the disease, rather than studying only symptomatic or more severe cases. Due to our screening protocol, we detected nearly 25% of all documented COVID-19-positive cases among parturients in our country.

One limitation of our study is its retrospective nature. Another limitation is the relatively homogenous, multiparous, healthy population admitted to our community hospital. Our outcomes may, therefore, not be generalizable to all populations. This is reflected by the relatively mild course of disease in most women in the current cohort. Additionally, since the study focused only on women infected at or immediately before the time of delivery, our results cannot be generalized to those infected with COVIDfirst and during the second trimesters of pregnancy.

Conclusion

We found that COVID-19-positive parturients had higher rates of composite adverse outcomes than healthy parturients, with symptomatic women having higher rates of adverse outcomes than asymptomatic women.

Ethical approval

The study was approved by the Mayanei Hayeshua Medical Center Institutional Review Board (MHMC-0043-20, 12/10/2020).

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

L. H., E. E., S. J. L., Y. S., D. R., I. O., A. R., and A. T. reviewed the literature and wrote the paper. L. H. performed the statistical analyses for this study. All authors read and approved the final manuscript.

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References

World Health Organization [Internet]. Listings of WHO's response to COVID-19 [online]. Available from:

https://www.who.int/news/item/29-06-2020-covidtimeline.

- [2] World Health Organization [Internet]. Coronavirus disease 2019 (COVID-19) situation report–51. Geneva, Switzerland: World Health Organization; 2020 [cited 2020 Nov 18]. Available from: https://apps.who.int/iris/handle/10665/331475.
- [3] Ramsey PS, Ramin KD. Pneumonia in pregnancy. Obstet Gynecol Clin North Am. 2001;28(3):553–569.
- [4] Vlachodimitropoulou Koumoutsea E, Vivanti AJ, Shehata N, et al. COVID-19 and acute coagulopathy in pregnancy. J Thromb Haemost. 2020;18(7):1648–1652.
- [5] Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol. 2004; 191(1):292–297.
- [6] Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: report of two cases & review of the literature. J Microbiol Immunol Infect. 2019; 52(3):501–503.
- [7] Kotlyar AM, Grechukhina O, Chen A, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. Am J Obstet Gynecol. 2020; 224(1):35–53.e3.
- [8] Karimi-Zarchi M, Neamatzadeh H, Dastgheib SA, et al. Vertical transmission of Coronavirus disease 19 (COVID-19) from infected pregnant mothers to neonates: a review. Fetal Pediatr Pathol. 2020;39(3): 246–250.
- [9] Huntley BJF, Huntley ES, Di Mascio D, et al. Rates of maternal and perinatal mortality and vertical transmission in pregnancies complicated by severe acute respiratory syndrome coronavirus 2 (SARS-Co-V-2) infection: a systematic review. Obstet Gynecol. 2020; 136(2):303–312.
- [10] Allotey J, Stallings E, Bonet M, for PregCOV-19 Living Systematic Review Consortium, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020; 370:m3320.
- [11] Prabhu M, Cagino K, Matthews KC, et al. Pregnancy and postpartum outcomes in a universally tested population for SARS-CoV-2 in New York City: a prospective cohort study. BJOG: Int J Obstet Gynecol. 2020;127(12):1548–1556.
- [12] Khoury R, Bernstein PS, Debolt C, et al. Characteristics and outcomes of 241 births to women with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-

- 2) infection at five New York City Medical Centers. Obstet Gynecol. 2020;136(2):273–282.
- [13] Zambrano LD, Ellington S, Strid P, CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status – United States, January 22-October 3, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(44):1641–1647.
- [14] Laboratory testing for coronavirus disease (COVID-19) in suspected human cases. WHO reference number: WHO/COVID-19/laboratory/2020.5. Interim guidance 19 March 2020. https://apps.who.int/iris/bitstream/handle/10665/331501/WHO-COVID-19-laboratory-2020.5-eng.pdf?sequence=1&isAllowed=y.
- [15] Meyer R, Bart Y, Tsur A, et al. A marked decrease in preterm deliveries during the coronavirus disease 2019 pandemics. Am J Obstet Gynecol. 2021;224(2): 234–237.
- [16] Lopian M, Kashani-Ligumsky L, Czeiger S, et al. Safety of vaginal delivery in women infected with COVID-19. Pediatr Neonatol. 2020;S1875-9572(20):30174–30171.
- [17] Rottenstreich A, Tsur A, Braverman N, et al. Vaginal delivery in SARS-CoV-2-infected pregnant women in Israel: a multicenter prospective analysis. Arch Gynecol Obstet. 2021;303(6):1401–1405.
- [18] Chen L, Li Q, Zheng D, et al. Clinical characteristics of pregnant women with Covid-19 in Wuhan, China. N Engl J Med. 2020;382(25):e100.
- [19] Knight M, Bunch K, Vousden N, UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ. 2020; 369:m2107.
- [20] Who.int. 2020. Coronavirus disease (COVID-19) World Health Organization. [online] Available from: https://www.who.int/emergencies/diseases/novel-coronavirus;2019 [cited 2020 Nov23].
- [21] Who.int. 2020. Israel country overview | World Health Organization. [online] Accessed 2020 Nov 23. Available from: https://www.who.int/countries/isr/.
- [22] The Forum for Preemies in Israel. Preemies in the shadow of coronavirus [Press release]; 2020 [cited 2020 Nov 23]. Available from: https://cdn.doctorsonly.co.il/2020/11/%D7%93%D7%95%D7%97-%D7%9E%D7%A6%D7%91-%D7%94%D7%A4%D7%92%D7%99%D7%9D-%D7%9C%D7%A9%D7%A0%D7%AA-2020.pdf.