

COVID-19 & Pregnancy Complication During Early Pandemic: A Narrative Review

Ahmed Eladely^{1*}, M.D; Maria Hill¹, MPH; Ahmed Abdelhaleem¹, M.D; Zahid Imran¹, M.D; Ahsan M. Khan¹, M.D; Daisy Sangroula², M.D

¹Clinical Research Coordinator, Internal Medicine — Infectious Diseases Division, University of Louisville, Louisville, KY, USA, ²Director of Obstetric Anesthesia, Department of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY, USA

*ahmed.eladely@louisville.edu

Abstract

Background: Coronaviruses have caused 3 outbreaks in the past 2 decades. The novel one is SARS-CoV-2, which causes COVID-19. Pregnant women have somewhat altered immune state, which may make them more vulnerable to COVID-19 and its complications. Extensive research is needed to better understand the clinical course of COVID-19 in this population.

Objective: This review article discusses the comparison of previous coronaviruses' outbreaks, clinical presentations, and complications in pregnant women and newborns.

Study Design: We conducted literature search for case series and case reports about pregnancy outcomes in pregnant women with COVID-19 during the early phase of pandemic.

Results: In case series, 37 of 129(28.6%) pregnant women with COVID-19 disease had preterm delivery and 14 of 67 pregnant women had fetal distress. The rate of preterm labor in normal pregnant women who are healthy and not infected with any virus worldwide is approximately 11%.

Conclusion: Based on the articles reviewed, preterm delivery appears to be the most common complication in COVID-19 pregnant patients. Other complications include fetal distress, stillbirth, ICU admission and severe disease leading to fetal demise and maternal mortality. Pregnancy outcomes seem to be better with Covid-19 compared to SARs and MERS. However, most of these publications are from the early part of the pandemic when protocols for care for pregnant women were being worked out and comprehensive knowledge of the disease process in pregnant women was still in developing stage.

Introduction

COVID-19 disease is caused by the SARS-CoV-2 virus which was first recognized in a cluster of pneumonia patients in China in December 2019. [1] As of early August 2020, infected cases are exceeding 20 million worldwide with more than 730 000 deaths. [2] Pregnant women's health is an important issue which is still under addressed in this pandemic as well as in previous outbreaks of SARS and MERS. Pneumonia due to viral causes may have higher mortality and morbidity during pregnancy. [1] Physiologic changes that occur during pregnancy are thought to affect pregnant women's susceptibility to infection and clinical severity of illness. [1] Previous epidemics have demonstrated how pregnant women are more susceptible to infection and clinical severity, including the 1918-1919 influenza pandemic and the 1957-1958 Asian flu epidemic. [1] The case fatality rate for the 1918-1919 influenza pandemic was 27% and even higher when exposure was in the 3rd trimester and the case fatality rate for the Asian flu epidemic was twice as high as for infected pregnant women compared to women who were not pregnant. [1] The Swine-origin influenza A (H1N1) virus also causes respiratory disease that also demonstrated higher susceptibility in pregnant women. [3] In 2009, during the H1N1 epidemic, pregnant women were found to be at a higher risk of complications and were four times more likely to be hospitalized than the rest of the pregnant population. [3]

Recommended Citation:

Eladely, Ahmed; Hill, Maria; Abdelhaleem, Ahmed; Imran, Zahid; Khan, Ahsan M.; and Sangroula, Daisy (2020). "COVID-19 & Pregnancy Complication During Early Pandemic: A Narrative Review," *The University of Louisville Journal of Respiratory Infections*: Vol. 4, Iss. 1, Article 74.

Received Date: October 5, 2020

Accepted Date: November 4, 2020

Published Date: December 16, 2020

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Funding Source: The author(s) received no specific funding for this work.

Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

This review article discusses the comparison of previous coronavirus outbreaks, clinical presentations, and complications in pregnant women and newborns.

Methods

On May 1st, 2020 we conducted a comprehensive literature search using PubMed and EMBASE. The search covered the articles on COVID-19 and pregnancy. The following combinations of terms were used to find the articles: COVID-19, COVID, pregnancy, maternal complications, and neonatal complications. From the search results, several case reports and series were identified.

Inclusion criteria: Positive polymerase chain reaction (PCR) or chest tomography (CT) was used to confirm the diagnosis, the patient was pregnant at time of admission, article was written in English and clinical outcomes were mentioned.

Exclusion criteria: Article is not a case series or case report, unable to obtain the full text, written in language other than English, COVID-19 suspected cases without PCR or CT confirmation or unreported clinical outcomes.

Results

Based on the results of the literature search, 9 case series and 6 case reports were included in this literature review. For easy interpretation case series and case reports were summarized separately.

Case Series

The clinical characteristics of mothers are reported in **Table 1**. Overall, the total number of patients included in the nine studies were 181. One hundred and thirty-three pregnant women were in the 3rd trimester, 26 in the 2nd trimester and 22 in the 1st trimester. The maternal age ranges from 23 years old to 40 years old with most of the patients below 35 years old. The diagnosis was made using PCR, chest CT or both. CT findings included bilateral or unilateral patchy lung consolidation or ground glass opacities. Underlying comorbidities that presented before SARS-CoV-2 infection included vaginal bleeding, cholecystitis, polycystic ovary syndrome and others. Laboratory findings included maternal lymphopenia, elevated AST and ALT.

The maternal clinical outcomes are reported in **Table 2**. The most common reported complication in mothers was preterm delivery defined as delivery before 37 weeks' gestational age which presented in 37 out of 129 patients (28.68%). The second most reported complication was fetal distress that was reported in 14 out of 67 patients (20.89%). Cesarean section (CS) is the most common reported mode of delivery (113/126 (89.68 %)).

Lian Chen et al. reported 8 (57%) out of 14 preterm delivery to be iatrogenic. [4] Now it is established that COVID-19 infection is not an indication for CS, and in fact it might increase the clinical deterioration in these patients. [5]

S. Hantoushzadeh et al. reported 9 severe cases that required intensive care unit (ICU) admission and mechanical ventilation, death occurred in 7 patients. Out of those 7 patients, 5 experienced worsening of the disease after delivery. The other 2 had serious complications before delivery with intrauterine fetal death (IUFD). The only 2 living patients were still hospitalized at the study time, one achieved slow recovery and was extubated, but still hospitalized. The other one was still critically ill and intubated. [6]

The neonatal outcomes are reported in **Table 3**. The most common complication reported in the neonates was low birth weight (LBW), defined as newborn birth weight < 2500 g, reported in 14 out of 49 neonates. LBW was seen with the preterm delivery (13/14 were preterm and 1/14 was full term). Other complications include stillbirth, rash and GI problems. Admission to neonatal ICU and mechanical Ventilation (MV) were also reported.

Case Reports

We collected 6 studies with a total 8 patients and 8 neonates delivered. Maternal age range was from 27 to 41. There were 3 twin sets with 2 sets delivered. All patients were in the 3rd trimester. More details about maternal characteristics are mentioned in **Table 4**. Laboratory findings include lymphopenia in all patients, and elevated liver enzymes in 3 out of 5 patients. There were no cases with gestational hypertension, preeclampsia or PROM.

The maternal and neonatal complications are reported in **Table 5**. The most common complication reported was preterm delivery in 5 of 8 patients. Intensive care unit (ICU) admission and mechanical ventilation occurred in 2 of 8

patients. Seven patients were delivered by cesarean section while one patient had a normal vaginal delivery. No maternal mortality was reported.

There were 2 neonates admitted to a neonatal intensive care unit (NICU) with mechanical ventilation. One of them intubated due to excessive sedation to the mother. Those two neonates were born to the 2 mothers admitted to ICU. No stillbirth, LBW, neonatal asphyxia or death were reported.

Table 1. Maternal clinical characteristics

Author	No. of Patients	Age Range	Trimester of Pregnancy	Comorbidities	Abnormal Laboratory Findings		
					Maternal Lymphopenia (<1.0)	ALT Elevated	AST Elevated
H. Chen, et al ²⁰	9	26-40	3rd	Gestational hypertension (1) Pre-eclampsia (1) PROM (2)	5	3	3
H. Zhu, et al ²¹	9	25-35	3rd	Scarred uterus [1] Vaginal bleeding in 3rd trimester [1] PROM (3)	NA	NA	NA
Y. Chen, et al ²²	4	23-34	3rd	Cholecystitis [1]	2	0	0
N. Yu, et al ¹³	7	29-34	3rd	Hypothyroidism [1], Polycystic ovary syndrome [1], Scarred uterus (3)	NA	NA	NA
L. Chen, et al ⁴	118	NA*	1st (22) 2nd (21) 3rd (75)	NA	51/116	21/93	20/94
X. Hu, et al ²³	7	30-34	3rd	0	NA	NA	NA
Y. Liu, et al ²⁴	13	22-36	2nd (2) 3rd (11)	PROM (1)	NA	NA	NA
S Chen, et al ²⁵	5	25-31	3rd	Gestational diabetes (2), Pre-eclampsia (1)	3	0	0
S. Hantoushadeh, et al ⁶	9	NA**	2nd (3) 3rd (6)	Obesity [3], Subclinical hypothyroid [1], Advanced maternal age [5], Underweight [1], Gestational diabetes (2), PPROM (1)	0/8	5/9	7/9
Total	181		1st (22) 2nd (26) 3rd (133)		61/142 (42.96%)	29/120 (24.2%)	30/121 (24.79%)

* The median age was 31 years.

**The author reported a 5-year range for each patient's age to protect the patients' identity.

Table 2. Clinical outcomes in pregnant women with COVID-19

Author	No. of Patients	Abortion	Preterm delivery	Fetal distress	Delivery mode	ICU admission	Mechanical ventilation	Maternal death
H. Chen, et al	9	0	4	2	CS	0	0	0
H. Zhu, et al	9	0	6	6	CS (7), NVD (2)	0	0	0
Y. Chen, et al	4	0	0	0	CS (3), NVD (1)	0	0	0
N. Yu, et al	7	0	0	0	CS (7)	0	0	0
L. Chen, et al	118, Delivered (68)	Spontaneous (3), Induced (4), Ectopic (2)	Spontaneous (6), Induced (8)	NA	CS (63), NVD (5)	1	NIMV	0
X. Hu, et al	7	0	0	0	CS (6), NVD (1)	0	0	0
Y. Liu, et al	13, Delivered (10)	0	6	3	CS (10)	1	ECMO (1)	0
S. Chen, et al	5	0	0	0	CS (2), NVD (3)	0	0	0
S. Hantoushzadeh, et al	9, Delivered (7)	0	7	3	CS (6), NVD (1)	9	IMV (9)	7
Total	181	9/178 (5.06%)	37/129 (28.68%)	14/67 (20.89%)	CS 113/126 (89.68%), NVD 13/126 (10.32%)	11/63 (17.46%)	10/63 (15.87%)	7/181 (3.87%)

Table 3. Neonatal outcomes in pregnant women with COVID-19

Author	No. of pregnant women	Live Birth	Still-birth	Neonatal Demise	Low Birth Weight	NICU Admission	Mechanical Ventilation
H. Chen, et al	9	9	0	0	2	0	0
H. Zhu, et al	9 (1 twin pregnancy)	10	0	1	7	0	0
Y. Chen, et al	4	4	0	0	0	1	0
N. Yu, et al	7	7	0	0	0	0	0
L. Chen, et al	118 (2 Twin pregnancy)	70	0	0	NA	NA	NA
X. Hu, et al	7	7	0	0	0	0	0
Y. Liu, et al	13	9	1	0	NA	NA	NA
S. Chen, et al	5	5	0	0	0	0	0
S. Hantoushzadeh, et al	9 (3 Twin pregnancy)	6	4	2	5	1	1
Total	181 (6 Twin pregnancy)	127	5/187 (2.76%)	3/127 (2.36%)	14/49 (28.75%)	2/47 (4.26%)	1/47 (2.13%)

Table 4. Maternal clinical characteristics

Study Author	No. of Mothers	Cases	Maternal Age	Neonate Delivered	Trimester at Admission	Comorbidities
S. Iqbal, et al ²⁶	1	1	34	yes	3rd	No
H. Xia, et al ²⁷	1	1	27	yes	3rd	No
M. Alzamora, et al ²⁸	1	1	41	yes	3rd	Diabetes mellitus
W. Schnettler, et al ²⁹	1	1	39	yes	3rd	Mild myotonic dystrophy, Bicuspid aortic valve, history of 2 previous low-transverse cesarean deliveries, and history of mild cerebrovascular accident
E. Koumoutsea, et al ³⁰	2	case 1	40	yes	3rd	Familial neutropenia Gestational Diabetes Mellitus, HELLP Syndrome*
		case 2		yes	3rd	Asthma and obesity
C. Fan, et al ³¹	2	case 1	34	yes	3rd	No
		case 2	29	yes	3rd	No
Total	8	Cases		8		

Table 5. Maternal and neonatal clinical outcomes

Author	Cases	Preterm	Maternal ICU Admission & MV	Fetal Distress	Delivery Mode	Neonatal ICU	Neonatal MV
S. Iqbal, et al.	1	No	No	No	NVD	No	No
H. Xia, et al.	1	No	No	Yes	CS	No	No
M. Alzamora, et al.	1	Yes	Yes	No	CS	Yes	Yes
W. Schnettler, et al.	1	Yes	Yes (ECMO)	NO	CS	YES	Yes
E. Koumoutsea, et al.	Case 1	Yes	No	No	CS	No	No
	Case 2	Yes	No	Yes	CS	NA	NA
C. Fan, et al.	Case 1	No	No	No	CS	No	No
	Case 2	Yes	No	No	CS	No	No
Total		5/8	2/8	2/8	CS 7/8, NVD 1/8	2/7	2/7

Discussion

The following are lessons from previous coronaviruses outbreaks:

Coronaviridae family

Coronaviridae is a large family that includes four genera of coronaviruses Alphacoronavirus, Betacoronavirus, Deltacoronavirus, and Gammacoronavirus. They are enveloped, single-stranded RNA viruses. They infect a wide range of birds, animals, and humans. There are seven species that cause human infection including endemic coronaviruses (4 species), SARS, MERS and, recently, SARS-CoV-2. Their clinical manifestations range from mild to severe upper and lower respiratory disease. SARS and MERS caused significant outbreaks in 2002 and 2012 respectively. [1] SARS, MERS and SARS-CoV-2 are under the genus beta-coronavirus that might originate from bat virus. SARS-CoV-2 shares 90% of the genetic material of bat virus while SARS shares 80 % and MERS 50%. [3] Therefore it is important to understand the effect of SARS and MERS on pregnancy during previous epidemics in order to help predict SARS-CoV-2 behavior and guide the management of pregnancies until sufficient studies and data about the novel coronavirus are available.

Pregnancy complications of SARS and MERS

Limited data about pregnant women with SARS or MERS is available, so interpretation should be made wisely. SARS was associated with worse clinical outcomes in pregnant women than non-pregnant. [3] It caused several adverse events like spontaneous abortion, intrauterine growth restriction (IUGR) IUGR and severe maternal illness up to maternal death. [1] Maternal outcomes depended on the trimester of presentation. [7] Analysis suggests that pregnancy increases susceptibility to MERS and is associated with severe adverse outcomes with admission to ICU and death. [1] Mortality rate of SARS infection during pregnancy was 25% and even higher in MERS infection. [3] There is no vertical transmission noted in babies born to pregnant women infected with SARS or MERS. [1] SARS-CoV-2 seems to follow the same path according to the available information although few cases of Covid-19 infection have been reported in neonates born to Covid-19 positive pregnant women. A large study was conducted in the UK on a national cohort of women in which they reported 12 (5%) of 256 infants tested positive for SARS-CoV-2 with 6 of them within the first 12 hours of life. [8] Yet further investigation on vertical transmission is occurring to give more solid and accurate information.

Placental pathology of SARS

Only one study reported the pathology of placenta of mothers with SARS, which showed variable findings including increased subchorionic fibrin, fetal thrombotic vasculopathy and areas of avascular chorionic villi. [9] These abnormalities suggest placental malperfusion. Interestingly, the placenta appeared normal in pregnant women convalescing from SARS infection in the first trimester. This is in stark contrast to those infected in the third trimester, as they showed extensive placental pathology. [9] We did not find any available published study about placental pathology of mothers with MERS infection.

Clinical presentation and complications of COVID-19

SARS-CoV-2 has an average incubation period of about 5 days (2-14 days). [7] COVID -19 may present with fever, cough, dyspnea, anosmia, fatigue, nausea, loss of smell and taste, vomiting or diarrhea. Clinical presentation varies from asymptomatic to flu-like symptoms, pneumonia, or ARDS and severe respiratory failure. [7] So far there is no evidence that pregnant women have increased risk for COVID-19. [10] There is no difference between pregnant and non-pregnant women in terms of clinical course. [11] Despite that, Liu H et al noted a difference in laboratory values and CT scan. They concluded an increase in leukocytosis and elevated neutrophil ratio in pregnant patients compared to non-pregnant adults. Also, complete consolidation and mixed consolidation with ground glass appearance were prevalent in pregnant cases in contrast to non-pregnant adults where pure ground glass appearance was common. [12] The obstetric complications which have been reported include miscarriage, preeclampsia, and cesarean section with preterm birth <37 weeks being the most common adverse event. [11] However, one study found very good outcomes of COVID-19 pregnant patients whom acquired the infection in late pregnancy. [13]

In our review, incidence of preterm delivery was 28.68% and the incidence of fetal distress was 20.9%. Not all preterm delivery was the result of fetal distress. Some of the preterm deliveries were due to maternal preference. The preterm delivery rate in the general population is 11%. [14]

Although delivery through Cesarean section was reported as disproportionately high in these studies (89.6%), not all Cesarean sections were performed due to obstetric or fetal indications. The early Chinese National Health commission guidelines favored CS to normal vaginal delivery (NVD) in COVID-19 cases due to fear and uncertainty about vertical transmission risk. [15] Some of the pregnant women with Covid-19 chose to be delivered before reaching term to proceed with further treatment for Covid-19 and/or to avoid prolonged labor which was thought to be potentially

detrimental for disease progression. Lack of knowledge, uncertainty about the potential harmful effect of Covid-19 to pregnant women and fetuses, psychological stress and panic surrounding the pandemic might have contributed to the high cesarean section rates and preterm deliveries. Even in the absence of Covid-19, cesarean sections due to maternal request are significantly higher in China compared to the United States. The incidence of cesarean delivery resulting from maternal request is estimated at 2.5% of all births in the United States. [16] A retrospective cohort study of 66,266 patients in mode of delivery in China reported that 24.7% of women underwent cesarean delivery due to maternal request. [17]

Another significant outcome seen in Covid-19 pandemic was low birth weight in (28.75%) of the babies born to pregnant women with Covid-19 disease. This number is like preterm delivery rate (28.68%) in these studies which partially explains the low birth weight.

Although these reports from the early pandemic show a grim outcome on cesarean section rates, preterm deliveries and low birth weight babies, a few more recent studies from New York have shown more positive results. A recent prospective study including 241 Covid-19 positive pregnant women in New York Hospitals showed that the rate of cesarean birth was 41.5% (100) overall, but only 10 (10%) of the cesarean deliveries were performed for worsening maternal respiratory status. The incidence of preterm labor was 14.6% in this group of patients which is higher than worldwide average of 11%, but significantly less than preterm delivery rates reported earlier during the pandemic (28.6). [14] Furthermore, a report on pregnant women with Covid-19 disease in New York that reported more than 1000 cases did not show significantly increased C-section rates. Their Cesarean section rate was 31% which is similar to national average. [18]

ACOG guidelines recommend that Cesarean section should be reserved for obstetric indications and fetal indications, and that Covid-19 disease itself is not an indication for Cesarean section. [19] Adherence to ACOG guidelines has helped prevent not only unindicated preterm delivery and low birth weight babies but also morbidity related to Cesarean section itself. Detection of asymptomatic and mildly symptomatic Covid-19 disease because of the availability of test kits, confidence of health care providers in taking care of these patients due to increasing information about the disease process also might explain less severe disease and better outcomes in these more recent studies.

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