Pregnancy outcomes of pregnant women with confirmed SARS-CoV-2 infection: A review.

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Abstract

In December, 2019, a series of patients presented with pneumonia of unknown cause in Wuhan city, Hubei province of China. The clinical signs and symptoms were different from bacterial pneumonia and resembled viral infection. Gene sequencing analysis from respiratory tract samples of infected patients showed that a novel coronavirus is the causative agent of this infection. The International Committee on Taxonomy of Viruses has designated the virus that causes the novel coronavirus disease (COVID-19) as SARS-CoV-2.

Keywords: Tumors, Gestational trophoblastic tumors, Gynecology.

Accepted on 27 October, 2021

Introduction

Since December 2019, the novel coronavirus disease has spread rapidly from China to almost all parts of the world. In March 2020, the World Health Organization (WHO) declared a global pandemic of COVID-19 caused by SARS-CoV-2. With 43,965, 951 global cases and 1,166,908 global deaths as of 28th October 2020, COVID-19 has become a global public health crisis of grave concern [1].

A critical element in the management of any infectious disease threat is the care and protection of vulnerable populations. Pregnant women and their fetuses comprise a vulnerable group during pandemics of infectious disease. As the number of cases are globally on rise at an exponential rate, evidence on the incidence, transmission, and effect of COVID-19 in pregnant women and their newborns remains inadequate [2]. Pregnant women are reported to be disproportionately affected by respiratory diseases, which are associated with increased infectious morbidity and high maternal mortality rates. Pregnant women are not thought to be more susceptible to the infection than the general population. However, changes to the immune system mean that pregnant women may be more vulnerable to severe infection. Furthermore, lungs and cardiovascular system of the pregnant women is already under stress due to COVID [3].

Evidence from other similar viral diseases, such as influenza A/H1N1, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS) showed that pregnant women are at a higher risk of severe maternal and neonatal mortality and morbidity. Some evidence suggests that the risk of critical illness may be greatest in the later terms of pregnancy [4].

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) share similarities with SARS-CoV-2 as they are β -

coronaviruses having somewhat identical genomic structures. In SARS epidemic, 8098 cases were reported and its case fatality rate was about 10.5% whereas, in MERS epidemic 2519 individuals got infected and case fatality rate was around 34.4%. Importantly SARS-CoV and MERS-CoV have also been reported to cause maternal morbidity and mortality. In current pandemic caused by SARS-CoV-2 a few studies have reported adverse maternal and perinatal outcomes of COVID-19 however, extent of adverse outcomes is still unclear and research is continued. Considering the importance of the matter we conducted a review of the literature to assess the extent of adverse maternal and perinatal outcomes of COVID-19 during pregnancy [5].

Methods

The maternal and fetal outcomes of COVID-19 infected mothers were estimated by reviewing published articles, websites and other sources of information till 15th July, 2020. Relevant databases like Google Scholar, PubMed, Scopus, Medline, and Embase were searched electronically by using terms like "COVID-19 infection in pregnant women" "COVID-19 and pregnancy" and "transmission of COVID-19 from infected mothers to newborns". Articles included in the current review were case reports, case series and retrospective studies mostly because limited data were available [6].

Inclusion criteria for the current review were studies of pregnant women having confirmed COVID-19 infection (SARS-CoV-2 RT-PCR) [7]. Exclusion criteria were studies having information about newborns but missing information about pregnancy and maternal outcomes.

The outcomes of our study were divided into three main headings;

General health of pregnant women.

Citation: Rahat T, Naz F, Saima N. Pregnancy outcomes of pregnant women with confirmed SARS-CoV-2 infection: A review. J Pregnan Neon Med 2021;5(4):1-8.

Terminations of pregnancy/Mode of delivery and complications.

Fetal outcomes.

All titles and abstracts were reviewed independently by three researchers for relevance and inclusion in the current review. In case of disagreement, consensus was developed by discussion. Required data about COVID-19 symptoms, maternal outcomes and perinatal outcomes was extracted by the same researchers [8].

At first, general health of confirmed COVID-19 pregnant women were analyzed to assesses different parameters such as; sign/symptoms, development of COVID Pneumonia, ICU admission and mechanical ventilation and death. Secondly, maternal outcomes in terms of terminations of pregnancy/mode of delivery and complications in COVID-19 positive patients were assessed [9]. Maternal outcomes included were; Abortions, Pre-term birth, Premature rupture of membranes delivery (PROM), Cesarean and Pregnancy related complications. Finally fetal outcomes (abortions, IUD, Preterm birth, peri-natal and neonatal deaths) were assessed. The perinatal outcomes included were; Apgar score at 1 and 5 minutes, Fetal distress, Asphyxia, perinatal death (stillbirth or neonatal death), development of COVID Pneumonia, Neonatal Intensive Care Unit (NICU) admission, mechanical ventilation and death. Maternal COVID-19 symptoms at presentation and symptoms of SARS-CoV-2 RT-PCR and/or IgM antibodies positive newborns at birth were also included in the present review [11-15].

Data analysis

Data were entered and analyzed by using IBM-SPSS Statistics 20 software for calculation of median and percentages. MedCalc Statistical Software version 16.4.3 was used for calculation of pooled proportions. The percentages shown in of the results section are pooled proportions and the rest are reported as frequency and percentages.

Results

General characteristics of included articles are detailed. Four studies were retrospective studies, two were case series and two case reports in the selected criteria, and as a result 181 pregnant women were included in all selected studies. In some studies some or other information was missing, therefore mentioned in tables as "not reported" (Table 1) [16-20].

Table1: Characteristics of studies included in the current review.

Author	Study location	Duration	Number of pregnant women	Study design	Maternal age (years) (median)	Vertical transmission	Vertical transmission evaluated by	Test kit used
Liu Y et al[21]	China	December 8, 2019 to February 25, 2020	13	Retrospective study	30 (22-36)	No	SARS-CoV-2 Quantitative RT- PCR	not reported
ZENG et al[25]	Wuhan, China	January 2020 to February 2020	33	Case series	not reported	12114 -0.09	SARS-CoV-2 Quantitative RT- PCR	(Coronavirus PCR Fluorescence Diagnostic Kit [BGI])
Chen H et al[22]	Wuhan, China	Jan 20 to Jan 31, 2020	9	Retrospective study	28 (26-40)	No	SARS-CoV-2 Quantitative RT- PCR	(COVID-19 Kit (Bio Germ, Shanghai, China)
Hui Zeng[23]	Wuhan, China	February 16 to March 6, 2020	6	Retrospective study	not reported	44349 -0.333	SARS-CoV-2- IgM antibodies	(CLIA assays kit YHLO)
Lan Dong[27]	Wuhan, China	43831	1	Case report	29	Yes	SARS-CoV-2- IgM antibodies	not reported
Maria Claudia Alzamora[28]	Peru	43891	1	Case report	41	Yes	SARS-CoV-2 Quantitative RT- PCR	not reported
Jie YAN[24]	China	January 20 to March 24, 2020	116	Retrospective study	30.8 (24-41)	No	SARS-CoV-2 Quantitative RT- PCR	not reported
Cuifang Fan[26]	Wuhan, China	43831	2	Ca se series	34/ 29	No	SARS-CoV-2 Quantitative RT- PCR	(Bioperfectus Technologies, China)

Description of Maternal symptoms at presentation and progression of disease severity of each study. Fever seems to be the most common symptom followed by cough, sore throat, dyspnea, pneumonia, admission in intensive care unit and

patients on mechanical ventilators were also reported in most of the studies (Table 2) [29].

Table2: Clinical features of SARS-CoV-2 positive pregnant women.

Author	Fever	Cough	Sore throat	Dyspnea	Pneumonia per	Intensive care u	nit admission	Mechanical
(Study location)					computed tomography diagnosis			ventilation
[Duration]					uiugiiooio			
Liu Y et al	10/13	02/13	01/13	03/13	01/13	01/13		01/13
(China)	(77.0%)	(15.3%)	(7.70%)	(23.0%)	(7.70%s)	(7.70%s)		(7.70%s)
[December 8, 2019 to February 25, 2020][21]								
ZENG et al	08/33	10/33	No	No	33/33	No		No
(Wuhan, China)	(24.2%)	(30.3%)			(100%)			
[January 2020 to February 2020] [25]								
Chen H et al	07/09	04/09	02/09	01/09	08/09	Not reported		No
(Wuhan, China)	(77.7%)	(44.4%)	(22.2%)	(11.1%)	(88.8%)			
[Jan 20 to Jan 31, 2020][22]								
Hui Zeng	not reported	not reported		not reported				
(Wuhan, China)								
[February 16 to March 6, 2020] [23]								
Lan Dong	Yes	No	No	No	Yes	No		No
(Wuhan, China)								
[Jan 2020][27]								
Maria Claudia Alzamora	Yes	No	No	Yes	Yes	Yes		Yes
(Peru)								
[March 2020] [28]								
Jie YAN	59/116	33/116	not reported	not reported	8/116	8/116		8/116
(China)	(50.9%)	(28.4%)			(6.9%)	(6.9%)		(6.9%)
[January 20 to March 24, 2020] [24]								
Cuifang Fan	02/02	No	1/2	No	02/02	No	No	
(Wuhan, China)	(100%)		(50.0%)		(100%)			
[Jan 2020][26]								

Detail of maternal and fetal outcomes are reported and pooled proportions are reported. The age range of 181 pregnant women with COVID-19 infection from selected 8 articles was 22 to 41 years. Gestational age at the onset of COVID-19 symptoms ranged from 25 to 39 weeks. Out of 181 pregnant women, 155 newborns survived, there was 01 spontaneous

abortion, 01 still birth, 01 neonatal death. Whereas, 17 women were still pregnant till the end of study while fetal outcome of 06 pregnant women was not reported (Table 3) [30].

Table3: Pregnancy outcomes of SARS-CoV-2 positive pregnant women.

Author (Study location) [Duration]	Number of pregnant women	Gestational age at onset of illness (weeks)	Maternal outcome	Fetal outcome	Premature rupture of membranes (PROM)	Premature deliveries	Cesarean deliveries
Liu Y et al	13	35	All survived	01 still birth	01/13	6/13	10/13

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China Chin								
ZENG et al (Wuhan, China) January 2020 to Exbrusivy 2020 to Jan 31, 2020 22%) 24.4 2020 (36-39) 37 All survived All survived All survived 22.2%) (44.4%) (100	[December 8, 2019 to February 25,		(25-38)			(7.70%s)	(46.1%)	(76.9%)
(Wuhan, China) (Jan 20 to Jan 31, 2020)[22] (Jan 20 to Jan 31, 2020)[23] (Jan 2020)[23] (Jan 2020)[23] (Jan 2020)[27] (Jan 2020)[27] (Jan 2020)[27] (Jan 2020)[28] (J	ZENG et al (Wuhan, China) [January 2020 to	33	not reported	All survived	All survived			
(Wuhan, China) [February 16 to March 6, 2020][23] 01 34 survived No Yes Yes Lan Dong (Wuhan, China) [Jan 2020][27] 01 34 survived survived No Yes Yes Maria Claudia Alzamora (Peru) [March 2020][28] 01 33 survived survived No Yes Yes Jie YAN (China) [January 20 to March 24, 2020] [24] 116 (36-39) 38 (36-39) All survived 01 spontaneous abortion 01 neonatal death 6/114 (5.26%) 21/99 (21.2%) 85/99* (85.9%) Cuifang Fan (Wuhan, China) [26] 02 37 survived survived No No No Yes Cuifang Fan (Wuhan, China) [26] 20 survived survived No Yes Yes	(Wuhan, China) [Jan 20 to Jan 31,	09		All survived	All survived			
(Wuhan, China) [Jan 2020][27] Survived No Yes Yes Maria Claudia Alzamora (Peru) 01 33 survived No Yes Yes Jie YAN (China) 116 38 (36-39) All survived 01 spontaneous abortion (5.26%) 6/114 (5.26%) 21/99 (21.2%) 85/99* (85.9%) [January 20 to March 24, 2020] [24] 02 37 survived survived No No No Yes Cuifang Fan (Wuhan, China) [26] China) survived Survived No Yes Yes	(Wuhan, China) [February 16 to	06	3rd trimester	not reported	not reported	not reported	not reported	
Alzamora (Peru) [March 2020][28] Jie YAN (China) [January 20 to March 24, 2020] [24] 02 37 Survived Survived Survived Survived Survived Survived Survived Survived No No Yes Yes Yes	(Wuhan, China)	01	34	survived	survived	No	Yes	Yes
(China) (36-39) (36-39) abortion (5.26%) (21.2%) (85.9%) [24] 02 37 survived survived No No Yes Cuifang Fan (Wuhan, China) [26] 36 survived survived No Yes Yes	Alzamora (Peru)	01	33	survived	survived	No	Yes	Yes
Cuifang Fan (Wuhan, China) [26] 36 survived survived No Yes Yes	(China) [January 20 to March 24, 2020]	116		All survived	abortion			
(Wuhan, China) [26]		02	37	survived	survived	No	No	Yes
*99 patients delivered whereas, pregnancy of rest of the patients was continued.	(Wuhan, China) [26] [Jan 2020]				survived	No	Yes	Yes

On the basis of pooled proportion of reported symptoms, the most common symptom of COVID-19 among pregnant women was fever 50.77% (88/175), followed by cough 28.43% (49/174), dyspnea 23.05% (5/58) and sore throat 18.69% (4/58). COVID-19 Pneumonia was developed in almost one third, 30.90%, (54/175) of the pregnant women, 8.3% (10/132) were admitted to ICU and 8.3% (10/132) required mechanical ventilation [31]. The most common outcome observed in

84.98% (140/164) of the women was cesarean deliveries followed by premature deliveries 24.67% (38/158) and premature rupture of membranes 7.64% (12/174). No maternal death was reported by any of the included studies. Vertical transmission was observed in about 2.95% (7/164) of newborns (Table 4).

Table4: Pooled proportion of various maternal parameters infected with Covid-19.

Parameters	Studies	Pregnancies (n/N)	I2, (95%C-I)	Pooled Proportion (95%C-I)			
Symptoms and severity							
Fever	7	88/175	71.67 (38.53 - 86.94)	50.777 (43.278 to 58.249)			
Cough	6	49/174	0.00 (0.00 - 61.70)	28.431 (21.970 to 35.619)			
Sore throat	4	21276	0.00 (0.00 - 83.86)	18.691 (6.728 to 37.453)			
Dyspnea	4	21306	34.94 (0.00 - 77.28)	23.051 (9.557 to 42.351)			

Pneumonia	7	54/175	96.75 (95.04 - 97.87)	30.905 (24.279 to 38.166)			
ICU admission	4	10/132	54.08 (0.00 - 84.81)	8.324 (4.278 to 14.299)			
Mechanical Ventilation	4	10/132	54.08 (0.00 - 84.81)	8.324 (4.278 to 14.299)			
Outcome	Outcome						
PROM	6	12/174	0.00 (0.00 - 66.71)	7.646 (4.218 to 12.547)			
Premature deliveries	7	38/158	62.81 (15.56 - 83.62)	24.672 (18.302 to 31.975)			
Cesarean deliveries	8	140/164	0.00 (0.00 - 59.35)	84.980 (78.749 to 89.963)			
Maternal death	7	0/175	0	0			
Vertical transmission	8	7/164	77.96 (56.54 -88.83)	2.952 (0.976 to 6.714)			

Out of 7 newborns that tested positive for COVID-19, 02 developed fever, 02 had dyspnea, 01 had asphyxia, 01 had respiratory distress syndrome, 01 had cyanosis, 03 developed COVID pneumonia, 04 required NICU admission and 02 required mechanical ventilation. APGAR score at 1 and 5 minutes was reported for only five newborns. One neonate had APGAR score of 03 and 04 at 1 and 5 minutes, respectively. Another neonate had APGAR score of 06 at 1 minute and 08 at

5 minutes. Rest of the neonates had AGAR scores ranging from 8-10 at 1 and 5 minutes [32]. Since the most commonly observed pregnancy outcome was caesarean section, therefore indication of cesarean section is also given according to the reported cases. The most common indication reported is COVID-19 Pneumonia 46% (45/98), followed by previous C-section 18% (17/89) and fetal distress 13% (14/104) (Table 5) [33].

Table5: Indication for cesarean delivery.

Indications	No. of Studies	n/N	%
COVID-19 Pneumonia	5	45/98	45.92
Previous C-Sec	2	17/94	18.09
Fetal Distress	3	14/104	13.46
Failure to progress	1	31168	5.88
Preeclampsia	2	34455	5.32
Abnormal Fetal Growth	1	31079	2.35
Placenta Previa	1	31107	3.53
Others	4	18/106	16.98

Discussion

In the current study, review was done on the available data till 15th July 2020; however published studies after 15th July 2020 are also included in discussion section for the better comparisons on the wider range of currently available data. Majority of our review findings are consistent with other reviews conducted worldwide. Age range of COVID positive pregnant women observed in current review was from 22 to 41 years, almost same age range is seen in most of the articles; National university hospital Singapore study stated age range from 23-40 years, another review on 324 pregnant women shows maternal age ranged from 20 to 44 years [34].

Gestational age reported in our study at the onset of COVID-19 symptoms ranged from 25 to 39 weeks, most of the studies are in line that pregnant women are infected with said infection during second and third trimester. On the other hand

gestational age at the time admission ranged from 5 to 41 weeks [35].

The most common symptom of COVID-19 among pregnant women was fever followed by cough, dyspnea and sore throat whereas; COVID-19 Pneumonia was developed in almost one third of the pregnant women. These types of findings are similar in most of the individual studies, case series as well as in reviews. For example a systematic review reveals the same sequence of events regarding fever, cough and dyspnea. They reported severe pneumonia from 0% to 14% among the case series [36].

With reference to the mode of delivery, the most common outcome of pregnant women observed in current study in about 85%was cesarean deliveries followed by premature deliveries (24.67%) and premature rupture of membranes (7.64%), respectively. As it was observed in the reviewed articles around 85% COVID-19 pregnancies were landed up in caesarian

section, and in almost half of the cases COVID-19 Pneumonia was the main indication for C-section.

In a review conducted on pregnancy outcome of 108 pregnant women reveled that 91% of them were delivered by C-section. In another study, out of 48 deliveries, 46 were delivered through C-section and only 02 were delivered vaginally [37]. In the review on 324 pregnant women 78% had C-section. In most cases of available literature the indication for the c-section was not clearly stated, and it is certainly possible that the decision was influenced by the understandable anxiety towards the potential consequences of a new viral infection.

Further studies are recommended in this regard to clarify whether c-section shall be opted or not if COVID Pneumonia develops in infected pregnant women. Whereas pneumonia followed by admission in ICU having mechanical ventilators observed in current review were also reported in almost same severity in other published data, however no adverse maternal outcome was seen; findings are in same line with current review [38].

It was seen that as compared to COVID positive non-pregnant women, pregnant women were more prone to be admitted in ICU (aRR=1.5 at 95% CI) and landed up with mechanical ventilation (aRR=1.7 at 95% CI). It is postulated that there is a risk of severe COVID-19 disease in pregnant women.

In 13 states of USA data was collected by hospital surveillance network in COVID-19 associated hospitals called COVID-NET on 598 hospitalized pregnant women from 1st March to 22 August 2020, it revealed that 54.5% were asymptomatic while from 272 symptomatic patients 16.2% were shifted to ICU and 8.5% were given invasive mechanical ventilation.

On the contrary a retrospective case series study conducted in China on 21 full term pregnancies reported no admission in ICU, while findings of that study are debatable since study was conducted on only 21 cases. Similarly, another study conducted in China reveals that neither pregnancy nor child birth aggravate the symptoms of COVID-19 [39].

Same is seen with other possibilities of outcomes in current review such as; miscarriages, still births, fetal distress, PROM, preterm deliveries. About 25% women had preterm delivery, however a study conducted in China on few COVID-19 pregnant women found that no newborn was preterm or had any postpartum complications. Whereas, some studies shows both maternal and fetal complications including fetal distress, preterm delivery and even death of mother, on the contrary no serious consequence in the form of maternal death is observed in pregnant women in the current review.

According to another study, the rate of miscarriage and preterm delivery cannot be solely attributed to COVID infection since no comparison group is included and further prospective research is recommended to provide evidence. On the other hand COVID-NET surveillance revealed that about 97.8% of patients gave live births while 2.2% had lost their pregnancies.

Vertical transmission of COVID-19 from mother to her fetus is highly debatable in the available literature. In our review vertical transmission was observed in about 2.95% of newborns and out of 7 newborns that tested positive for COVID-19, 03 developed COVID pneumonia, 04 required NICU admissions and 02 neonates' required mechanical ventilation.

In comparison with a systematic search on 1316 pregnant women 11.3% neonates were admitted to ICU with 2.2%. perinatal death. Moreover, no vertical transmission was observed in that review. Similarly, a vast number of studies showed no evidence of vertical transmission.

Although limited knowledge is available on giving evidence on vertical transmission of COVID-19, however current literature is providing some solid reasons in the favour of vertical transmission; perhaps prospective studies are strongly recommended to add the evidence [40].

Limitations

Mostly case reports/series and retrospective studies are available in literature and the same were included in the current review.

Conclusion

Study findings concluded that although maternal death is not very common, however, adverse maternal and fetal outcomes are associated with COVID-19 in the form of severe illness and worse birth outcomes. Moreover, unusual increase in the rates of caesarian sections is also noticed. Evidence of vertical transmission of COVID-19 infection from pregnant mothers to their fetuses is also observed, yet debatable until proved otherwise on the studies/trials to be conducted on the larger scale.

Funding

These findings emphasize the importance of preventive measure to be taken by pregnant women from COVID-19 infection.

Recommendations

More studies with larger sample size and age and time matched control group shall be done encompassing complete information regarding maternal and perinatal outcomes. All data available till now is on smaller scale and mostly retrospective therefore, provision of facts require a larger scale data on prospective studies.

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