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Systematic Review

A systematic review of risk factors, obstetric and perinatal outcomes in COVID-19 infection in pregnancy

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ABSTRACT

While most women affected with COVID-19 during pregnancy have a mild illness 14% develop a severe critical illness that required hospitalization and oxygen support, and 5% of patients mandate intensive care. With more exposure to the illness in pregnancy, the clinical and treatment outcomes are changing. This review analyses the obstetric outcomes and risk factors reported recently from the literature, 185 potentially relevant articles published from January 2020 to August 2021 were reviewed. And 13 articles potentially eligible for inclusion underwent full-text review /cohorts/case series of not less than 9 cases that met the search criteria were included in the quantitative analysis. The range of the number of cases per population was 9,2475. A total of 4703 pregnant women with gestational age above 20 weeks and SARI/critical cases reported were 2589 cases. Outcomes in pregnant women with COVID-19 infection are not essentially different from non-pregnant women of similar age. Very few studies suggest vertical transmission as a possibility but the neonatal outcome is largely unaffected. Caesarean section rate has been coming down from 85.9% to 22% in recent times of which one-third of them was attributed to COVID-19 infections directly. Preterm labor was not found to be an independent risk factor for COVID-19 infection in the second COVID-19 wave. No increase in preterm birth in vaccinated pregnant women. Estimates of the overall case fatality ratio for COVID-19 appear to be in the range of 1-2% (0.5-10%) in high-income countries, and 2.4% in middle-income countries. Still, data regarding the impact on the fetal and neonatal outcomes of COVID-19 infection is unclear.

Keywords: Severe acute respiratory illness in pregnancy, Clinical outcomes, Maternal mortality attributed to COVID-19 in pregnancy

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a novel corona virus, was first reported in December 2019 in Wuhan in China. While most people are affected by a mild illness. 14% develop severe illness that required hospitalization and oxygen support, in 5% of patients mandate Intensive care.[1] When the disease progresses in severity, acute respiratory distress syndrome (ARDS), septic shock, thrombotic manifestations, of multi-organ failure, with acute kidney liver and cardiac injury ensues.[2]

Old age comorbid conditions like cardiac disease, diabetes mellitus hypertension, obesity are risk factors for mortality.[3] There are very few data on impact of COVID-19 infection in high risk populations like pregnancy and children. The available data are from retrospective studies and in women in the third trimester.

Rachel et al in a systematic review of chest CT findings reported pregnant Patient were more frequently found with advanced COVID-19 CT findings consolidation of lungs (40.9% verses 21.0-31.8%) and plural effusion (30% verses 5%) when compared to general population.[4]

Physiological changes in pregnancy factors such as basal atelectasis from gravid uterus, lower lung and cardiac reserves and increased oxygen consumption (30%) predispose the pregnant woman to poor outcomes during respiratory illnesses. Clinical presentations could be atypical or misleading in pregnant patients with COVID-19 with normal temperature (56%) and leukocytosis.[5]

Aim

The aim of the study was to review and assess risk factors and clinical outcomes in severe acute respiratory illness associated with COVID-19 infection in pregnancy from literature.

METHODS

Online databases of Pubmed and Google scholar were accessed for review articles, case series on COVID infection in pregnancy, severe acute respiratory illness (SARI) of COVID-19 infection in pregnancy in literature from published articles in English and non-English articles from January 2020 to August 2021. Pregnancies that were diagnosed by reverse transcription PCR were included. Keywords used for the search 'pregnancy, mother child, mother to child transmission', COVID-19, SARS COVID-19, severe acute respiratory illness of COVID-19 infection, hospital admission for COVID-19 infection, ARDS, critical respiratory illness in pregnancy, clinical outcomes in pregnancy with COVID-19 infection in pregnancy, preterm labor and caesarean section in COVID-19 infected mothers, maternal mortality due to COVID-19 infection, neonatal positivity for COVID-19 infection, perinatal morbidity and mortality as outcome variables second COVID-19 wave, COVID-19 vaccination in pregnancy. Studies with overlapping data were omitted for quantitative analysis. Case reports, case series less than nine in number were also exclude for quantitative analysis.

Studies with observational design both prospective and retrospective studies of systematic reviews, meta-analytical studies, case-series, cross-sectional, case-control, and cohort were included for quantitative analysis, editorials, correspondences and animal studies and reports from social or conventional media were excluded for quantitative analysis. The assessment of the selected full texts, as well as the data extraction of the outcome and independent variables, was carried out by the author an electronic form (excel file) was prepared to collect quantitative variables and analysis on excel sheet.

This was not a formal systematic review or meta-analysis, as we did not expect there to be an adequate number of high-quality studies to warrant such an approach as it is too early in this pandemic. We embarked on this study to conduct a systematic literature overview, with explicit criteria for article selection and abstraction.

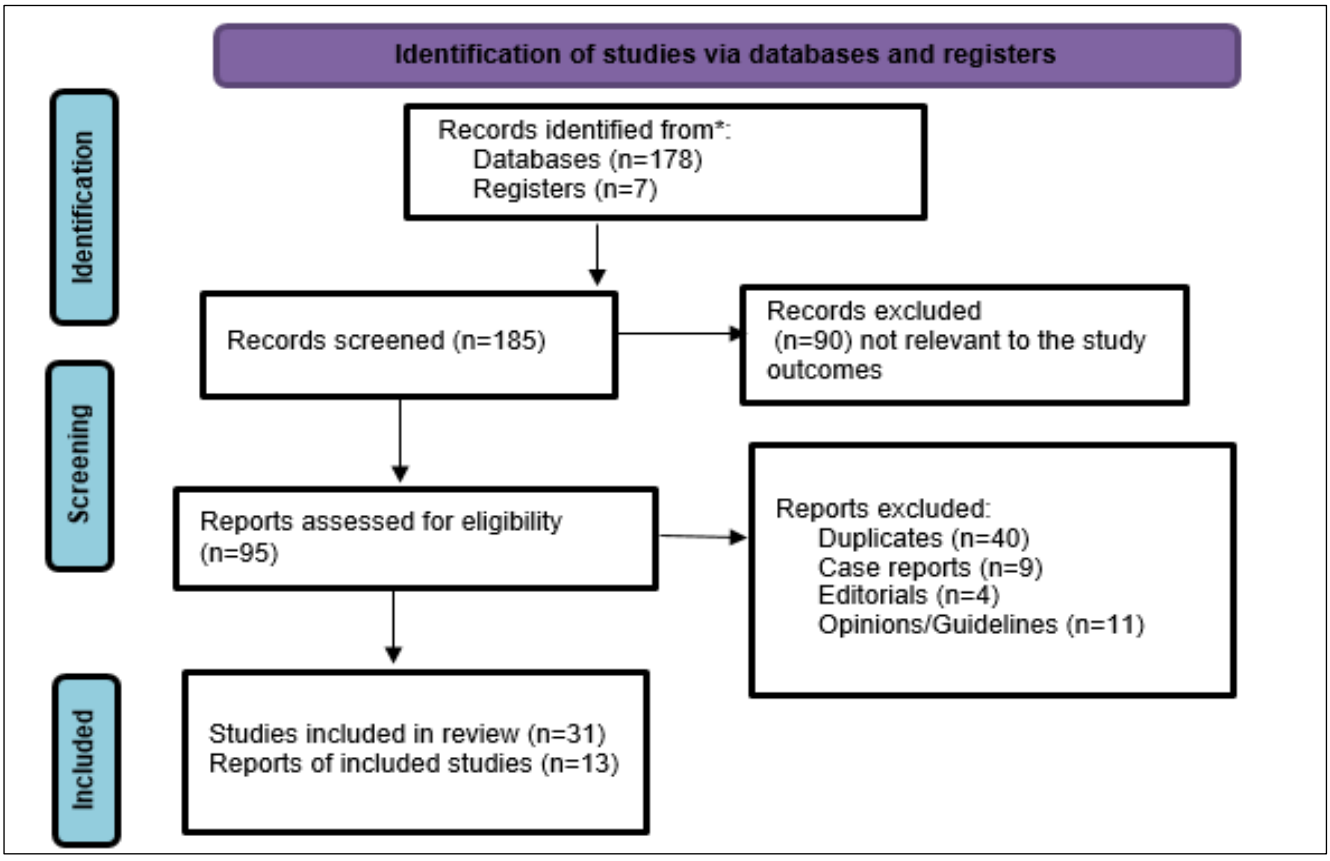

Figure 1: Identification of studies through databases and registers.

RESULTS

Overall, 185 potentially relevant articles were reviewed. After an initial screening of the titles and abstracts, full text 52 reviews (34 systematic analysis/meta-analysis reviews, were excluded from quantitative analysis for duplication of data. 12 articles potentially eligible for inclusion underwent full-text review/cohorts/case series of not less than 9 cases that met the search criteria were included in the quantitative analysis. The range of number of cases per population was (9,2475). A total of 4703 pregnant women with gestational age above 20 weeks as reported in 2589 cases of SARI/critical cases were included in the study caesarean section rate was 85.9% in initial reports to 22% in the recent past. One third of them was attributed to COVID-19 infection directly. Preterm labor was not found to be an independent risk factor for COVID-19 infection. Median duration of hospital stay was 6-8 days for SARI and 9-10.5 days for critical illness. 9% of SARI.[6,8] Vertical transmission to neonate has been reported, but the effect of the infection on the neonate is still unclear. Neonatal deaths have been reported but whether COVID-19 infection is attributed to the loss is unknown. Miscarriage reports in China were 4.6-5.2%. 4.6/100000 maternities (1.3 to 11.2) in UK. No increase in preterm birth in vaccinated pregnant women. Second COVID wave did not suggest increase in preterm births attributable to COVID-19 infection.

But high rates of maternal mortality were attributed to COVID infection in middle income countries like Iran, Brazil and Mexico with poor access to critical care facilities. Other parts of Europe, US or Asia with appropriate intensive care facility, have reported no attributable maternal mortality due to COVID infection.

DISCUSSION

Yan et al in one of the earliest reports of COVID-19 infection in pregnancy retrospectively reviewed clinical records of 116 pregnant women pregnant women with COVID-19 pneumonia from 25 hospitals in China. The most common symptoms at onset were fever (50.9%, 59/116) and cough (28.4%, 33/116); 23.3% (27/116) patients presented without symptoms. 33 % of caesarean sections were indicated for COVID pneumonia. 1/8 whom were in first and 2nd trimester had a missed abortion, (5.2%, 6/116) received non-invasive ventilation, two (1.7%, 2/116) received invasive mechanical ventilation, and one (0.9%, 1/116) received extracorporeal membrane oxygenation?[3] There was one case of severe neonatal asphyxia that resulted in neonatal death. The mother of this neonate had developed severe pneumonia and septic shock and progressed to critical disease after admission and required invasive ventilation.[3]

Ashokka et al reported in a cohort of 147 pregnant patients (WHO-China joint mission report) that 6 to 8% of the cohort were either severely ill, 1% were critically ill (respiratory failure requiring mechanical ventilation, shock, or other organ failure that requires intensive care).[6] Williams et al in a cohort study of 64 pregnant women with severe or critical COVID-19 infection, 44 (69%) had severe and 20 (31%) critical illness had pulmonary co morbidities in 25%, cardiac in 17%, and an BMI was 34 kg/m^2. ARDS set in 70%, there was one case of maternal cardiac arrest, which was revived but no maternal, fetal or neonatal deaths occurred. Eighty-eight per cent (15/17) of pregnant women with critical COVID-19 delivered preterm, 94% of them via caesarean.[7] Breslin et al reported in a retrospective. 14/43 (32.6%). One third of the patients 14/43 (32.6%) patients presented without any COVID-associated symptoms, comorbidities in 41.5%- diabetes, 7%- cardiac, 7%- asthma, 18%- obstetric admission, one patient had preterm labor. The clinical presentation was dry cough in 19, 65.6%, fever n=14, (48.3%), myalgia in 11 (37.9%) headache, 27%, shortness of breath in 7 women. 37 (86%) women possessed mild disease, four (6.9%-9.3%) cases were severe pneumonia manifested severe disease.[3,7,9] And two (1-4.7%) progressed to critical disease these percentages were not different from those described for non-pregnant adults with COVID-19 infections.[6-8] ARDS set in in 70% of women quickly. The need for intubation appeared on 8 or 9th day since admission.[8]

Prabhu et al in a prospective cohort study reported differences in outcomes between pregnant women with and without coronavirus disease 2019 (COVID-19) among 675 pregnant women consecutively admitted for delivery, for 28 days from 24 March 2020 in three New York City hospitals. 70/675 (10.4%) of the pregnant women >20 weeks of gestation admitted for delivery were positive for SARS-CoV-2, of whom 78.6% were asymptomatic. Caesarean delivery rates were high in symptomatic group, 46.7% in symptomatic COVID-19, 45.5% in asymptomatic COVID-19 and 30.9% in women without COVID-19 (p=0.044). Postpartum complications (fever, hypoxia, readmission) occurred in 12.9% of women with COVID-19 versus 4.5% of women without COVID-19 (p<0.001). Placental pathology demonstrated increased abnormal fetal vascular perfusion, indicative of thrombi in fetal vessels, in women with COVID-19 versus women without COVID-19 (48.3% versus 11.3%, p<0.001). Three women were admitted for hypoxia one (6.7%) in ICU. Preterm delivery rate was not increased in women with COVID-19 infection contrary to other studies.[9]

Two cases of cardiomyopathy complicating pregnancy and puerperium of COVID positive patients admitted. Both recovered after intensive care. Of those with severe disease, the case fatality rate was 49%, whereas the overall case fatality rate was 2.3%.[10]

Knight et al in a large rapid cohort study 427 pregnant women admitted to hospital with confirmed SARS-CoV-2 infection between 01 March 2020 and 14 April 2020 in 194 obstetric units in the UK reported the outcome in 427 COVID-19 infected pregnant women. The estimated incidence of admission to hospital with confirmed SARS-

CoV-2 infection in pregnancy was 4.9 (95% confidence interval 4.5 to 5.4) per 1000 maternities, and 145 (34%) had pre-existing comorbidities. Four women (0.9% of those admitted; 4.6 (1.3 to 11.2) per 100000 maternities) had a miscarriage, at a range of 10 to 19 weeks' gestation.). 53 (80%) had iatrogenic preterm births, 32 (48%) due to maternal COVID-19**,** 12% were delivered preterm solely because of maternal respiratory compromise. Almost 60% of women gave birth by caesarean section; but most caesarean births were for indications other than maternal compromise due to SARS-CoV-2 infection five (1%) women died 3 of direct cause due to COVID-19 infection case fatality rate was 1.2% (95% confidence interval 0.4% to 2.7%) and a SARS-CoV-2 associated maternal mortality rate of 5.8 (1.9 to 13.5) per 100000 maternities. Twelve (5%) of 265 infants tested positive for SARS-CoV-2 RNA five babies died. Three deaths were unrelated to SARS-CoV-2 infection; for two stillbirths, whether SARS-CoV-2 contributed to the death was unclear.[11]

One in 10 pregnant women admitted to hospital in the UK with SARS-CoV-2 infection needed respiratory support in a critical care setting, and one in 100 died. One in 20 of the babies of mothers admitted tested positive for SARS-CoV-2; The rates of critical care unit admission and mortality among pregnant women admitted to hospital with SARSCoV-2 infection were comparable to the rates among the general population of women of reproductive age admitted to UK hospitals with infection, of whom 20-35% receive critical care and 1-4% die.[12]

Collins et al reported the incidence of requirement for intensive care among pregnant women with SARI was higher in Sweden between 19 march -20 April 2020 was 14.4 per 100000 (95% CL 7.32-23.4) for pregnant women and 2.5 per 1000 (95%CI 1.8-3.5) for non-pregnant women in similar age group.[13]

Vertical transmission

Although earlier reports suggested no evidence of vertical transmission there is emerging evidence that now suggests that vertical transmission is probable. Two reports have published evidence of IgM for SARS-COV-2 in neonatal serum at birth. Since IgM does not cross the placenta, a neonatal immune response to in utero infection is suspected. Three of 33 infants born to mothers with COVID-19, developed early-onset infection. However amniotic fluid, cord blood, and breast milk, were negative for SARS-CoV-2 in these cases. Clinical symptoms from these infants infected with COVID-19 were mild and outcomes were favourable.[13,14]

Among the early reported four studies, 47% of the pregnant had preterm labor.[15-18]

In many reports women were in third trimester or delivered in two weeks since onset of illness The effect of COVID infection on intrauterine fetal growth abnormalities are yet to be established.[15,17,18] An initial report from Lombard by Ferrazi et al reported 19/42 women with COVID-19 pneumonia, (50%) women who underwent caesarean section was indicated for COVID infection. All women recovered. Maternal mortality due to COVID-19 infection in pregnancy is reported to be 0.5 to 10% in pregnancy with an overall rate of 2% reported in developing countries than in developed countries.[19]

Patients in the SARI subgroup had significantly higher pre-gestational body mass indexes, and heart and respiratory rates and a greater frequency of fever or dyspnea on admission compared with women with a non-severe disease progression.[19-21]

In a retrospective cohort study of 68 pregnant women with COVID-19, symptomatic women (n=46), 27.3% had preterm delivery and 26.1% needed respiratory support while none of the asymptomatic women (n=22) had preterm delivery or need of respiratory support (p=0.007 and 0.01, respectively).[22] Lokken et al reported 46 pregnant women tested positive for COVID-19 in Washington from multiple institutions. One in seven pregnant patients was hospitalized for respiratory concerns and one in eight had severe COVID-19 disease.[23]

Dorigatti et al from Brazil, Mexico and Iran report maternal mortality 16/367 (4%).[24] The Iranian series which reports 9 pregnant women with severe COVID-19 disease, includes five stillbirths at gestational age from 24-38 weeks and a neonatal death of 28 week twins. Among the early reported cases, 15/32 (47%) women affected by COVID-19 delivered preterm, in a third of reported preterm delivery was indicated for fetal distress.

Preterm birth was common (21.8%), usually medically indicated (18.4%). Maternal intensive care unit admission was required in 7.0% and 3.4% required intubation. Maternal mortality was less, 1%). Rate of maternal intensive care admission was higher in cohorts in women with co-morbidities (beta=0.007, $p<0.05$) and maternal age over 35 years (beta=0.007, $p<0.01$). Neonatal nasopharyngeal swab RTPCR was positive in 1.4%. Vertical transmission of the virus probably occurs, albeit in a small proportion of cases.[25]

Blitz et al in a retrospective cohort study data evaluated from seven hospitals in New York City and Long Island between March 2020 and June 2021, incorporating both the first and second waves of the COVID-19 pandemic in the USA reported women with SARS-COV-2 infection experienced increased incident of preterm birth during the second wave compared to the first wave (13.6% verses 8.7%) unadjusted OR 1.65, 95% CI 1.16-2.39, $p<0.006$, but they did not show increased incident of pre-term birth on multiple logistic regression modeling in the second wave compared to the first wave.[27] The confounding factors were identified as racial and ethnic groups with an increased risk for pre-term labor. Therefore it was stated that symptomatic COVID-19 infection in pregnancy is associated with an increased risk for medically indicated

pre-term labor but not for spontaneous preterm labor. It is also found that risk of preterm labor was not different in patient with resolved preterm COVID infection and or asymptomatic patients when compare to women without infection.

However in larger case series from New York, Wuhan, Netherlands and Lombardy in developed nations, no maternal deaths were reported although there were cases with critical illness.[1,7] Pereira reports from Puerta de Hierro University Hospital, Madrid, Spain, one-third of them developed pneumonia, of whom 5% presented a critical clinical status similar to other studies. CRP and D-dimer levels positively correlated with severe pneumonia and the neutrophil/lymphocyte ratio decreased as the patients improved clinically NLR decrease suggested a favourable outcome for pregnant women. 78% of patients had vaginal delivery in this study highest reported, with no adverse maternal and neonatal outcome.[26]

In a recent systematic review and meta-analysis of 2567 SARS-CoV-2 infection and pregnancies for 17 studies reported by Khalil et al 6th April-8th June 2020, and half by caesarean section (48.3%). The Black, Asian or minority ethnic group (50.8%); obesity (38.2%), and chronic comorbidities (32.5%) were the associated risk factors. The most commonly reported clinical symptoms were fever (63.3%), cough (71.4%) and dyspnoea (34.4%) consistent with previous studies. The commonest laboratory abnormalities were raised CRP or procalcitonin (54.0%), lymphopenia (34.2%) and elevated transaminases (16.0%).[28]

Mario Isaac Lumbreras- Marquez 2020 from Mexico reports 308 COVID positive pregnant women including seven maternal deaths. Older age, diabetes mellitus, obesity and other co morbid conditions were strongly associated with maternal mortality as in previously reported studies. Besides of the seven maternal death cases, only two received intensive care and only one received mechanical ventilation. Poor or no access to intensive care still looms large as a pronounced risk factor in developing countries. In contrast with previous findings, the present study reports a 2.3% case fatality rate among parturients with COVID-19, which is an alarming statistics.[29]

Menezes et al 2020 studied adverse outcomes of 2475 cases of pregnant and postpartum women diagnosed with COVID-19 ARDS until July 14, 2020 according to the National Acute Respiratory Syndrome Surveillance System database in Brazil. Among 2475 cases of COVID-19 ARDS, 8.2% died. Of those mothers who died, 5.9% were not hospitalized, 39.7% had no access to ICU admission, 42.6% did not receive mechanical ventilation, and 25.5% did not have any respiratory support. Multiple logistic regression analysis revealed, postpartum period, black ethnicity, age >35 years, obesity, diabetes,, or lack of Family Health Strategy support, living more than 100 km from the notification hospital were associated with increased risk of adverse outcomes.[30] Theiler et al reported pregnancy in birth outcomes after COVID-2 vaccination in pregnancy from comprehensive vaccine registry and delivery database among patient 16-55 years between 10 December 2020 and 19 April 2021 at a hospital in Mayo clinic health system. In this Cohort study of 2002 patients with pregnancy 140 (7%) visits received COVID-19 vaccine during pregnancy.[31] 212 (10.6%) suffered COVID-19 infection during pregnancy. Patients vaccinated during pregnancy were less likely to be infected with COVID-19 infection before delivery than unvaccinated pregnant women [2/140 (1.4%) verses 210/1862 (11.3%)]; p<0.00131. No increased preterm births or adverse effects were observed among vaccinated pregnant women.[31]

Alpesh et al from National registry of COVID-19 in pregnancy India in which a total of 771 pregnant women (97.23%, n=793) gave birth of which 455 cases (59.01%) underwent a lower segment caesarean section (LSCS).[32] 32 cases (3.54%, n=904) had severe acute respiratory infection (SARI). 455 cases (59.01%) underwent LSCS. Fifty-six women (7.19%, n=779) required critical care and ten women (1.01%, n=989) died.[32]

Common symptoms at onset were fever. 50.9%-75.5% is fever, cough 28.4%-69.8%. 6.5%-78.6% were asymptomatic in US and in China it is 23.3% in India 84.3% the highest rate of asymptomatic patients. Dyspnea in China was 37.8% and 42.2% in US. Caesarean section rate among SARI were reported to be very high, in China it is 85.9%, in US-94%, 80%-Iran, in Italy-22%, overall CI (37.5%-44.4%) in US, In UK it is 60%, and in India-59.01%. Preterm labor rate was 6.1% Chinese studies. No increased PTL or spontaneous abortions are attributed to COVID-19 infection in pregnancy. European studies suggest 8.7%-26%. UK study report 25%.

But now many of them were due to COVID-19 infection were not analyzed, PTL in Iran was 60%. Neonatal mortality rate reported Iran was highest 28.5%, 6%-UK, 2.3% in Mexico, 1.5% in India, 1% in China. US, Italy and Spain studies no neonatal death was reported. Maternal Mortality Rate reported among SARI patients was high in Iran (80%), in Brazil 8.2%, in India 1.01%. However in US, even among critical cases, with access to optimal critical care, No MMR was reported. Among pregnant with SARI cesarean Section rate reported was 50% in Italy, 94% in US.

These figures continue to change in view of different testing regime and management protocols, population demographics and availability of critical care facilities round the globe. SARI COVID-19 infection in pregnancy can progress to a serious critical illness and leading to maternal and fetal loss. Early and appropriate intervention with high suspicion index, involving the obstetrician, neonatologist radiologist anaesthetist, infectious disease specialist is recommended for optimal clinical outcomes. Still the impact of COVID-19 infection in pregnancy is

unclear as the effect on early pregnancy is still yet to be reported. Possibility of vertical transmission is a probable interpretation but the consequences are yet to known to affect fetus.

Evidence before this study

Miscarriage reports in China were 4.6-5.2% reported in China most studies reported then included women in later part of pregnancy. Preterm labor and caesarean section rates reported initially was high in studies reported previously and the proportion of cases attributed to respiratory illness due to COVID-19 was not differentiated initially and therefore apparently the figures were high.

The effects of COVID-19 in early pregnancy and intra uterine growth retardation were unknown.

Very few studies suggest vertical transmission as a possibility. Neonatal outcome attributed to COVID-19 infection was unclear initially. COVID-19 vaccine was unavailable previously and the possible effects on pregnancy was unknown.

Added value of this study

This study provides an overview analysing the maternal and neonatal outcome of a large number of pregnant women with COVID infection-19 with SARI/ critical illness including developed nations, middle and low income countries. Outcomes in pregnant women with COVID-19 infection are not essentially different from non-pregnant women of similar age in developed countries with access to optimal intensive care facilities.

No increase in adverse outcomes or preterm births in vaccinated pregnant women were reported. Even though vertical transmission was considered as a possibility in COVID-19 positive neonates. Neonatal outcome was largely unaffected.

In the second wave of COVID-19 infection reports suggest symptomatic COVID-19 infection in pregnancy is associated with an increased risk for medically indicated pre-term labor but not for spontaneous preterm labor. Geographical variation in the ICU admission rate was observed even among the developed nations, in UK and Sweden were different. Miscarriage reports in China were 4.6-5.2%, 4.6/100000 maternities (1.3 to 11.2%) in UK which was not very different from non-COVID pregnant women. No increase in preterm birth in vaccinated pregnant women was observed. Second COVID wave did not suggest increase in preterm births attributable to COVID-19 infection.

In developed countries neonatal and obstetric outcome is favourable where appropriate critical care is accessible. But maternal mortality is high among the poorly resourced nations as reported in Mexico, Brazil and Iran where access to critical care could be still lacking. Estimates of overall case fatality ratio for COVID-19 (including asymptomatic and symptomatic infections) appear to be in the range of 1-2% in high income countries, and 2.4% in middle income countries. Risk factors like poor socio-economic factors and proximity and means to appropriate intensive care was attributed to high maternal mortality in developing nations.

Implications of all the available evidence

Universal testing for pregnant women for COVID-19 infection, high suspicion of index especially in postpartum period and women with co-existing co morbidities and appropriate implementation of critical care management is key to optimal clinical and pregnancy outcomes. COVID-19 vaccine must be recommended and offered to pregnant women.

Limitations

Many studies report a heterogeneous data where a uniform design could not be observed for a meaningful derivation of epidemiological significance, with overlapping cases, the results may be duplicated or the evidence may be blurred.

The evidence from studies on case reports and case series in literature must be judiciously interpreted. The infrastructure and critical care levels round the globe is dissimilar.

The maternal outcome and maternal mortality in developing countries like India are unconfirmed, with not many scientific reports as yet, although the media reports maternal deaths across the nation.

Many authors admit to circumstantial missing crucial details, universal screening techniques of both mother and neonate could not be ensured in all the studies reported; many patients who were asymptomatic were lost for follow up. Some studies report based on self -reporting of maternal outcomes that can alter the statistical value. Many studies do not segregate severity of the disease and the obstetric outcomes.

Strength of the study

This study includes large number of pregnant women with COVID infection and obstetric outcomes reported. The systematic reviews, multi-centric studies with cohorts, retrospective studies and case series were analysed with meticulous exclusion of overlapping cases, from the beginning of the pandemic. This study also includes risk factors like social factors contributing to very high maternal mortality and in middle income nations with poor access to medical facility.

This study also adds the impact of second COVID wave on preterm labor and effects of vaccination among pregnant women.

Table 1: Studies and clinical outcomes for SARI.

Authors	Period	Study type	N	GA (weeks)	SARI	Critical illness	PTL	CS	NMR	MMR
1.Yan et al Multi-centric (China) 25 hospitals[3]	Decem-ber 2020 20.2.202 0	Retro-spective review	116	38-IQR 36-39	8/116 (6.9%)	6/116.2%	6.1 %	85/99 (85.9%)	1/100 1%	Nil
2.Rebecca et al Multi-centric 12 institutions in US[7]	l5.3.202 0 to 20.4.202 0	Cohort	64	Mean 29+6	44/64 (69%)	20/64 (31%)	17/64 (27%)	(94%)	Nil	Nil
3.Noelle B et al (US)[8] 2 Institutions	13-27 March 20220	Retro-spective	43	(32.6-38) 37 medi-an	4/43 (9%)	2/43 (4.7 %)	2/18 (11%)	19/43 (44.4%)	Nil	Nil
4.Sedigheh et al 7 Hospitals (Iran) Multi-centric[25]	mid-February to mid-March 2020;	Retro-spective voluntary reporting	9	24 to 38	8/9 (77%)	1/9 (11%)	3/5 (60%)	4/5 (80%)	2/7 (28.57%)	7/9 (77.7 %)
5.Ferrazi et al 12 hospitals (Lombardy)[19]	1-20 March 2020	Retro-spective	42	24 to 38	7/19 (36. 9%)	4/19 (21.1%)	11/42 (26. 1%)	18/42 42.9%) 95% CI (27.7-59)	Nil	Nil
6.Knight et al (UK)[11] Multi-centric, 194 obstetric units	1 March to 14 April 2020	Cohort, prospective	427	.>37 weeks (74%)	104/ 427 (24%)	41/427 (10%)	66/266 (25%)	156/266 (60%)	2/2 (6%)	5/427 (1%)
7.Savasi et al 12 hospitals (Italy) Multi-centric[20]	23 February to 28 March 2020	Cohort	77	2/3 in 3rd trimes-ter	14/77 (18%)	6/77 (8%)	9/ 77 (12%)	nm	Nil	Nil
8. Lokken et al Multi-centric 35 hospitals (Washing-ton)[23]	21 Mar to 17 April 2020	Retro-spective review	46	nm	6/46 (16%)	1/46 (2.1%)	nm	3/46 (37%)	Nil	Nil
9.Perira A et al Madrid 1 hospitals[26]	14 March to14 April 2020	Retro-spective review	60	nm	18/60 (30%)	3/8 (5%)	2/23 (8.7%)	6/23 (22%)	Nil	Nil
10.Prabhu et al (New York) Multi-centric 3 hospitals[9]	24.3. 2020 to 22.4. 2022	Prospective cohort	70	20 weeks	2/70 (2.8%)	1/70 (1.4%)	Not increa-sed	46%	Nil	Nil

Continued.

Authors	Period	Study type	N	GA (weeks)	SARI	Critical illness	PTL	CS	NMR	MMR
11. Mario Isaac Lumbreras (Mexico)[29]	From December 2020 till 17 May 2020	Retrospective review data from the Mexican Ministry of Health	308	nm	38/308 (10%)	10/308 (3.2%)	nm	7/308 2.3% CFR	nm	nm
12. Mariane O. Menezes et al 2020 (Brazil Matia)[21]	From December 2020 till 14 July 2020	Retrospective National registry review	nm	nm	nm	2475 ARDS	nm	nm	8.2%	nm
13. Alpesh et al 2021 (India)[32]	28 April 2020 to 28 August 2020	Observational study National registry on COVID-19 infection in pregnancy	966		32/966 (3.52%)	56/966 (7.16%)	(13.3 %)	455 (59.01%)	12 (1.54%)	10/989 (1.01 %)

CONCLUSION

Clinical features, severity and maternal outcome of COVID-19 infection in pregnancy is not different from non-pregnant women of similar age group. But in contrast, in the developing countries maternal mortality attributed to COVID-19 infections is still very high. Postpartum period, older age, diabetes mellitus, obesity, cardiac illness, social factors living in peri-urban area and poor access to critical care facilities were strongly associated with increased maternal mortality. Recent studies suggest early pregnancy complications and preterm labor were not different from non COVID pregnant women. In the recent past, unlike at the onset of the pandemic, judicious decision in developed countries for caesarean has decreased the incidence of caesarean sections indicated for COVID-19 maternal severe illness. The on-going pregnancies may soon throw a light on the effects on fetus early in pregnancy. Still data of impact on fetal and neonatal outcome by COVID-19 infection is unclear.

Recommendations

Most studies report one third of the pregnant mothers with COVID infection are asymptomatic. But the progression to severe acute respiratory illness and rapid deterioration to critical illness even in asymptomatic antenatal mothers is a matter of concern and calls for universal screening. Outcomes from large number of pregnant women in early pregnancies is expected shortly may be considered for a comprehensive overview. Data on impact of COVID-19 infection on intrauterine growth restriction, neonatal and long term effects is awaited. More studies on effects on vaccination in pregnancy is expected.

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