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The Effect of Covid-19 on Outcomes of Maternal and Neonatal Health

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ABSTRACT

Background: The rapidity with which the coronavirus has been increasing and spreading means that there would be difficulty in catching up with how to control it , so whatever knowledge that has been gathered must be shared concisely. The data's reporting on the outcomes of maternal and neonatal health affected with coronavirus is highly limited since sample size is less and findings have been varied across the world. Since the management policies for dealing the massive pandemic is ever changing in every country, it leads to difficulties in understanding the reliability and interpretation.

Objective: To understand and evaluate the effects of COVID-19 or SARS-CoV-2 on the maternal and neonatal outcomes. This was done by conducting a systematic review of all available literature regarding the pregnancy affected by SARS-CoV-2.

Methods: A systematic review has been conducted to understand and evaluate the outcome of maternal and neonatal health when affected by coronavirus or SARS-CoV-2. A comprehensive literature search was done on PubMed using keywords such as 'covid 19', 'SARS-CoV-2', ' pregnancy', 'maternal mortality', 'neonatal mortality', ' vertical transmission', 'treatment modality', ' gestational age ', 'delivery method'. Eligibility criteria have been all confirmed cases with laboratory findings and clinically diagnosed cases, patient being pregnant when admitted to the hospital and available features or symptoms and outcomes. The exclusion criteria has been all reports with unspecified date and location, incomplete data and unpublished reports.

Results: From all data collected the maternal age ranged from 20-44 years and the gestational age of pregnancy at time admission was 5-41 weeks which was tabulated from laboratory confirmed and clinically diagnosed cases. The most common symptoms seen were fever, cough, dyspnea, myalgia and fatigue. The severe pneumonia has the rate of occurrence of 0% to 14%, most of which had required intervention al medical care. CT findings were positive in all of these cases.

Conclusion: there has been reporting of high maternal and neonatal mortality even though majority of the women who had been affected with covid were discharged without any complications. But we haven't been able to completely rule out occurrence of vertical transmission hence a careful follow up and monitoring of all pregnancy with covid 19 is warranted.

Key words: Covid-19, Maternal, Neonatal, Health

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INTRODUCTION

The severe acute respiratory syndrome coronavirus -2 has caused a worldwide pandemic which had been spreading rapidly without any restrains affecting over hundred millions individuals. And so the rapidly growing virus demands need for understanding the effects of this virus and identifying and protecting the vulnerable group of population. From the previous coronavirus outbreaks which had affected the human population that is the middle east respiratory syndrome also known as MERS and severe acute respiratory syndrome also known as SARS , we have learnt that pregnant women are at an extremely high risk for having a poor outcome. As known for previous viruses admission to medical care is very common. Understandably enough information had not

been collected about people who are at greater danger in developing infections and further complications during this pandemic. Exactly 90% of the kids are asymptomatic and those who are symptomatic are competitive mildly affected the disease progressive. And death is very rare. However the presentation of severe clinical features is around 6.7% in neonates under age of one year. Pregnant women who were a confirmed case of COVID-19 at time of pregnancy, have a higher risk having their child having some affliction with the disease. But as of now the chance of the transmission of covid transplacentally is rare. However there is big risk of contamination of newborns child born from mothers who are a confirmed case of covid. The clinical onset of symptoms neonates are very evident even if the ate usually asymptomatic. Unstable vital signs and abnormal respiratory and cardiovascular findings have been reported in neonates. Hence it is deemed essential that very close follow-up of those neonates confirmed with covid should be done [1].

The rapidity with which th coronavirus has been increasing and spreading means that there would be difficulty in catching up with how to control it , so whatever knowledge that has been gathered must be shared concisely. The datas reporting on the outcomes of maternal and neonatal health affected with coronavirus is highly limited since sample size is less and findings have been varied across the world. Since the management policies for dealing the massive pandemic is ever changing in every country, it leads to difficulties in understanding the reliability and interpretation.

Objective

To understand and evaluate the effects of coronavirus disease 2019 (COVID-19) on the maternal and neonatal outcomes. This is done by performing a systematic review of all available literature regarding the pregnancy affected by covid.

METHODS

We have conducted a systematic review articles to understand and for evaluation outcome of maternal and neonatal health due to effect of COVID-19 during Pregnancy. A thorough literature search was conducted via PubMed. The keywords used for search were as follows: COVID-19, SARS-CoV-2, pregnancy, gestational age, neonatal mortality, maternal and neonatal outcomes, covid in pregnancy, vertical transmission, transplacentally transmission. The articles which were eligible were selected based on covidn19 confirmed cases, covid during pregnancy, cases which had obvious clinical features or symptoms, wmd availability of data on outcomes. Articles were excluded on the basis of lack data, unspecified locations, unpublished articles, lack of reporting of the outcomes of the maternal and neonatal health. This study was conducted according to Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) statement.

Search strategy

For this systematic review, the searches were carried out through PubMed. No time frame limitations were given. The search were based of key words search as : covid-19, pregnancy, maternal mortality, neonatal mortality, covid in pregnancy, comorbidity, methods of delivery, post partum outcomes, vertical transmission, transplacental transmission, SARS-CoV-2, treatment COVID-19, period of gestation with COVID-19 , complications, clinical features, sample for covid. For further consideration for inclusion the full text articles were reviewed. Criteria for eligibility were as follows: laboratory conformation of coronavirus through the qRT-PCR. Or through the Fluorescence PCR. availability of obvious clinical features for both mother and neonate, reports which were written in English, women who were pregnant during the time hospitalization, availability of data regarding outcomes of both mother and child . The criteria for exclusion of articles, reports or series were cases which were not confirmed via a laboratory findings, unreported outcomes, duplicate reporting, any efforts were made to make sure there were no overlapping of cases.

Study selection

Titles relevant for the systematic review had been selected from the first screening. After first screening the procedure was repeated for exclusion of ay case series amd reports that only have less than 10 cases. This was done to avoid duplication of cases. Only the potential relevant articles had been included. References from original articles amd review articles were further searched. For further consideration for inclusion the full text articles were also taken.

Data extraction, outcome measures, quality measures

The information regarding population, outcome, study design and results were taken from, selected studies. Other than that authors names , institutions and countries, sample size, maternal age , period of gestation at the time of hospitalization, complications during or after pregnancy, period of gestation at the time delivery, the methods of delivery, severity of disease, lab and radiological findings, outcomes of both mother and child , and sample collection and type of sample. The evidence pointing towards or supporting vertical transmission had been recorded. Any reports or series that did not give any data on the outcome were represented as not reported.

RESULTS

The clinical manifestations of SARS-CoV-2 at hospital admission which included laboratory, the treatment modality received the outcomes of the maternal and the neonates. These data were corresponding to the maternal and neonatal features.

Majority of the cases had originally been from China but cases from Europe, Australia and America had been included. Data from two different styles of diagnosis that

is laboratory confirmed and clinical diagnosed, have been included however, the data from these two styles have been differentiated. A laboratory confirmed case of SARS-COV-2 was defined as any qRT-PCR or quantitative reversed transcriptase-polymerase reaction assay positive result of maternal pharyngeal swab specimens [2]. The treatment given to the majority of the confirmed COVID-19 positive patients have antibiotic treatment for the vast majority (70.7%) and the rest were given antiviral therapy and corticosteroids (37.8% and 17.6 % respectively). Out of all Hydroxycholoroquine was given as a treatment modality to two cases. On the computed tomography, almost all the women who were positive have positive findings that were patchy shadowing or ground-glass opacity.

These cases presented mainly which symptoms such as fever, cough, dyspnea, myalgia and fatigue. The rate of pneumonia which is severe in nature amongst all the case reports had been 0 to 14%, with most them requiring admission in the intensive care unit (ICU). All of these patients had positive CT findings. Reports of abortion or spontaneous miscarriage had been reported from around 4 of the case series. On the time of admissions to the hospital for delivery, most COVID-19 positive women underwent cesarean section [2].

The most common indication given for cesarean section was reported as fetal distress. However it was difficult to understand how fetal distress was represented in these patients. Whether it referred to any abnormal CTG or cardiotocography findings or any other signs such as abnormal fetal scalp lactate or blood flow or meconium-stained fluid [3].

In the reports a case of each neonatal asphyxia and death had been reported. Out of 155 cases of neonates all except 3 had come negative for SARS-CoV-2 when they had under nucleic acid testing in throat swab. In a case series ofm9 cases with severe SARS-CoV-2, it was reported that there had been seven maternal death, four intrauterine death which also included twin pregnancy and two neonatal deaths. From the case reports 2 confirmed positive COVID-19 cases were seen in neonates and two maternal fatalities and one intrauterine death was seen [2].

In one specific case neonate born from 41 year old woman who had significant exposure to COVID-19, had tested positive for SARS-CoV-2 from a throat swab taken. The mother was an known case of diabetes mellitus.

She had presented at 33 weeks of gestation which the chief complaints of low grade fever , dyspnea, malaise amd fatigue which were all progressive in nature, present since four days. The respiratory samples which were taken , had tested as positive.

The patient was placed on ventilator support after development of severe respiratory failure on the 5th day of onset of symptoms. She was started on Hydroxycholoroquine, oseltamivir, meropenem, azithromycin and vancomycin.

The patient had undergone cesarean section since there had been preterm labour due to respiratory status which had been compromised. Neonate isolation had been enforced without any delayed cord clamping. Also immediately after birth skin to skin contact had also not been done. Weight at birth was 2.9 kg and APGAR score 6 and 8 at 1 and 5 minutes, respectively. The neonate wasn't exposed to any members of the family and breastfeeding wasn't initiated also. The neonate was admitted in Neonatal intensive care unit, isolated from other COVID-19 cases. This was also the first pediatric case at the hospital. No abnormalities were seen on chest X-ray. The neonate tested positive for SARS-CoV-2 from the nasopharyngeal swab taken 16 hours post-delivery. The test was also repeated 2 days later following which it still remained positive. However there were no presence of anti SARS-CoV-2 immunoglobulin-M and Immunoglobulin-G. Due to delay of testing, the chance of neonatal infection could not be entirely ignored. Ventilatory support was needed for 12 hours followed which the neonate was extubated and was placed on continuous positive airway pressure with fairly good results [2].

There have been reports of total of 6 admissions to the neonatal Intensive Care unit and there was also one death.(4). In ll the six neonates who were admitted , the common symptoms were shortness of breath. Fever was also present as a symptom along with thrombocytopenia among the abnormal liver function. Also tachycardia, pneumothorax ad vomiting was also present. Among ten neonates eight were born via cesarean section and six were born prematurely. Both prematurity and the need of cesarean section as a mode of delivery has lead to higher rate of morbidity among the neonates [4].

Another report was presented regarding two cases of neonates born from covid positive mother [5]. One was of full term pregnancy, who developed a low grade fever. Later on the neonate developed abdominal distension and on lab work lymphocytopenia was also present both on the third day of onset. The following day diffused haziness was revealed on the chest radiograph taken.

The neonate was discharged nine days post-delivery. The second case delivered at 36+5 weeks via obstetrical delivery. The neonate developed a mild pneumonia along with along lymphocytopenia. The treatment modality provided were antibiotics following which the neonate was discharged after 2 days.

However there had been quite a few cases where complications occurred such a case of pregnancy where there was multiple organ dysfunction syndromes with acute respiratory distress syndrome occurred. This progressed to an emergency cesarean section [6]. Ventilator support was given to the mother along with extracorporeal membrane oxygenation (ECMO). However the neonate was a stillborn. The condition of this patient is yet unknown (3). The evidence for transmission of COVID-19 vertically from the mother to her fetus was not present in any available literature.

A case was reported wherein both mother and neonate had the same findings on QRT-PCR [7]. Around 40 weeks of gestation the mother presented with fever. And on CT chest there were ground-glass opacities in the lungs. She immediately had to undergo emergency caesarean delivery. The neonate had normal APGAR score. The child was moved to neonatology department after 10 minutes of delivery for observation where on laboratory examination there was elevated creatine kinase , deranged LFT and Lymphocytopenia but was clinically stable. However the mother had been wearing an N95 mask and had had no contact with the child. The mother' labs tested positive for SARS-CoV-2 when tested. The neonate was also tested for covid after 36 hours of birth, which resulted in confirmed positive. Swabs from placenta and umbilical blood were taken which were reported negative. This lead to the conclusion that vertical transmission could not be completely excluded. Both mother and the child successfully recovered and were discharged [3].

SARS-CoV-2 and early pregnancy

The possible impact of COVID in early pregnancy that's from conception to 12 weeks of gestation has had very little evidence. It is known that seasonal influenza is linked with comparatively higher rates of miscarriage [8]. Which leads to the need of population level monitoring and community level testing to establish the link between covid and miscarriages in early stages of pregnancies?

SARS-CoV-2 and late pregnancy

One can expect adverse pregnancy outcomes in case if the other is covid positive such as intrauterine growth retardation, preterm birth and intrauterine death, if infected in later pregnancy that is later than 24 weeks of gestation [9]. It is extremely crucial to understand the trend linked with COVID-19 and its effect on outcomes in late pregnancy by assessment of population level data. As of now the risk of severe COVID-19 infection in later pregnancy does not seem any different than that to general populace which seems reassuring.

Corticosteroid use

Antenatal corticosteroids have shown to lead to a very significant morbidity and mortality benefit for neonates when given to mothers if and when there is a possibility for preterm delivery. The usage of corticosteroids given to nonpregnant patients who are SARS-CoV-2 positive been they were in situations of severe infection, had been associated to increased mortality and poorer prognosis according to thr early observations. However the study wasn't oriented to the severity of the infection and the comorbidity of the patient. However in the corticosteroid arm of the RECOVERY trial, the treatment had been modified to include prednisolone or hydrocortisone since dexamethasone was known to cross placenta. But pregnant women had to been included in the first report. So according to the findings a suggestion was brought up that the existing guidelines be followed for administration of the corticosteroids in the situation of iatrogenic preterm delivery in case of a SARS-CoV-2 positive mother in case of poor maternal health. Additionally the use of corticosteroids is warranted in cases when maternal health becomes severe either during the pregnancy or during postpartum [10].

SARS-CoV-2 and its effect on postpartum

Neonatal outcomes

In majority of the reports regarding the neonatal outcomes, neonates born to SARS-CoV-2-positive mothers have had no adverse outcomes . In many studies which have been comparing the outcomes in those neonates who were born either from mothers who are confirmed positive cases of covid 19 or mothers who were in general unwell but confirmed negative cases of covid 19. In this study it was reported that there haven't been any significant differences in the adverse neonatal outcomes rates. A higher rate of preterm birth has been reported by many studies conducted on covid positive mothers. However there had been denominator population to compare to. And the cause for the preterm deliveries in all these cases had been reported as due to iatrogenic due to declining or deteriorating maternal condition.

Breastfeeding

The studies have shown inconclusive reports regarding transmission of SARS-CoV-2 from breast milk. However alone case study was presented wherein the breast milk sample had tested positive for covid which had been tested 4 separate times [11]. However in another case study, breast milk was collected from 9 mothers who were SARS-CoV-2 positive. But all the test came out as negative. As of now the current guidelines state that the mother's must continue to breastfeed whether or not they tested positive for covid 19 during birth of their child or during the post party period. Although they are expected to follow basic hygiene and hand washing. The SARS-CoV-2 positive mothers must also wear masks during breastfeeding, if it is available. Since on the basis of known reports neonatal infection from COVID-19 is usually asymptomatic or usually mild, the advantages of breastfeeding outweigh far greatly to the potential risk of transmission risk.

DISCUSSION AND CONCLUSION

Effectively the major finding of this systematic review are that A) the commonly seen symptoms have fever, cough, dyspnea, myalgia and fatigue; B) after hospitalization the CT of the chest of COVID-19 positive patents shows mainly patchy shadowing or ground glass opacity. The laboratory findings of these patients have shown Lymphocytopenia and raised CRP although they had somewhat normal leucocyte count ; C) In the all the case series that had been read through showed that the number of cases of severe pneumonia ranged from 0% to 14% ; D) seven maternal death had be reported in the case series (2); E) There is no obvious increase in

the occurrence of any risk or dangerous complications arising in pregnancy, such as pre clampsia or eclampsia due to covid 19; F) In pregnant mothers with positive SARS-CoV-2 there had been reports of only few cases of termination of pregnancy or spontaneous abortion had been reported. ; G) Due to lack of completeness of the period of gestation of pregnancy there an obvious scarcity of data ; H) The average period of gestation of women at has been ranging from 28 to 41 at the the of reporting. And mostly all these women had to undergo lower segmental cesarean section. I) Around 3 cases of neonatal covid positive cases were reported among the case series and another one neonate tested positive from the throat swap sample among the case reports. In another case series a neonate was confirmed positive for SARS-CoV-2 one and 36 hours post birth, whose mother was a confirmed case of COVID-19 . However on QRT-PCR of the placenta and umbilical blood the result was reported as negative for SARS-CoV-2. Hence the disapproved the idea that there had been a intrauterine vertical transmission covid 19 [12,13].

However the theory that vertical transmission of COVID-19 had been brought forth with evidentiary support from the presence of Immunoglobulin-M antibodies in the blood samples taken from 3 neonates born to mothers who were cases of SARS-CoV-2 which were laboratory-confirmed [14,15].

However the throat and nasal swabs taken from the above mentioned neonates had tested negative for covid. Furthermore it was proved that SARS-CoV-2 antibodies had been derived transplacentally from the covid positive mother and was not actively induced due to an apparent covid infection since on testing the neonate for levels of IgG and IgM, it was observed that there was a sudden decrease in Immunoglobulin-G levels within 2 weeks, together with a decline in Immunoglobulin-M levels. Although many cases have raised suspicion for a likelihood of possibly vertical transmission such as a case where there was maternal death the amniotic fluid , swabs of throat and nose of the neonate had tested positive for SARS-CoV-2 [16], and in a case of neonate where the respiratory samples which had been taken tested positive for SARS-CoV-2 [17]. However supplementary evidence in the above mentioned cases which could have possibly made the theory of vertical transmission more concrete could not be presented since the authors could not measure the specific SARS-CoV-2 antibodies. This case was unusual hence held a special interest since the mother had been possible affected with COVID-19 which might not have been evident prior to delivery of then child. But as soon as the patient delivered the child the, the condition of the patient deteriorated dramatically. The similarly between the cases above mentioned were that in both the cases the others had been already infected with SARS-CoV-2 preterm and deteriorated rapidly due to severe COVID-19.

There seems to be at least 2 mechanisms through which there could have been a covid 19 infection in intrauterine through vertical transmission.

ACE-2 or Angiotensin-converting enzyme-2 which is expressed in the placentas of humans [18] has been recently indicated due to the sensitive cells having putative surface receptors [19], for the SARS-CoV-2. Hence this exposes the prospect of a transplacentally transmission of SARS-CoV-2 due to ACE-2.

More specifically, for the facilitation of the efficacy and amd easy of replication, TPRSS2 or transmembrane protease serine 2 cleaves the viral surface spike protein or S-protein of the SARS-CoV-2. Also there has been developing evidence of recruiting and co-opting of additional host proteases by SARS-CoV-2 for transmissibility [20,21]. A number of articles reflect on effects of Covid-19 pandemic on maternal health [22-28].

However women who are pregnant have been universally excluded from clinical trials which have been investigating potential therapeutic options despite the obvious increased susceptibility of pregnant women to the effects of coronavirus. There are only few ongoing investigation that have included pregnant women which includes those investigating treatments with fairly well established record for use in pregnancy like Hydroxycholoroquine. Therefore we urge the researchers to conduct investigations which are inclusive of pregnant women and all marginalized groups of people to form informed and well represented evidence based data.

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