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Coronavirus disease 2019 (COVID-19) and Pregnancy

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Women perhaps are more exposed to coronavirus disease 2019 (COVID-19), caused by the novel coronavirus (CoV) called as the severe acute respiratory syndrome-CoV-2 (SARS-CoV-2), as compared to men, due to their greater contribution in healthcare and social services. Globally, around 70% of health and social service providers constitute of female. The pandemic is also poising serious threat to female sexual and reproductive health. Particularly, pregnant women are at risk and need special antenatal care besides routine health services. SARS-CoV-2 infection leads to the path of an exaggerated immune reaction in an infected individual. This leads to 'cytokine storm' causing massive tissue damage, systemic inflammation, increased body temperature, and in turn, these may lead to multiple organ failure. The gonads are also susceptible to damage and impairment in reproductive functions. Thus, it is vital to acquire information on the impact of this virus on gestational changes and pregnancy outcome. Given the limitation of data on COVID-19 mediated changes in pregnant women, this article also reviews the effects of two previous coronavirus infections - severe acute respiratory syndrome (SARS) caused by SARS-CoV and the Middle East respiratory syndrome (MERS) caused by MERS-CoV to predict the possible impact of the novel SARS-CoV-2 on pregnancy outcomes. Analysis of available literature reveals that unlike coronavirus infections of pregnant women caused by SARS and MERS, COVID-19 seems less likely to cause maternal death. Importantly, alike SARS and MERS, there were no confirmed cases of intrauterine transmission of SARS-CoV-2 from mothers with COVID-19 to their fetuses. Further broad-spectrum research is necessary to reach a consensus regarding the vertical transmission of SARS-CoV-2 and whether it adopts any other mechanisms to affect pregnancy outcomes.

Keywords: COVID-19; inflammation; miscarriage; pregnancy; SARS-CoV-2**.**

The appearance of novel coronavirus (CoV) infection that originated in Wuhan, China in December 2019, has emanated in an infestation that has rapidly tumefied to become one of the most noteworthy public health impendences of current century[1-4]. This novel CoV is termed as severe

acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and the disease it produces has been named coronavirus disease-2019 (COVID 19) [5]. It has become a global pandemic as declared by the World Health Organization (WHO) on March 11, 2020[6]. It causes respiratory infection which often leads to major pneumonia and can even turn fatal[7].

Genetic, virologic, epidemiologic and clinical aspects of SARS-CoV2 are being intervened to recognize its exact mechanism of human transmission and propagation[8]. It has been reported that SARS-Cov-2, alike human pathogenic coronavirus SARS-CoV, binds with angiotensin-converting enzyme-2 (ACE2) receptor located on the target cells in host body. The expression of ACE2 have been shown in epithelial cells of the lung, intestine, kidney, and endothelial cells[9] as well in the placental cells[10].

The etiopathology of fetal COVID-19 and vertical transmission of SARS-CoV-2 from mother to fetus have sparsely been documented, but mostly remain opaque[9, 11]. Since COVID-19 is a prominent public health issue, adequate understanding about pathology of this disease in pregnant women is very essential which will serve to provide better obstetrical management to these patients. Contemporarily, few case histories of the Zika, Ebola and Marburg virus along with the other agents clearly showed the vertical maternal-fetal transmission which can be an intimidation about the health and constancy of an affected mother and fetus[12, 13].

Transmission of SARS-CoV-2

SARS-CoV-2 is believed to be transmitted from bats to human via intermediate animal at the Huanan Seafood Wholesale Market of Wuhan[14, 15]. Since then, the virus soon spread all over the globe through human to human transmission. Individuals without symptoms of COVID-19 (asymptomatic or silent carrier) can also be a possible source for the spread of novel Coronavirus. Thus, social isolation is proposed to control this contamination due to communication[16].

Unlike the other respiratory pathogens (e.g. common flu or rhinovirus), the emerged nascent novel coronavirus can also be transmitted by the dispersion of infected droplets from symptomatic COVID-19 patients[17]. Other possibility is airborne transmission, which can also be elevated by the prolonged exposure in a suffocated or non-airy space[17]. This viral contamination is prominent among the hospital staffs and professionals, and high within the hospitals or nursing homes, as well as via relatives and other nearest contacts[18].

Pathophysiology of SARS-CoV-2 infection

The nascent emerged novel SARS-CoV-2 virus has embraced structures with nucleocapsid whose genetic material consists of a single-stranded RNA that is positive (or sense) strand which encodes mRNA (messenger RNA) and protein[19]. The genomic and viral structure with the disease-causing mechanisms of SARS-CoV-2 should be contemplated[19]. The viral single stranded positive sense RNA (~30 kb) has a 52 cap structure and 32 poly A tail. The viral RNA serves as template for translation of polyprotein 1a/1ab (pp1a/pp1ab) and these polyproteins encode nonstructural proteins (nsps) forming the replication transcription complex (RTC)[20]. The RTC synthesizes subgenomic RNAs (sgRNAs)[21] with common 52 leader and 32 terminal sequences, located between open reading frames (ORFs). The sgRNAs are used to produce the subgenomic mRNAs[22]. Minimum of six ORFs can be observed in the CoV genome. Except the ORF1a and ORF1b, the other open reading frames encodes for various structural proteins (like spike protein, proteins of membrane envelope, nucleocapsid and accessory protein chains)[22]. Various CoVs represent significantly specially structured accessory proteins which are been enormously translated by the specific sub-genomic RNAs[23].

The functions of structural and non-structural proteins are intricately related to the pathophysiology and virulence mechanism of CoVs. It is been explained that nsps can directly hinder the innate immunity response of the infected individual[24]. Structural proteins are not only crucial for the envelope, but also may promote the virus assembly and their release. Nevertheless, maximum of these subsequent observations has not been elaborated yet such in those of nsp-2 and -11[25]. The spikes on viral surface are made up of homotrimers of S-proteins also known as spike glycoproteins, composed of S1 and S2 subunits[26]. Of note, in SARS-CoV-2, the S2 subunit contains a fusion peptide, a transmembrane domain, whereas cytoplasmic domain is highly conserved[19]. Thus, it could be a target for antiviral (anti-S2) compounds. Though SARS-CoV-2 shares 79.0% nucleotide

identity to SARS-CoV[27], many structural features are different to some extent, for example, the spike receptor binding domain has only 40% amino acid identity with other SARS-CoV, ORF-3b and ORF-8 encoded proteins are not identical with SARS-CoV[28]. Following the comparison of the gene sequences between SARS-CoV-2 with that of SARS-CoV, Angelette et al. have reported that the transmembrane helical segments encoded nsp2 and nsp3 in ORF-1ab which denotes that, the position of 723 has glycine residue in place of serine and 1010 position is engaged by proline instead of the isoleucine[29]. The SARS-CoV-2 gene sequences were published by the researchers in several International Gene Banks for instance Gen Bank, helped researchers to find the evolutionary tree of the CoV-2 virus and to specify the strains which differed due to mutations. Few recent studies have mentioned about 'spike mutation' which had already emerged in late November 2019, is being multiplicated in a jumping manner among the human beings[30, 31]. It is suggested that mutation is the key for potential disease relapse.

Due to the shortage of extensive clinical data it is not feasible to produce concrete information about the symptoms and clinical manifestations of CoV-2. However, it is quite evident that the viral infection leads to the path of exaggerated immune reaction in an infected individual. This leads to 'cytokine storm' causing massive tissue damage. Interleukin-6 (IL-6) is one of major cytokines contributing significantly to elicit an uncontrolled immune response in COVID-19 patients. It is produced by the activated leucocytes primarily at the site of inflammation. IL-6 contributes to host defense through the stimulation of acute phase protein responses, induces the differentiation of B-lymphocytes, capable of crossing the blood brain barrier and initiates the synthesis of other inflammatory mediators, such as prostaglandins in hypothalamus which is one of the major factors that attribute to elevated body temperature[32]. Thus, induction of high levels of IL-6 release along with other cytokines like interferon gamma (IFNã) leads to pathogenicity related with systemic inflammatory responses. This results in a feedback circuit to induce surge of various pro-inflammatory cytokines and may cause cytokine release syndrome (CRS)[33]. CRS is been characterized by fever and multiple organ dysfunction connected with chimeric antigen receptor (CAR)-T-cell therapy, therapeutic antibodies and haploidentical allogenic transplantation[34].

COVID-19 and pregnancy: Current scenario and previous experience

The outbreak of COVID-19 has put the public health sector and medical infrastructure in a state of urgency to provide care to the patients as well as to adapt to fast evolving treatment regime[35]. During the previous outbreaks of SARS and MERS, clinicians took time to treat or invent vaccine for pregnant women to cover the fetal safety[36]. A constraining reason is important to remove the pregnant women from consideration, possibly in this hefty contagious hazard[37] The mediations for the mother and fetus during the treatment of pregnancy, the merits should be carefully administered as well as the possible risks. Following the close observation of COVID-19 cases during the treatment which are fully set up is mandatory to ensure and report the proper information on the status of pregnancy with the inclusion of maternal and fetus outcome. In a case control study, between pregnant and non-pregnant women with SARS CoV, it has been reported that the pregnant women did not show any unusual clinical symptoms[38]. Ramifications and unpropitious situations including the staying duration in hospital, kidney failure, septicemia and disseminated intravascular coagulopathy (DIC) in conceived women were statistically and considerably expanded[39, 40]. Need of ventilation had increased death rate among the pregnant women as compared with non-pregnant women has been reported[38]. Moreover, some studies also reported the same that, the pregnant women were observed more frequently with ventilation and hemodialysis as treatment tool because of renal failure, and positive cerebrospinal fluid for SARS-CoV[41, 42] without any reporting case of stillbirth from the affected pregnant women. The mothers were seen with exaltation for their recovery and the neonates were also reported as negative for SARS-CoV RNA test[43]. According to Maxwell et al., out of seven pregnant mothers who were admitted with SARS-CoV in designated SARS unit, two of them were passed away and four mothers were recommended for intensive care unit (ICU) supervision and ventilation. Two vitiated pregnant women had come out from that unpropitious condition but

had neonates with intrauterine growth restriction (IUGR) without clinical evidence of SARS-CoV infection among the live newborns[44]. According to Ng et al., placental pathological examination among seven infected pregnant women inferred that two of them who were recovering from SARS-CoV during the early gestational period, the placentas were found to be normal. Besides that, elaboration of expanded sub-chorionic and intervillous fibrin were reported in three women may be due to impaired maternal to placental blood flow[45].

COVID-19 and pregnancy complications: Susceptibility and severity

In lieu of current researches and evidences, it can be suggested that during COVID-19 pandemic, men are more susceptible to the infection than women[3, 46-49]. According to the studies, regarding SARS or MERS, a concrete inference cannot be drawn about the tendency of infestation among the conceived women. So far, this novel coronavirus is not at all gender bias, the above-mentioned information about the infestation of COVID-19 on the basis of gender difference is based only on some following subsequent situations like susceptibility, subjection and detection of contamination. No references or studies has given the proven data about the expansion of infestation of COVID-19 among these would be mothers. According to the preceding studies, related to SARS and MERS, a quite abnormal clinical observation had been noticed in conceived women that may lead from severity to death without any foregoing symptoms (Table 1)[9, 37, 50-62]. Agitation or high temperature with acute respiratory tract distress observed among 80% of the hospitalized patients[3]. Few clinical observations were suggested by Chen et al.[9], about few pregnant women whose symptoms has somewhat similarities with non-pregnant adult women also in some aspect. Out of nine pregnant women subsequent observations are being followed: (a) high temperature in seven of them, (b) respiratory distress in four, (c) three of them were suffering from myalgia, (d) pain or irritation in the throat with some sorts of discomfort in each of the two women, (e) reduced lymphocyte count or lymphocytopenia was observed among five of them, (f) each of them had pneumonia but by god's grace no death reports has been confirmed yet. Everybody was placed for surgical or c-section delivery, followed by, the observed Apgar scores were 9-10 at 5 minutes and 8-9 at one minute.

According to a study conducted by Zhu et al[54], another series of nine pregnant women along with 10 infants into which one set of twins were observed following symptoms: out of nine pregnant women prior 1 to 6 days of delivery, four of them were confirmed, two cases were observed at the day of parturition exactly and three cases were confirmed after delivery. No differences administered in the perspective of COVID-19 symptoms when compared with infected and non-infected individuals. Few more complications observed within those nine pregnant patients, such as six of them was observed with development of intrauterine fetal distress, seven of them had to be considered with C-Section or surgical delivery, and out of those ten infants, six were found with premature delivery. So far, these information and reports has been concerned, confirm or exact conclusion about the severity among pregnant women in the perseverance related with COVID-19, is still under scrutiny.

Besides the other physiological changes, the pregnant women undergo cardio-respiratory and immunological changes leads to become more susceptible for the development of severe health issues after infection with any respiratory virus. It has been observed that, 1% of pregnant women infected with influenza-A subtype H1N1 virus, but 5% of all H1N1 related deaths were also accounted for them[63].

Moreover, SARS CoV and MERS CoV both are responsible for onset of such multiple complications during pregnancy provoking urgent use of endotracheal intubation and intensive care unit (ICU), even causing renal failure and death[45, 64]. But surprisingly, COVID-19 causes less severe infection than SARS CoV and MERS CoV to the pregnant women. The study described earlier conducted by Chen et al[9], observed only fever and coughing as primary signs of laboratory confirmed COVID 19 women with positive third trimester of pregnancy. Symptoms like muscular pain, sore throat, diarrhea and shortness of breath were also included later. Within those nine affected pregnant COVID-19 patients, most of them were reported with abnormally lesser count of lymphocytes with higher C reactive protein, besides the presence of multiple patchy ground

glass shadows in the lungs observed on chest CT scan. Due to COVID-19 infection, 22.22% of nine affected patients were observed with fetal distress and separately 22.22% of nine affected patients were again were found with premature rupture of feto-placental membrane although all nine patients were staying alive without developing the severe COVID-19 pneumonia. Lei et al.,[65] also conducted a study among nine pregnant women (pregnancy of mid trimester onwards or during the postpartum period) with confirm COVID-19 showing similar report as previous study but only one woman was kept under the ICU care and ventilation for the sudden appearance of acute respiratory distress syndrome, as the viral infection was diagnosed two days after the delivery. Both the studies also described that the clinical characteristics of COVID 19 pneumonia are similar for both the group of patients pregnant and non-pregnant[2, 66]. Thus, the healthcare professionals who are pregnant, have to aware and must use personal protective equipment (PPE) and follow the infection control guidelines prior exposure to the patients with COVID-19. Simultaneously, prevention and control practices against the infection are also important part to protect all the healthcare professionals in clinical settings[67].

COVID-19 and pregnancy: Measures, diagnostic testing and vaccination

The indications and manifestations of COVID-19 like respiratory distress, cough and high body temperature[55], should not be neglected, thus, must be diagnosed in a proper way not only in normal adults but also in pregnant individuals. Before taking the pregnant women inside the delivery unit or prenatal care unit the diagnosis procedure is to be presented usually. An individual with the symptoms has appointment, should be instructed all the does and don'ts and if prior the next call the patients feeling any severity, should immediately be provided with proper face musk by health personnel and must be isolated from the gathering.

The patient should be isolated in an isolation room to prevent from the cross-contamination from one room to the other rooms. This isolation room includes a ventilation system that releases a 'negative pressure' (a pressure lower than the surrounding pressure). The patient should be kept inside the isolation room till the proper testing of the appropriate prototypes are not been received. Simultaneously, notifications must be sent to the infection control departments governed by the local or state or national health departments in a serious content. The urgent samples required are the swab of upper and lower respiratory tract specimens and plasma, but stool and urine testing can be done later.

Till date COVID-19 vaccine is not been invented yet. Different organizations that also refer the "National Institute of Health" with their efficient warriors are doing their best jobs to discover, depending on that SARS-CoV-2 virus genetic sequence published online on 28th April 2020[68]. Scientists and researchers may correlate research outcomes with that of invention related to SARS and MERS vaccines[69]. The real-life saver saints those who have sacrificed their valuable life for the nation as well as whole world and are trying to reach the unknown fact where they can relief the mankind from this unknown deadly disease.

Management of COVID-19 during pregnancy

The COVID-19 outbreak is really a crucial time for each and every human being, but it is a more challenging time for the conceived women who need special care and close observations. A maximum level of equipment and facilities are recommended which must incorporate a close observation and prior detection of an emergency situation and proper monitoring of the worst clinical conditions for example premature delivery or still birth is most important. Other clinical complications like respiratory abnormality detected in mother, can be cause of irregular heart rate pattern in fetus. Not only those previous studies related with SARS and MERS has explained that in extreme conditions when uncontrollable respiratory troubles occur in the patient, sometimes artificial ventilation might not enough tackle that situation. Extracorporeal membrane oxygenation (ECMO) is the one and only way out at that crucial moment to be managed by the trained experts only[70]. Some event of relief is gained by the affected mother after delivery or not, it is still not known but before taking any steps related to delivery, should be consulted with the professional who is in the supervision[71].

Research works are on their own way but still no medications against COVID-19 has been invented and stamped by the US food and drug

Table 1. Studies on the effects of SARS-CoV-2 infection and its impact on pregnancy outcomes.

Study type	Sample Size	Subject details	Findings / Outcome
Retrospective Case Study [50]	One	30-week-pregnant woman with COVID-19	• A preterm male infant weighing 1.83 kg was delivered uneventfully, with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively • The patient and her infant had an uneventful postpartum and neonatal course.
Retrospective Case Study [51]	Three	Patient 1: 34-year-old with a history of hypothyroidism for four years and epiglottic cysts reported COVID-19 positive. Patient 2: 34-year-old without any medical history was reported COVID-19 positive. Patient 3: 30-year-old with a history of gestational hypertension during her first pregnancy was reported COVID-19 positive.	• A healthy male newborn was delivered by cesarean delivery by patient 1 with Apgar scores at 1 and 5 minutes were 8 and 9, respectively and all the samples of newborn was reported negative for COVID-19 test. • A healthy female newborn was delivered by cesarean delivery by patient 2 with Apgar scores at 1 and 5 minutes were 8 and 9, respectively. But the newborn showed slightly decreased responsiveness and muscle tone which returned to normal later and all the samples of newborn was reported negative for COVID-19 test. • A healthy female newborn was delivered by vaginal delivery based on maternal request and Apgar scores at 1 and 5 minutes were 8 and 9, respectively. All the samples of newborn were reported negative for COVID-19 test.
Retrospective Case Study [52]	One	A 30-year-old who had confirmed COVID-19 at 36 weeks 2 days of gestation without obstetric co-morbidities	• The cesarean section was performed uneventfully without discomfort or poor muscle relaxation. The neonate was 2730 g, with Apgar score at 1 and 5 min of 7 and 9, respectively. • The neonate was not infected
Retrospective Case Study [37]	Two	Patient 1: 38-year-old and was admitted for induction of labor at 37 weeks' gestation due to poorly controlled type 2 diabetes mellitus and intrahepatic cholestasis of pregnancy followed by reported SARS-CoV-2 positive. Patient 2: 33-year-old and was admitted for induction of labor at 37 weeks' gestation due to worsening chronic hypertension with medical history of mild-intermittent asthma and type 2 diabetes mellitus.	• For patient 1: Intrapartum, the patient's temperature increased to 38.5oC (101.3oF). a rapid decline in tidal volumes and minimal end-tidal carbon dioxide were noted. Auscultation revealed wheezes with minimal air movement. Severe bronchospasm was suspected and medically managed and followed by SARS-CoV-2 testing appears positive. Did not mention the status of newborn. • For patient 2: approximately 25 hours after delivery, and 60 hours after presentation to Labor and Delivery, the patient developed a cough that progressed to respiratory distress. Vital signs included temperature of 39.4oC (102.9oF), tachycardia (pulse 130s beats/minute) and 88% oxygen saturation on room air, and she was dyspneic and diaphoretic. There was no description for newborn.
Retrospective case Study [53]	One	A 30-year-old pregnant woman at 35 weeks' gestation; she had been confirmed positive for SARS-CoV-2 infection at her local hospital on the basis of a sputum sample.	• She had 2-days history of dry cough without fever, chills, or shortness of breath before attending the hospital. • On the delivery day, although the woman's sputum was positive, serum, urine, feces, amniotic fluid, umbilical cord blood and placenta, and breast milk samples were negative. • She delivered a healthy infant, suggesting that mother-to-child transmission is unlikely for this virus
Retrospective case analysis [9]	Nine	All subjects were pregnant, and all were found as COVID-19 positive	• All nine patients had a caesarean section in their third trimester. • Seven patients presented with a fever

			and other symptoms. • Fetal distress was monitored in two cases. • Five of nine patients had lymphopenia (<1·0 × 10? cells/L). • Three patients had increased aminotransferase concentrations. • None of the patients developed severe COVID-19 pneumonia or died till the study was processed for the publication. • Nine livebirths were recorded without any report of neonatal asphyxia. • All nine livebirths had a 1-min Apgar score of 8-9 and a 5-min Apgar score of 9-10. • Amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples from six patients were tested for SARS-CoV-2, and all samples tested negative for the virus.
Retrospective analysis [54]	Nine	Pregnant women and their 10 neonates including twins. Initially all nine pregnant women were COVID-19 positive	• For the pregnant women, clinical symptoms were noted before delivery among 4 cases, on the day of delivery among 2 cases, and after delivery among rest of the 3 cases. • Among 10 newborns, 4 were full-term infants and 6 were born premature besides that, 8 singletons and 2 twins were observed. • 2 infants appeared as small-for-gestational-age (SGA) and only 1 infant as large-for-gestational-age (LGA). • Some symptoms were observed in the neonates like shortness of breath, fever, thrombocytopenia, accompanied by abnormal liver function, rapid heart rate, vomiting, and pneumothorax. • Till the date of publication of this study, 5 neonates were reported as cured and discharged, 1 has died, and 4 neonates remain in hospital with stable condition although these nine neonates reported negative result for their Pharyngeal swab specimens.
Retrospective analysis [55]	13	Chinese patients with SARS-CoV-2 admitted to hospitals all were pregnant with age between 22-35 years with 25th to 38th weeks of gestation period.	• All the patients cooperated for successful delivery • 10 C-section delivery, 6 premature delivery were reported • 12 newborns were survived out of 13 livebirths • As there were no reports for vertical transmissions, all the newborns were tested negative for SARS-CoV-2.
Retrospective, single-center, descriptive study [56]	Seven	All were pregnant (range: 37 to 41 weeks)	• Clinical manifestations were fever (six [86%] patients), cough (one [14%] patient), shortness of breath (one [14%] patient), and diarrhea (one [14%] patient) • All the patients had caesarean section and the outcomes of the pregnant women and neonates were good. • There were no intensive care unit admissions for mothers throughout the study period, including before and after delivery. • The neonatal birthweights and Apgar scores were normal • Four infants were taken home and were not tested for SARS-CoV-2. Remaining three neonates were tested for SARS-CoV-2 and one neonate was infected with SARS-CoV-2 36h after birth.
Case study [57]	116	Pregnant women with COVID-19 pneumonia	• The most common symptoms were fever (50.9%, 59/116) and cough (28.4%, 33/116); 23.3% (27/116) patients presented without symptoms. • Of the 116 cases, there were 8 cases (6.9%)

			of severe pneumonia but no maternal deaths. One of 8 patients who presented in the first trimester and early second trimester had a missed spontaneous abortion. • Of 99 patients, 21 (21.2%) who delivered had preterm birth, including six with preterm premature rupture of membranes. The rate of spontaneous preterm birth before 37 weeks' gestation was 6.1% (6/99). • One case of severe neonatal asphyxia resulted in neonatal death. Furthermore, 86 of the 100 neonates tested for SARS-CoV-2 had negative results; of these, paired amniotic fluid and cord blood samples from 10 neonates used to test for SARS-CoV-2 had negative results.
Clinical analysis [58]	Five	Pregnant women confirmed COVID-19. Gestational weeks ranged from 38th weeks to 41st weeks	• All pregnant women did not have an antepartum fever but developed a low-grade fever (37.5?-38.5?) within 24 hours after delivery. • All patients had normal liver and renal function; two patients had elevated plasma levels of the myocardial enzyme. • Unusual chest imaging manifestations, featured with ground-grass opacity, were frequently observed in bilateral (three cases) or unilateral lobe (two cases) by computed tomography (CT) scan. • All labors smoothly processed, the Apgar scores were 10 points 1 and 5 minutes after delivery, no complications were observed in the newborn. • No newborns showed the signs of perinatal COVID-19 infection, umbilical cord blood and amniotic fluid were not applied for virus detection due to the lack of reagent. No complications of placenta infarction and chorionic amniotic inflammation were reported. All patients were advised to stop breastfeeding and empirically given oseltamivir and azithromycin for treatment.
Population based cohort study [59]	427	Pregnant women admitted to hospital with confirmed SARS-CoV-2 infection between 1 March 2020 and 14 April 2020	• Most pregnant women admitted to hospital with SARS-CoV-2 infection were in the late second or third trimester. • 281 (69%) were overweight or obese, 175 (41%) were aged 35 or over, and 145 (34%) had pre-existing comorbidities. 266 (62%) women gave birth or had a pregnancy loss; 196 (73%) gave birth at term. Forty-one (10%) women admitted to hospital needed respiratory support, and five (1%) women died. Twelve (5%) of 265 infants tested positive for SARS-CoV-2 RNA, six of them within the first 12 hours after birth. • Almost 60% of women gave birth by caesarean section; most caesarean births were for indications other than maternal compromise due to SARS-CoV-2 infection. One in 20 of the babies of mothers admitted to hospital subsequently had a positive test for SARS-CoV-2; half had infection diagnosed on samples taken at less than 12 hours after birth.
Clinical analysis [60]	617	Pregnant women with COVID-19	• Ninety-three women (15.1%) had required oxygen therapy and 35 others (5.7%) had a critical form of COVID-19. • The severity of the disease was associated with age older than 35 years and obesity, as well as preexisting diabetes, previous preeclampsia, and gestational hypertension or preeclampsia. • One woman with critical COVID-19

			died (0.2%). • Among the women who gave birth, rates of preterm birth in women with non-severe, oxygen-requiring, and critical COVID-19 were 13/123 (10.6 %), 14/29 (48.3 %), and 23/29 (79.3 %) before 37 weeks and 3/123 (2.4 %), 4/29 (13.8 %), and 14/29 (48.3 %) before 32 weeks, respectively. One neonate (0.5 %) in the critical group died from prematurity.
Clinical analysis [61]	16	Pregnant women (age group: 24 to 34 years old) who were clinically diagnosed or diagnosed with COVID-19 in the third trimester of pregnancy. There was a total of 45 pregnant women who did not incorporate COVID-19 (part of the Non-COVID-19 group) during cesarean delivery (to eliminate the possible impact of different delivery methods on the comparison of pregnancy outcomes)	• 16 pregnant women who were clinically diagnosed or diagnosed with COVID-19 in late pregnancy, including 15 cases of normal type and 1 case of severe type • Among them, there were 11 cases of labor, scarred uterus, premature rupture of membranes, and 1 case of fetal distress • This study analyzed the results of biochemical tests, novel coronavirus nucleic acid tests, and chest radiographs of 10 neonates with complete clinical data collected during the delivery of COVID-19 pregnant women. The other 6 neonates were born with a shortage of isolation wards. Transfer to the outer court • Of these 10 cases, 9 were term infants and 1 premature infant • Ten cases of neonatal coronavirus pharyngeal swab nucleic acid tests were negative in 10 cases. Three newborns were diagnosed with bacterial pneumonia based on medical history symptoms • there was no neonatal disease or death
Retrospective clinical analysis [62]	10	Pregnant women of age between 29 to 35 years old with gestational weeks of 33+6 to 40+5 weeks, were admitted to hospital with confirmed SARS-CoV-2	• Among the 10 observed pregnant women, all of them were diagnosed mild COVID-19, and none of the patients developed severe COVID-19 symptoms or died. • Two patients underwent vaginal delivery, two patients underwent intrapartum cesarean section, and the remaining six patients underwent elective cesarean section. They delivered including 9 singletons and 1 twin newborn. • All eleven live births had a 1-min Apgar score of 8–9 and a 5-min Apgar score of 10. • Four newborns were premature, two of them had a birthweight lower than 2500 g • After 14 days, eleven newborns were recorded no neonatal death or neonatal asphyxia was observed, and no one presented with fever, cough, or diarrhea.

administration[69]. Regarding previous researchers related to the invention of medicine applied on animal models of MERS has been examined for the sake of SARS-CoV-2[70] Pneumonia developed as a foremost sign and symptom in COVID-19 patients were not advised to take corticosteroid-based medicines until and unless the accessory symptoms are not being prominent. The main reason to avoid this corticosteroid was confirmed by previous researchers related to MERS which unworthy as it can proceed to detain MERS-CoV approval[72]. Any conclusion regarding the lung maturation of fetus by applying corticosteroids must be taken under the advice of the in-charged professionals or neonatologists in addition with the infectious disease specialists. These information are subjected to be improvised time to time on the basis of further data on pregnant women available in relation with COVID-19.

Care of infants born to mothers with COVID-19

According to the previous studies related to SARS and MERS no cases had been found related to infection in neonates after delivery. In contrary, according to recent published media report, a chance of maternal to fetal transmission in a 30hours neonate was found which was supposed due to intrauterine contamination with COVID-19 after detection[73]. The studies flashed by Chen et al[9] and Zhu et al[54], out of 18 women (19 neonates) were contaminated during the gestational period (probably 3rd trimester) with SARS-CoV-2, but not laboratory detection of contamination from mother to baby during the period immediately before or after the birth. Trial of amniotic fluid, blood from umbilical cord and samples from infant's throat became negative for SARS-CoV-2, analyzed on six patients confirmed by the study of Chen et al[9], Zhu et al[54], suggested that other than the intrauterine transmission, other possibilities could be there after analyzing the complications based on the following symptoms: (a) abnormally breathing in six of them, (b) dyspnea or cyanosis among three of them, (c) intestinal bleeding in two of them, and (d) death of one among them due to multi-organ failure. However, throat swab testing of all infants was found to be negative for SARS-CoV-2.

So, it is not clear that whether SARS-CoV-2 is been communicated from mother to baby or not. Besides that, it can be stated that, the infestation of an infant with COVID-19 can be a contamination either in uterus or during the period around the birth (perinatally) is not confirmed because of the insufficient information till now. An early discussed study, conducted by Chen et al[9], imposes a close observation regarding newborn death and fetal death or any kind of neonatal respiratory discomfort has not been confirmed caused by COVID-19 yet amidst three months pregnant mothers if also they had experienced C-section delivery. Besides those, among the nine pregnant patients, four women were observed with premature delivery but those were not subjected to COVID 19 infection; although the study calculated an Apgar scoree" 9 at 5 min for all the newborns. The study also observed the negative result for COVID-19 tested in amniotic fluid sample, umbilical cord blood sample collected from six pregnant women and throat swab samples from the six neonates which may confirm the not only the absence of vertical transmission from the COVID-19 positive patients to the newborn during the late pregnancy via the intrauterine environment but also via the breastfeeding as virus free colostrum of was detected from the COVID 19 infected women. But, as the transmission of virus happens through close contact, thus firstly the newborns were allowed to be separated from the affected mothers, at least for 14 days as incubation period of the virus, to confirm the effect of virus appearance among the newborns and mothers were allowed for the breastfeeding until they were tested negative. It has been stated earlier that all nine COVID-19 positive women attained Cesarean delivery, although the time interval between symptomatic diagnosis of the viral infection and Cesarean delivery was found to be lesser which rising a question for any risk of vertical transmission if mentioned interval will be greater. However another study by Shek et al. demonstrated that there is no relation of SARS CoV with inheritance i.e. this infection is not inherited[74] although currently no evidences were found regarding pregnancy linked with any unfortunate incidences like miscarriage, restricted fetal growth, spontaneous preterm birth and congenital anomalies during the COVID-19 pneumonia infection also. In early human placenta (first trimester), a mass level of ACE2 expression had been found in four main cell types, such as decidual stromal cells, decidual perivascular cells in deciduas and villous cytotrophoblast, and syncytiotrophoblast in placenta; on the contrary, the expression of ACE2 has been observed with very low level in extravillous trophoblast at first trimester and found to be elevated at the 24th week of gestational period as per the recent study[10, 75]. From the above studies, it might be inferred that due to high levels of ACE2 expression in placental cells, these cells are highly susceptible in SARS-CoV-2 infection. The possible rout of transmission from mother fetus is the mother-fetus interface which is known as syncytiotrophoblast which is the ectoenvelope of the placental villi creating the straight way to the maternal blood flow[10, 76]. So, it is still unknown that, whether from mother to fetus transmission of this deadly COVID-19 infection is possible or not. For this reason, isolation of the

infected mothers from their respective infants, as suggested at the time of H1N1, is really a judicious decision[77].

The transmission of SARS-CoV-2 through mother's breastmilk is not been confirmed yet from a mother who has already recovered from COVID-19; although, on the same perspective, another study was conducted by collecting the breastmilk specimen from a mother with her recovery period of 130 days after the manifestation of infestation, which showed the presence of antibody against SARS-CoV in that breastmilk[41]. On the contrary, an infected mother at her 7th week of gestation showed the absence of antibody at 12th and 30th day after delivery[78]. Randomly, six pregnant mothers were tasted for the presence of COVID-19 in breastmilk but all test reports were appeared to be negative in a study conducted by Chen et al[9]; thus all those mothers were motivated for breastfeeding. No data or information has been confirmed yet about the duration of isolation and will be marked by close observation on the basis of future cases among the neonatologists and the persons of infection control board. On the basis of the proven data will concise the confusion about this deadly, incourigeous COVID-19 infection in pregnant mothers.

CONCLUSION

At present, data are limited pertaining to the impact of COVID-19 upon the pregnant women based on which pregnancy-specific care can be recommended. However, experiences gained from previous pandemics owing to SARS, MERS, and other respiratory infections, risks associated with pregnant COVID-29 patients can be presumed. It is essential to include the records of COVID-19 mediated changes (if any) on gestation and/or the maternal and fetal outcomes, in the recorded database of COVID-19. As the pandemic COVID-19 reaches every 'nook and corner' of the communities across the globe, it is necessary to be more attentive for prevention of further spreading by providing some rapid implementations of management measures for outbreak control. Standard rigorous team-based actions are to be taken to care, manage as well as to improve any case of acute respiratory tract infection to any pregnant woman infected with COVID-19.

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