

# The consequences of COVID-19 and its vaccine on pregnant and lactating mothers

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## Abstract

The single-stranded RNA virus (coronavirus 2019) pandemic has represented a massive influence on health care professionals and communities around the world. This virus is accompanied by a range of respiratory disorders. Morbidity and mortality are in elevation among pregnant mothers. COVID-19 vaccine is considered safe for the majority of the population. Safety concerns were raised toward pregnant mothers and the COVID-19 vaccine. In the present study, data were taken out from relevant manuscripts; from 20<sup>th</sup> April 2021 to 25<sup>th</sup> December 2021. In this study, literature reviews from the most comprehensive health database on 100 papers published during 2020 and 2021 were used. This review article aimed to assess the present evidence available in the literature about the possible effect of COVID-19 on pregnant mothers and their fetuses and, to address considerations for maternal COVID-19 vaccine based on the review of existing data to aid in spreading the awareness about the benefits of vaccine that could save lives. In general, COVID-19 vaccines resulted in reducing the ability of virus transmission and patients' hospitalization. COVID-19 vaccines will never cause infection of corona virus. Evidence showed that COVID-19 vaccines from any brand will reduce the mortality and morbidity. However, available data indicated that possible deterioration of the clinical conditions of pregnant mothers infected with COVID-19 cannot be excluded. Primary outcomes did not show clear safety signs among pregnant mothers who received COVID-19 vaccines. This is because pregnant and lactating mothers were excluded from COVID-19 vaccine studies. Thus, data to lead vaccine decision-making are inadequate. More longitudinal follow up studies are necessary to reinforce the safety of the vaccine.

**Keywords:** COVID-19, Pregnant mothers, breastfeeding, vaccine

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## Introduction

In December 2019, an epidemic happened in Wuhan in Hubei province in China. As the 1<sup>st</sup> case of pneumonia (pulmonary inflammation) was diagnosed, severe acute respiratory

syndrome-coronavirus disease 2019 (SARS-CoV-2 [COVID-19]) hastily spread around the world, being announced as a pandemic in March by the World Health Organization (WHO). Globally, as of 25 June 2021, there have been 179,686,071 confirmed cases of COVID-19, including

3,899,172 deaths, reported to WHO. SARS-CoV2 has taken medical care professionals by surprise, as its effects are comparable with other respiratory infections, and pulmonary is not just the organ being affected by this unusual pandemic.<sup>1</sup>

## Methods

An extensive search was conducted on electronic databases such as Scopus, PubMed, and Web of Science. Original studies published in English were included. Conference proceedings, experiments, and studies with qualitative designs were excluded in this study.

Removing duplicate articles, first electronically and then manually. The title, abstract, and the full text of the studies were assessed based on inclusion and exclusion criteria. Searches were made in many databases to identify, recent studies regarding COVID-19 during pregnancy and lactation periods. Data were taken out from relevant manuscripts; from 20th April 2019 to 25th April 2022. In this study, illegible literature reviews from the most comprehensive health database on 7 papers published in 2019 to 2022 were used (Table 1).

**Table 1.** Illegible review articles on pregnant and lactating mothers with COVID-19 included in the study.

Author / year [reference list]	Study location	No. of pregnant mothers	No. of lactating mothers
<i>Della Gatta et al., 2020</i> <sup>80</sup>	Italy	51	0
<i>Liu et al., 2020</i> <sup>84</sup>	China	13	0
<i>Brandt et al., 2021</i> <sup>86</sup>	Canada	61	0
<i>Lokken et al., 2020</i> <sup>93</sup>	USA	46	0
<i>Zhu et al., 2020</i> <sup>99</sup>	China	0	9
<i>Centeno-Tablante et al., 2021</i> <sup>101</sup>	China	0	77
<i>Liu et al., 2020</i> <sup>103</sup>	China	19	0

## Description of COVID-19

COVID-19 is a non-segmented, single-stranded ribonucleic acid (RNA) virus, producing infections from the simple common cold to severe serious infections. The genome of COVID-19 shares around 80% of SARS-CoV and around 50% of the Middle East respiratory syndrome-related to coronavirus (MERS-CoV), respectively.<sup>2</sup> COVID-19 is characterized by 4 genetic materials: a spike protein, the envelope, a membrane, and the nucleocapsid.<sup>3</sup> The favorable area of COVID-19 is the lung zone. COVID-19 attaches to the host receptor. Next the successful bound to the receptor of the host's cell, then the protein's spike experiences a conformational change for the viral envelope in order to bind to the cell membrane to release RNA into the host cell. This progress happens by the endosomal pathway. As soon as RNA goes into the host cell, then the viral replicates, that are fragmented into smaller units by enzymes

named proteinases.<sup>4</sup> The particles of the virus were translated into viral proteins by mRNAs and collected into virions on the endoplasmic reticulum and Golgi apparatus wherever they were secreted out of the cell by vesicles. Next of releasing, it is entered into the lung specifically into the alveoli, then into endothelial and blood cells. This results in activation of the immune system.<sup>5</sup>

## Clinical Manifestation of COVID-19

COVID-19 has been described to have 3 phases: the first phase; is an incubation interval starting from the day of infection it is around five days<sup>6</sup> which in many patients this period may be without any symptoms and the virus will survive inside the host undetectable. The second phase is when detecting the virus and patient may show mild signs and symptoms for example, an elevation in the body temperature. Finally, the third phase, when severe manifestations appear such as respiratory disorder and consequently

death.<sup>7</sup> Most cases have mild manifestations, but about 20% progress badly to severe illness. The most common manifestations include elevation in body temperature, coughing, muscle ache/tiredness, and shortness of breathing. Less common manifestations include are cough with sputum, headache, and frequent bowel motion. Incidence of bilateral pneumonia; consolidation parts is a frequent finding in about half of symptomatic cases.<sup>8-9</sup> Complications may encompass bilateral pneumonia, acute respiratory distress syndrome (ARDS), heart disorder, sepsis, respiratory tract superinfections, and shock.<sup>10</sup> Females are less probable to die or need hospital admission or enter intensive or respiratory care units when compared to males. Actually, females at the reproductive stage have a 60% less possibility of intensive care unit admission than males who are at the same age.<sup>11</sup>

### COVID-19 Transmission

COVID-19 infection spreads from individual to individual by respiratory droplets once interaction with the infected one (less than 2 meters) or through direct interaction with planes that are polluted by the patient's secretions.<sup>12</sup> Spread may happen throughout the patient's feces, but the transmission through this way is much less occurrence.<sup>13</sup> The likelihood of vertical spread (from mother to her neonate) is very un-probable and has not been proved in the Chinese COVID-19 epidemic<sup>14</sup> or even in the preceding outbreaks by further alike coronaviruses SARS\_CoV & MERS\_CoV.<sup>6-7</sup> According to scarce data, there is no proof of the existence of the virus in genital discharge, urine, fetal amniotic fluid, or breast milk.<sup>8</sup> The median period of viral shedding is about 20 days (being 75% at 24 days).<sup>15-16</sup>

### Pregnant Mothers with COVID-19

The modifications in the immune system of mothers during the pregnancy period make them more vulnerable to infectious diseases.<sup>17-18</sup> Furthermore, they suffer from signs and symptoms of COVID-19, with the hazard of negative maternal and newborn complications, preterm and underweight birth, spontaneous

abortion, applied of endo-tracheal intubation, intrauterine growth retardation, admission to the intensive care unit, kidney failure, intravascular coagulopathy, and spread to the fetus or neonate.<sup>19</sup>

Despite the fast-increasing total of patients with COVID-19 worldwide, data on the virus throughout gestation remain insufficient, being consequent generally from small sample studies. A higher rate of premature deliveries, pre-eclampsia, cesarean section, and death during delivery.<sup>15</sup> The deficiency of data on unplanned (spontaneous) abortion due to COVID-19 in the first trimester prevents the extrapolation of definite evidence for the impacts of this virus during the early period of pregnancy. The scarcity of reliable data has produced concern in patients with COVID-19, and the misinformation stated by the media could lead pregnant mothers to embrace dramatic options for example, elective abortion.<sup>20</sup> No teratogenic impact of the virus in the newborn has been discovered. A study observed that only 8% of newborns were born to infected mothers with COVID-19 confirmed positive to COVID-19,<sup>21</sup> that raises a significant query on the success degree of trans-placental viral infection (intrauterine spread) to the embryo/fetus inside the uterus. It is supposed that there will be an active replication of the COVID-19 inside the placenta. Nevertheless, if this is accurate, the mechanism involved in precluding the COVID-19 virus from arriving in the fetus is remain vague. Likelihoods may comprise the mother-fetal interface of placenta function as a strong and powerful barrier against viruses, or the absence of particular receptors which permit effective viral spread. The maternal placenta has an immunological barrier toward the admittance of pathological agents, in addition, to maintaining the immune tolerance to the cells of the fetus. Low viremia among pregnant mothers was found during COVID-19.<sup>22</sup> Nevertheless, the majority of data on the vertical transmission were grounded on mothers who had COVID-19 in the 3rd trimester, and data on the topic of transmission vertically in the early pregnancy period is still insufficient. Documented cases of the neonate

with COVID-19 possibly came through horizontal transmission.<sup>23-25</sup>

#### *COVID-19 investigations during pregnancy period*

The polymerase chain reaction (PCR) is considered as a golden standard test for diagnosing COVID-19.<sup>26</sup> The Chest X-ray (CXR) and also chest computed tomography (CT) can assist in early detection of the virus, and even may be used in order to evaluate the degree of the affected area and follow-up regimen after diagnosis. CXR may be quickly and simply achieved at the hospital while the patient is in his/her bed, even though chest CT scan is much more sensitive in the first phase of COVID-19. Nevertheless, worries about the possible congenital anomalies of the embryo or fetus because of exposure to radiation are inescapable. The safe cumulative amount of ionizing radiation throughout gestation is 5 rad, and no particular diagnostic test goes above this quantity. The dose of exposure for embryo or fetus from a 2 views CXR to maternal is just 0.00007 rad, also 10 chest CT slices give an exposure of <0.1 rad.<sup>27</sup> For that reason, the pregnant mothers with doubted COVID-19, CXR, and chest CT if required can be carried out securely and safely. Lung ultrasound has also been recommended for rapid identification of pneumonia among prenatal females.<sup>28</sup>

The efficacy of serological examination in detecting the COVID-19 virus is still to be confirmed. The accurateness of the IgM test is doubtful, because of highly false positivity.<sup>29</sup> Otherwise, examination for COVID-19 load in both mother's and fetus/embryo's plasma (viremia) instead of nasopharyngeal swab could assist in determining if the threat of transmission is confidently associated with mother viral load, moreover, aiding in estimation the transmission rate more accurately. Placental investigation can produce priceless information which may be critical and necessary to increase the understanding of COVID-19 pathogenesis and to detect underlying reasons for adverse pregnancy consequences. Histomorphological and ultrastructural alterations reported on the

placenta in mothers with COVID-19 are still limited.<sup>30</sup>

#### *Immune reaction during COVID-19 in pregnant mothers*

A study reported that there was an elevation in the total neutrophils, reduced total lymphocytes in cases of intensive care unit (ICU) in comparison with non-ICU. They also revealed that the elevation of neutrophils and dropping of lymphocytes are also associated with infection severity and death.<sup>31</sup> Parallel results were described by another study which detected those cases with COVID-19 have a tendency to have low lymphocyte amounts, high leukocyte amounts, and neutrophil: lymphocyte ratio, in addition to low amounts of monocytes, eosinophils, and basophils.<sup>9</sup> Lymphocytes are subordinate to white blood cells (WBC) that act an essential function in guarding the immunity against transmittable micro-organisms and other external harmful substances. These cells consist of natural killer (NK) cells, T cells (for cell mediated\_ cytotoxic adaptive), and B cells. Together NK and T cells are vital as a controller and defenders against infectious agents.<sup>32</sup> In COVID-19 patients, reduction of these cells has been accompanied by the ferocity of the infection. A study revealed that the total amount of NK and CD8+ T cells was diminished noticeably in cases with COVID-19 infection. They also observed a rise in the expression of NKG2A (inhibitory receptor of T cell and NK cell).<sup>33</sup> The elevation of NKG2A inhibits NK cells from carrying out their usual role.<sup>30</sup> Furthermore, cases with severe intensity infection display a meaningfully high percentage of CD14+, CD16+ inflammatory monocytes in peripheral blood than cases with mild intensity infection.<sup>34</sup> These cells release inflammatory mediators; the raised levels of cytokines for example tumor necrosis factor (TNF) may cause septic shock and multiorgan dysfunction or even failure that may cause damage in cardiac muscle and cardio-vascular failure detected in some cases with COVID-19. In ordinary gestation immune reaction, the function of NK cells is to guard the mother body against infections by releasing cytokines for example interferon-gamma (IFNg) and interferon alpha (TNF $\alpha$ ), that

function on other immune cells such as Macrophage for fighting the microorganisms. Natural Killer cells have also been revealed of being involved in the gestational period.<sup>35</sup> In usual gestation, the proportions of NK cells in the peripheral blood have a tendency for rise throughout 1st trimester, decline in 2nd trimester, and decline once more in 3rd trimester. Additionally, uterine NK (uNK) cells throughout the 1st trimester come to be gradually less granular and drop in amount, leaving very slight uNK cells at the time of delivery.<sup>36</sup> In humans and even in mice, uNK cells contribute in spiral artery transformation with trophoblast cells. The uNK cells have a restricted capacity to destroy trophoblast cells, and as a substitute, they regulate trophoblast invasion through secreting chemokines interleukin (IL)-8 and IFN-inducible protein (IP)-10. Moreover, uNK cells encourage vascular growth by releasing angiogenesis factors for instance vascular endothelial growing factors (VEGF) and placental growing factors (PIGF). Mutually VEGF and the PIGF are identified to perform a significant function in preserving healthy pregnancy period progress. Nevertheless, blown up stimulation of uterine natural killer (uNK) cells has been accompanying gestation complications for example spontaneous miscarriage and preeclampsia (PE).<sup>37</sup> Throughout the childbearing period, NK cells are managed by NK cells inhibitory receptors which include NKG2A. The activation of NK2GA receptors inhibits NK cells from killing trophoblast cells. Some researchers have connected the amplified NKG2A expression with usual gestational progress.<sup>38</sup> The pregnancy period has been defined as an anti-inflammatory phase from the time when inflammation might cause complications for both mother and fetal.<sup>39</sup> This may perhaps not completely be precise as many researchers conclude else. It has been stated that 1st trimester is a proinflammatory period and 2nd trimester is anti-inflammatory, and 3rd trimester moves back into a proinflammatory period. Throughout 1st trimester during embedding and placenta formation occur, the inflammatory response is aroused for permitting of the blastocyst to effectively

penetrate the uterine endometrium for embedding and invasion of the trophoblast.<sup>40</sup> At this moment a pregnant immune system declines, and she feels some discomforts such as nausea, vomiting, tiredness, and headache, indicative of the proinflammatory phase.<sup>41</sup> Furthermore, in the 2nd trimester, the anti-inflammatory state contributes, and the embryo/fetus grows and develops rapidly. Pregnant health also recovers and vomiting or nausea and other manifestations step by step dissolve. In the 3rd trimester, the fetus development is almost completed, and the delivery process commences. The immunity response is triggered once more for the laboring of the fetus and placenta. For that to take place, the immune cells attack the myometrium of the uterus consequently producing a proinflammatory state which triggers contractions of the uterus.<sup>42-43</sup> The swing in cytokines throughout gestation could produce vulnerability to transmissible diseases. COVID-19 is a pro inflammatory infection and thus may simply attack appropriate circumstances. For example, throughout the 1st and 3rd trimester of gestation are in a proinflammatory period that it is proper circumstances to the virus and are consequently at a greater threat of contracting an infection than the 2nd trimester. Nevertheless, at present no reports about the maternal-fetal spread of COVID-19 may be very improbable as the placenta generates a defensive mechanism against infectious agents. The placenta has remained described to dynamically produce defense against external infective agents through an antimicrobial act in the 1st trimester of gestation.<sup>42</sup> Trophoblastic cells motivate the expression of secretory leukocyte protease inhibitor (SLPI) and INF- $\beta$  that are identified of their inhibitory function for fighting the virus.<sup>44</sup> This process guards the embryo/fetus against viral invasions but does not necessarily guard pregnant women. So, sensitization of the placenta to persuade an immunity reaction generates susceptibility to infections among females during the pregnancy period. The binding site of COVID-19 is described as ACE2 receptor.<sup>45</sup> ACE2 receptor in prenatal period; a powerful function of the renin angiotensin system (RAS) during

childbearing has been recognized.<sup>46</sup> The ACE2 receptor is important for RAS because it is involved in the transformation of angiotensinogen into angiotensin I, then angiotensin I into angiotensin II, and angiotensin II into angiotensin (1–7) (vasodilator agents).<sup>47</sup> The expression of the ACE2 receptor has been described in the placenta.<sup>45</sup> COVID-19 is a probable danger for both mother and fetal health. The expression of ACE2 in the placenta was reported to be high in villous cytotrophoblast, syncytio-trophoblast cells, and in decidua throughout 1st trimester of the childbearing period.<sup>48</sup> Syncytio-trophoblast cells are contributing to mother and fetal gas exchange in addition to nutrient resources. From the time when ACE2 is greatly expressed in this area of the placenta, it is not only escalations the threat of maternal contracting COVID-19, but also probable spread from a pregnant woman to her fetus may take place.<sup>45</sup> The gravid females are much more vulnerable to developing SARS-COV-2 because of their immunity reaction which made them predisposed to develop COVID-19. In both healthy pregnant and pregnant with the current epidemic are manifest with reduced lymphocytes, NKG2A inhibitory receptors, and high ACE2, IL-8, IL-10, and IP-10, therefore the pregnancy period is considered as a threat for developing SARS-COV-2.<sup>49</sup>

### Intervention for Pregnant Mothers with COVID-19

The mild intensity of SARS-COV-2 recommended house isolating, fluid replacement, control of body temperature, use of home pulse oximetry.<sup>50</sup> Continued bedridden should be discouraged since that increases the risk of thrombosis accompanying both childbearing and SARS-COV-2. Home appointment during 24–48 hours to evaluate the medical progress and plan for follow up according to medical progress. Usual prenatal appointments, assessments, and abdominal ultrasounds must be pending till the end of the isolation interval (four weeks once the appearance of manifestations) or after negative PCR after two weeks since the existence of manifestations. While in the moderate and severe intensity of

infection hospitalization and vital signs checking in a high dependency isolated department. The intervention consists of O<sub>2</sub> therapy to maintain the Saturation of O<sub>2</sub> more than 94%, gradually comprising nasal cannula or mask subsequently continuous positive airway pressure (C-PAP) mask. Advanced treatments should be administered in coordination and organization with an anesthesiologist. Further support would need intensive care unit monitoring.<sup>51</sup> Pharmacological intervention according to specialist order may include Lopinavir, Hydroxychloroquine sulfate, Azithromycin tab, or injection. Previously mentioned managements are not contraindicated with gestation but necessitate informed consent of the patient for empathetic use.<sup>52-53</sup> If the patient suffers from an alveolar infiltrate or an elevation in the procalcitonin (suspected bacterial superinfection); administer a powerful antibiotic such as ceftriaxone. Management with prophylactic low-molecular-weight heparin for the period of hospitalization and two weeks afterward (independent on the D-dimer levels). There are safety worries about the use of medications for treating COVID-19 during gestation. Embryo/fetal safety and welfare must be evaluated on a regular basis according to gestational age and mother condition.<sup>11</sup>

### COVID-19 Vaccines

Immunization is one of the most significant accomplishments in public health. Over the past 5 decades, vaccination has led to the eradication and control of illnesses.<sup>54</sup> Immunization supports the immune system identify and fighting bacteria and viruses that caused diseases. Immunizations lower an individual's opportunity of getting COVID-19 and severe COVID-19. As of 24 June 2021, a total of 2,624,733,776 vaccine doses were administered around the world.<sup>1</sup> In a study, a group of people got the vaccine, and another group got a placebo (such as a sugar pill). After the first dose, the immunization seemed to be 50% effective. After the second dose, the immunization was 95% effective against COVID-19. This means, for every 100 individuals who got SARS-COV-2 among the placebo group, only 5 individuals got SARS-COV-2 among the vaccine

group. There were 9 patients with severe SARS-COV-2 among the placebo group and only 1 patient among the vaccine group. There were no serious safety worries.<sup>55</sup>

#### *Types of vaccines*

**Viral vector immunization:** AstraZeneca and Johnson & Johnson inoculations both used adenoviruses as a vector to deliver COVID-19 virus proteins to persuade protective immune reactions.<sup>56</sup> AstraZeneca inoculation uses the chimpanzee adenovirus vector and the Johnson & Johnson inoculation of a recombinant human adenovirus serotype 26 (Ad26) transporter. The platforms of both inoculations have been consumed in vaccines to fight the other viruses.<sup>57</sup> Sputnik V contains Ad26-S & Ad5-S virus particles, that are replication-deficient adenovirus category 26 and 5 virus units, separately expressing a complete length of the spike protein. The immunization is offered in 2 forms: frozen and lyophilized [58]. The lyophilized form of Sputnik just needs freezing (two to eight °C) and therefore it has a probability to serve faraway areas that may have a deficiency in refrigerators for transport and storing of the frozen form of inoculation.<sup>59</sup> The vaccine does not contain live human adenoviruses but contains human adenovirus vectors that cannot multiply in the body and are completely safe. The vaccine induces a strong response forming antigen-specific cells of both populations of T-lymphocytes: T-helper (CD4+) and T-killer (CD8+). It has elicited IgG response in 100% immunized participants in mean titers. Significantly higher than titers of COVID-19 convalescents. The vector is a virus that extractions a gene accountable for replication and it is usually used for the transmission of genetic particles from other viruses which are being immunized to fight into a cell. The gene coding S protein of COVID-19 spikes is implanted into every vector. No adverse drug event was observed in vaccinated, and SARS-CoV-2 challenged animals. Yet, no scientific or clinical proof of any side effects associated with the vaccine Sputnik V.<sup>58</sup>

**Messenger RNS (mRNA) inoculations:** Pfizer & Moderna, Moderna inoculations is a new inoculation technology constructed from mRNA.

Both inoculations encode COVID-19 genetic data in the form of RNA COVID-19 antigens to have functioned on the surface of the cell.<sup>60</sup> The immune cells in the host recognize these antigens and mount the immune reaction. Common misunderstandings comprise the mRNA could change the DNA of an immunized person and the mRNA might be transmitted to the embryo/fetus, with possibly dangerous consequences. Nevertheless, these vaccines do not go into the nucleus of the cells and thus it cannot change the DNA of the cell.<sup>61</sup> Some unpleasant reactions were more frequently stated after the 2nd dose than after the 1st dose and were commonly more frequent and severe in people aged 18–55 years than in those aged more than 55 years. The most common manifestation was included; tiredness, headache, muscle ache, chills, and pain at the injection site, and anaphylaxis (32% of cases experience a previous episode of anaphylaxis; previous experiences involved immunization, contrast media, sulfa medicines, penicillin prochloropyrazine, rubber, walnut, undetermined tree nuts, and jellyfish bites. anaphylaxis patients prescribed epinephrine as part of urgent intervention.<sup>62</sup> The Center for Disease Control (CDC) and Advisory Committee on Immunization Practices (ACIP) allowed approval for Moderna COVID-19 immunization for individuals 18 years and older.<sup>63</sup>

Fever because of immunization or even chills in some cases were described in more than a quarter of pregnant mothers after the 2nd dose and half of the nonpregnant females. No deaths because of anaphylaxis after immunization were reported.<sup>64</sup>

**Protein vaccines:** the Novavax vaccine is emerging as a recombinant inoculation adjuvant with saponin-based Matrix-M1™ adjuvant in order to stoppage the infection result from COVID-19. COVID-19 recombinant (r) spike (S) protein nanoparticle inoculation (COVID-19 rS) is manufactured from the full length, wild form COVID-19S glycoprotein (GP) constructed on Gen Bank gene order MN908947, nucleotides 21563-25384, from COVID-19 genome. The S protein is a category 1 trimeric glycoprotein of 1,273 amino acids which is formed as an inactive S0 ancestor. The S gene was codon

optimized for expression in *Spodoptera frugiperda* (Sf9) creature cells. The COVID-19 rS nanoparticle inoculation is proposed for injecting with Matrix-M1 adjuvant that is a saponin based adjuvant that has earlier been revealed to boost the immunogenicity of other nanoparticle inoculations in non-clinical and clinical studies.<sup>65</sup>

Inactivated virus: Sinopharm includes inactivated COVID-19 that produce an immunological reaction to the spike and nucleocapsid protein. As at this time available antibody tests for COVID-19 measure the quantity of IgM and or IgG to the spike or the nucleocapsid protein, a positive test might confirm either previous infection or previous vaccination. Checking the presence of antibodies is not currently suggested to evaluate the immune system to COVID-19 after Sinopharm vaccination.<sup>66</sup>

## A vaccine of COVID-19 during Pregnancy

COVID-19 vaccination shows an important decrease in placental and embryo/fetal viral problem. The concerns related to trans-placental vaccine transmission have not been labeled. Even though revealed facts of the protocols are accessible, the exact preparations of the cationic nanoparticles used for mRNA gathering of SARS-COV-2 inoculations are still at top of propriety list to the built-up pharmacological concerns and introductory welfare and safety records about the SARS-COV-2 mRNA inoculation throughout pregnancy reference during labor or post-delivery procreative toxicology research in rodents, that proven no existence of safety concerns. Usually, vaccines proposed for gravid women or lactating mothers depend on different kinds of studies' designs.<sup>67-68</sup>

The CDC, American College of Obstetricians and Gynecologists (ACOG), and Society for Maternal Fetal Medicine (SMFM) have each handout guide supporting the suggestion of SARS-COV-2 inoculations for gravid mothers. An important worry must be considered that many females of procreative age who contribute to the huge experiments may become gravid during the short period after vaccination.<sup>69</sup>

Antenatal women represent a significant slice of community, in addition to growth with development. Accessible management choices for SARS-COV-2 infection in both mother and embryo/fetal, to decrease threat of acquired communicable disease from hospital and progress badly of SARS-COV-2 infection. ACOG lately suggested that authorized COVID-19 inoculations can be presented to pregnant mothers. Both Food and Drug Administration (FDA) & the ACIP had determined to produce a reasonable evidence base for inoculation before administering to gravid mothers.<sup>70-71</sup>

### *More common brands of vaccines used around the world*

#### *-AstraZeneca and Johnson & Johnson*

Recurrently articulated fears and apprehensions about administering adenovirus vectors in gravid mothers is a theoretical possibility for adenovirus vector causing an infection of embryo/fetus. This worry is groundless, as both adenovirus vectors are weakened viruses which means the replication is incapable. In another word, vectors are infected human cells after immunization, but reproduction cannot occur in those cells, thus transporting COVID-19 proteins to pregnant mothers without transfer of viral vector to an embryo/fetus. Studies in animal models using adenovirus vectors has revealed no harmful effect in gestation, but experimental trials of these inoculations in humans so far have excluded antenatal mothers.<sup>72</sup>

#### *-Pfizer and Moderna*

mRNA is degenerated hastily inside the cell, making the spread of COVID-19 to the embryo/fetus impossible. There are no mRNA inoculations that were purposefully used in antenatal mothers in experiment settings, animal research on Moderna inoculation stated no effects on embryo/fetal growth in rodents that administered the inoculation before fertilization and during gestation.<sup>73-74</sup> Many pregnant mothers got the Pfizer and Moderna immunization; the gestational age mean at 1st dose was 23.2 weeks, with pregnant mothers (13%) getting their 1st vaccine dose in 1st trimester, (46%) in 2nd trimester, and (40%) in 3rd trimester. After the 2nd dose of vaccine,



there was no significant variance between groups, in gravid, breastfeeding mothers, and not pregnant groups.<sup>64</sup>

#### *-Novavax*

Antenatal mothers were excluded from the experimental trials of Novavax inoculation, this vaccine has collected safety data in preceding trials for respiratory syncytial virus (RSV) inoculation in antenatal mothers using an alike inoculation platform.<sup>65, 75</sup>

#### *-Sputnik V*

Accessible data on administration in antenatal mothers are inadequate for evaluating inoculation efficacy or inoculation-accompanied threats during the gestation period. Nevertheless, this vaccine is manufactured with an adjuvant which is usually used in many other inoculations, and for that, an excellent safety outline has been reported, including in antenatal mothers.<sup>58</sup>

#### *-Sinopharm*

The WHO suggested administering Sinopharm in antenatal mothers when the advantage of immunization outweighs potential risks. WHO does not recommend testing on pregnant mothers previous to vaccination.<sup>76</sup>

## **Brest Feeding and COVID-19 Vaccination**

Several reports have described the discovering of RNA viral in the milk of lactating mothers with COVID-19; though, there is no proof to suggest the consumption of milk from infected mothers rises the threat of spread to their neonates.<sup>77</sup> Milk from mothers is a passive basis of antibodies and many protecting elements. As stated by the present evidence, most global scientific organizations<sup>78</sup> permit breastfeeding if the mother and newborn status are favorable, continuously under interaction and droplet precautions (wear a mask, hand washing pre and post-contact, washing breast and areas that might be touched). Milk pulling out might be another alternative under firm sanitation measures, using a personal milk extractor. This means must be washed after every use with sufficient antiseptics. Breast milk must be

administered to the neonate by a not infected member in the family or healthcare personnel. There is no suggestion to discontinue breastfeeding in the case of postpartum mothers with SARS-COV-19 and established breastfeeding, but interaction and droplet precautions should be suggested.<sup>11</sup>

WHO does not suggest postponing gestation or terminating gestation as a result of vaccination. There are no data on possible advantages or threats of inoculation to breastfed infants. Because this is not a live virus inoculation, it is improbable to pose a threat to breastfeeding neonates. Vaccine electiveness is expected to be similar in breastfeeding mothers as in other adults. WHO does not recommend stopping breastfeeding after immunization.<sup>79</sup>

## **Discussion**

Many reports of newborn transmission and adversative results for neonates with COVID-19 have been described; nevertheless, approximately many of these data are confused by vagueness surrounding investigations and diagnostics of these newborns and other independent newborn diseases.<sup>80</sup> CDC received documents from national SARS-COV-2 case surveillance or the National Notifiable Diseases Surveillance System of MORE than one million females aged 15 to 44 years with investigation outcome assured the infection of COVID-19. Data on pregnant mothers' status were presented for (35.5%) females with laboratory-confirmed COVID-19 (88.7%) of whom were symptomatic. Among symptomatic females (5.7%) were stated to be pregnant. Pregnant mothers were more commonly Hispanic (29.7%) and less commonly non-Hispanic White (23.5%) in comparison with not pregnant females (22.6% Hispanic and 31.7% White). Among all females, cough, headache, joint pain, and electing in body temperature was the most commonly described as infection manifestations and it might be accompanied by an augmented threat of inborn malformations, such as spina bifida and spontaneous abortion throughout organic formation in 1<sup>st</sup> trimester of pregnancy period; most manifestations were stated less commonly by antenatal females than by not pregnant females, pregnant mothers were

considerably more probable than nonpregnant females to be entered to the ICU and established invasive ventilation. To decrease the danger for severe intensity disease and death because of SARS-COV-2, antenatal mothers should be advised about the significance of looking for rapid therapeutic management if they have manifestations to avoid health status deterioration because of the COVID-19 epidemic, which must be toughly stressed for antenatal mothers and their family members throughout every therapeutic encounter, involving pregnancy period care visits. A 1.5 of 1,000 patients were described among pregnant mothers with clinical manifestations, and 1.2 of 1,000 patients were described among nonpregnant females, reflecting more than half of them amplified threat for death associated with gestational period. Regardless of pregnant mothers' status, admissions to ICU, receiving of invasive ventilation, and death happened more frequently among females aged 35 to 44 years than among those aged 15 to 24 years. While non-Hispanic Black or African American females included 14.1% of females involved in the study, they revealed (36.6%) total deaths, including 9 of (26.5%) deaths among pregnant mothers and (37.4%) deaths among not antenatal females. High risk for admitting to the ICU among prenatal mothers was detected for entire strata but was especially remarkable among Asian females and non-Hispanic Native Hawaiian or Pacific Islander females. The danger for administering invasive ventilation among prenatal mothers aged 15 to 24 years was three times that of not gravid females, and among antenatal mothers aged 35 to 44 years was 3.6 times that of not antenatal females.<sup>81</sup> Furthermore, among Hispanic females, gestation was accompanied by 2.4 times the threat of death. Collectively, the contemporary offered data submit an estimated 2%-3% threat of vertical spread with a minimal rate of a newborn being infected with the virus.<sup>82</sup> WHO described longitudinal cohort research of 147 antenatal mothers with SARS-COV-2, just 8% and 1% were severe with the critical condition.<sup>83</sup> This recommends that most antenatal mothers with SARS-COV-2 with milder manifestations when compared to the general population.

Additional research described antenatal mothers with SARS-COV-2 pneumonia had a milder infection and better recovery.<sup>84</sup>

In a study that investigated more than two thousand SARS-COV-2 confirmed pregnant mothers with 746 childbirths, there were 3.4% females with the maternal serious condition need urgent intervention of mechanical ventilation, 0.9% mothers' death, and 21.8% premature/preterm labor, and less than 1% death during delivery.<sup>85</sup> In an additional study on 324 pregnant women with SARS-COV-2, it was described that approximately 14% of mothers with pneumonia need admission to critical care unit, with 9 of maternal mortality, 4 patients of miscarriage, 4 patients of missed abortion, and three patients of newborn mortality.<sup>86</sup>

Parental vaccination can decrease the danger of the maternal, embryo/fetus, and newborn by passive vaccination of the newborn by the trans-placental passage of protecting antibody into the blood circulation of the embryo/fetal/newborn, thus likelihood of rising the immunity of pregnant mothers and embryo/fetus. It is the zone of genuine worry and significance. Suggestions from the continuing research may reinforce inoculation assurance in antenatal mothers, and to pay extra exertion to attain protection among the whole community. A prove of the safety of inoculation products exactly during the gestation period is so significant. Its safety for couples' life, both maternal and newborn. Furthermore, reaction to immunization may be different from that of the overall community because of different physical and biological also vulnerabilities of gestation. These labors will aid in the reduction of the spread. There is an extensive claim to involve antenatal mothers in SARS-COV-2 inoculation study efforts to guard them and their children from COVID-19. Presently with inadequate presented data, obstetricians must consider the advantages and hazards of the SARS-COV-2 inoculation throughout the gestational period.

COVID-19 infection through the 1<sup>st</sup> trimester of the gestational period does not seem to predispose for early conception loss; its increasing occurrence did not vary between

mothers with miscarriage and mothers with continuing gestation. SARS-COV-2 looks to have a satisfactory maternal sequence at the commencement of the gestational period, constant with that has been detected throughout the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters.<sup>87</sup>

A total of 29 research studies described the histopathological outcomes on 6 cases 2<sup>nd</sup> trimester and 322 cases 3<sup>rd</sup>-trimester placenta from antenatal mothers positive to COVID-19 disease of many levels of intensity. They revealed negative pathognomonic histological forms in the mother placenta after COVID-19 mother infection, as demonstrated in a recent analysis by Sharps et al., 2020.<sup>88</sup>

A higher occurrence of maternal vascular mal-perfusion (MVM) of the placental bed was described in the placenta of pregnant mothers infected with COVID-19 by many studies.<sup>89-95</sup> It is a documented pattern of placental damage because of abnormal uterine perfusion, resulting in numberless pathological alterations. It is accompanied by important clinical sequelae, for example, preterm/premature labor, intrauterine progress restriction, and embryo/fetal death. Maternal low oxygenation level related to COVID-19 pulmonary illness could initiate uterine hypo-perfusion and then hypoxic ischemic damage to the placental tissues. A study described that (93%) 3<sup>rd</sup> trimester placenta discovered at least a sign of MVM, with infarcts and elevation fibrin deposition being most recurrently detected when compared with healthy controls where MVM was detected just in 30% of patients.<sup>96, 102</sup>

Variable amounts of immunoglobulin antibodies were observed in the milk of the majority lactating mothers samples gathered from mothers with COVID-19; nevertheless, the protecting ability of these antibodies against disease for neonates and infants needs further examination and study.<sup>64, 97</sup>

In preceding research about MERS, 3 of 11 (27.27%) pregnant mothers with MERS were labored before the term.<sup>98-98</sup> In preceding research on mothers with SARS-COV-2, they gave birth within two weeks after the manifestations appeared, the embryo/fetal growing is not likely to be diseased in this limited time and there were no offered data

about placenta pathology to the present day.<sup>99-101</sup>

Previous pandemics and inoculation safety among antenatal mothers' disproportionate proportions of mothers' morbidity, harmful perinatal consequences, and death result from the virus have been labeled even in previous pandemics. All facilities and services administering COVID-19 vaccines must have the required supplies and qualified medical personnel accessible and available in order to treat anaphylaxis.<sup>74</sup>

## Conclusion

Pregnant mothers do not seem to be further vulnerable to infection or serious deteriorating of health condition, but the current data are inadequate yet. Actually, in any COVID-19 patient, complications throughout the pregnancy period must be recognized and treated as early as possible. The wide range of medical expression, the high rate of asymptomatic forms, and the poor correctness of nasopharyngeal swab testing and its restricted availability have been the chief barriers to the acquisition of an actual understanding of the occurrence of the disease and its effect on pregnant mothers. The development of serologic examinations for the revealing of SARS-COV-2 immunoglobulin G (IgG) and immunoglobulin M (IgM) might be suitable to identify infected pregnant mothers who were infected early period during pregnancy.

The important function of the immune system in protecting the embryo/fetuses and newborns against COVID-19 disease has been suggested. Decidua basalis, being the maternal constituent of the maternofetal interface, comprises varied immune cells owned by the immunity containing NK cells, decidual macrophages, and CD4 T cells. Furthermore, the syncytiotrophoblast cells, an outer sheet of chorionic villi that are directly in contact with mother blood, do not have an intercellular gap junction, that prevents transporting of the pathogen from the mother circulation. Somatic difficulties may be involving trophoblastic basement sheaths generating further somatic obstruction against infectious agents. Mutually,

the immunity and physical barrier, in addition to the contact between decidual cells of immunity and the attacking of embryo extra villous trophoblastic can act as a function in placenta defensive mechanisms against COVID-19 invasion.

Constant safety observing of COVID-19 vaccines. When considered in the perspective of morbidity and mortality because of COVID-19, the advantage of the vaccine far outweighs the danger of anaphylaxis that is curable and can be treated simply.

COVID-19 has been linked with high mortality rates and more serious consequences throughout the gestational period. In antenatal mothers who develop SARS-COV-2 manifestation such as pulmonary inflammation, data had revealed a comparable rate of admitting to ICU of the not gravid females, high incidence of premature/before term and cesarean delivery.

It is still indistinguishable if this novel inoculation style will motivate immunity in the context of the prenatal period and if antibodies are transmitted competently to newborns by umbilical cord and breastfeeding. At this point, inoculation encouraged immunity was described in immunized antenatal mothers, breastfeeding, and not gravid controls compared with females with COVID-19 throughout the gestational period.

The COVID-19 vaccine must be available regardless of an individual's history of symptomatic or asymptomatic COVID-19 illness. Based on existing data, symptomatic re-infection is unusual within six months afterward an initial natural disease, and in a situation of restricted vaccine source, individuals with acute PCR definite SARS-COV-2 should not be immunized till they become cured and restored their health and the conditions for interruption of seclusion have been seen. The minimum period between infection and immunization is not known up till now. COVID-19 vaccine which efficiently prevents symptomatic infection is anticipated to also prevent ICU admission, need invasive ventilation, hospitalizations, and also deaths.

The inoculation should exhibit the possibility to decrease morbidity among the antenatal

mothers and their embryo/fetus. Furthermore, the deficiency of proof for the possible harmful effect of the inoculation on gestation or probable hurt to the embryo or fetus or pregnant must be searched.

### Author Contributions

ZAA planned, put the frame of the study, and collecting references. AMJS critically revised the manuscript. MAL revised with editing. AFO write the draft and collecting references.

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