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Preeclampsia In The Post-COVID-19 Era: A Narrative Review

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Abstract
Preeclampsia is still a significant contributor to maternal & perinatal death & morbidity worldwide, particularly in the post-COVID-19 era. This study investigates new trends in preeclampsia among pregnant females attending the Obstetrics & Gynecology Department at Qena University Hospital. Preeclampsia, distinguished by new-onset hypertension following twenty weeks of pregnancy, often accompanied by proteinuria, represents a spectrum of hypertensive disorders in gestation, ranging from gestational hypertension to severe manifestations like eclampsia and HELLP syndrome. The research aims to assess the prevalence, risk factors, & results of preeclampsia in the context of post-COVID-19 influences, such as changes in healthcare access, immune responses, and socioeconomic factors. A retrospective analysis was conducted on patient records from 2020 to 2023, focusing on demographic characteristics, clinical presentations, and maternal-fetal outcomes. Preliminary findings indicate an increase in preeclampsia cases, potentially linked to post-COVID-19 inflammatory responses and delayed prenatal care due to pandemic-related disruptions. Key risk factors identified comprise advanced maternal obesity, age, and a history of hypertension, with a notable rise in cases among women with prior COVID-19 infection. The research highlights the requirement for improved screening protocols and timely interventions to mitigate adverse outcomes. These results underscore the importance of adapting obstetric care to address emerging challenges in the post-COVID-19 landscape, emphasizing early detection and management of preeclampsia to improve maternal and perinatal health outcomes at Qena University Hospital.
Keywords: *Preeclampsia, post-COVID-19, Risk factors, Pregnancy outcomes*

1. INTRODUCTION

Hypertensive disorders throughout pregnancy are a primary contributor to maternal & neonatal death globally. Preeclampsia, whether with or without severe symptoms, is a gestation disease distinguished by the onset of hypertension, typically accompanied by proteinuria, happening predominantly following twenty weeks of pregnancy & commonly near term. This condition encompasses a range of hypertensive illnesses in gestation, start with gestational hypertension & advancing to severe characteristics, finally culminating in more severe symptoms, including eclampsia and HELLP syndrome (Erez et al., 2022).
Preeclampsia often manifests in late-stage gestations. The evolution of pregnancy-induced hypertension (PIH) is currently recognized to commence with gestational hypertension, characterized by new-onset hypertension, subsequently advancing to more severe types of hypertensions defined by specific laboratory & clinical criteria to be discussed upon later. It is essential to recognize that the comprehension of the pathophysiology of pregnancy-induced hypertension has advanced, & its diagnostic criteria have transformed, leading to a shift from the classical triad of swelling, proteinuria, & hypertension to hypertension & organ dysfunction (i.e., hepatic, renal, neurologic uteroplacental, or hematological). However, the latest definitions approved by authoritative organizations like the American College of Obstetrics & Gynecology (ACOG) have predominantly dependent on consensus & expert opinion rather than 1ry investigation(Reddy et al., 2021).

Preeclampsia pathophysiology

Preeclampsia may be classified into two 1ry subtypes: late-onset (or maternal) and early-onset (or placental) preeclampsia. Both exhibit distinct phenotypes and causes (Nirupama et al., 2021). It is believed that the progression of preeclampsia is caused by the defective placenta in cases of the early-onset type. Analysis of the preeclamptic placenta demonstrates several arterial sclerosis & placental infarcts. This is associated with placental hypoperfusion resulting from changed trophoblast invasion,

leading to placental ischemia. (Goswami et al., 2006)

Maternal preeclampsia results from the interaction among a healthy placenta & maternal variable that finally led to microvascular injury. This may be attributable to endothelial dysfunction of the mother. Maternal preeclampsia, occurring later in pregnancy, may be treated expectantly until thirty-seven weeks of pregnancy. Maternal preeclampsia happens in later stages of gestation, resulting in minimal or no alteration in arterial conversion, hence preserving placental perfusion (Dionisio & Favero, 2024).

Pre-eclampsia exhibits a complex pathophysiology, with abnormal placentation as the 1ry etiological factor. Cytotrophoblast cells exhibit defective invasion of the spiral arteries in pre-eclampsia. Current researches illustrate that cytotrophoblast invasion of the uterus represents a distinct distinguishing pathway in which fetal cells acquire specific attributes of the maternal endothelium they often replace. In pre-eclampsia, this mechanism of differentiation is interrupted. (Roberts et al., 2009) The anomalies might be associated with the nitric oxide pathway, which significantly controls vascular tone. Furthermore, the suppression of maternal NO production prevents the implantation of embryos. Elevated resistance of uterine arteria enhances sensitivity to vasoconstriction, resulting in oxidative stress & chronic placental ischemia. This chronic placental ischemia finding in complications of fetus like intrauterine death & intrauterine growth retardation. Concurrently, oxidative stress triggers the production of chemicals into the maternal circulation, involving free radicals, serum soluble vascular endothelial growth factor 1, oxidized lipids, & cytokines. These anomalies contribute to endothelial dysfunction characterized by thrombophilia, hypertension, & vascular hyperpermeability, compensating for the diminished flow in uterine arteries raising from peripheral vasoconstriction. (Uzan et al., 2011)

Early uterine artery Doppler abnormalities, such as increased PI/RI and notching, have been identified as predictors of preeclampsia, reflecting impaired uteroplacental circulation as a central mechanism in its pathophysiology. (Khodary et al., 2024)

Clinical Presentation

Preeclampsia may present itself clinically in a variety of ways, ranging from asymptomatic images to issues that are lethal for both the fetus and the mother of the patient. When the condition is severe, there is a possibility that the hepatic, neurological, renal, or vascular systems will be affected (Sperling et al., 2015).

The 1ry symptoms and signs related to this pathology divided by systems and organs: (Chappell et al., 2021)

Neurological: visual disturbances, seizures, clonus, hyperreflexia, or headache.

Hepatic: pain in the right upper quadrant or in the epigastrium.

Hematologic: petechiae or dark urine color.

Cardiorespiratory: dyspnea, tachypnea, chest confusion or pain.

Uterus-placental & fetal: transvaginal hemorrhage, reduced movements of fetus, uterus with elevated tone.

Trends of preeclampsia/eclampsia & maternal & neonatal outcomes

Following the twentieth week of pregnancy, a female who was previously considered to have normal blood pressure may develop preeclampsia, which is a syndrome that is defined through the new onset of hypertension & proteinuria. A woman who is pregnant and has gestational hypertension or preeclampsia may experience eclampsia, which is characterized by the onset of grand mal seizures. It is estimated that between two percent and ten percent of all pregnancies are affected with preeclampsia, which is the precursor to eclampsia. The prevalence of preeclampsia varies significantly from one country to the another. In Ethiopia, preeclampsia is one of the main reasons of death of mother, as is the case in the majority of other developing countries as well at the same time.(Sibai, 2005) , (Ahmed et al., 2025)

With regard to WHO, the presence of preeclampsia is assessed to be 7 times more prevalent in underdeveloped nations (2.8 percent of live births) than it is in affluent countries (0.4%). Eclampsia is related to a higher probability of maternal mortality in both industrialized countries (half to one & a half percent) & poor countries (as high as fifteen percent) (UNICEF, 2009)

The condition recognized as preeclampsia is a condition that happens throughout gestation & is categorized by elevated blood pressure, peripheral edema, & proteinuria. In addition to having a systolic blood pressure of at least 140 millimeters of mercury or a diastolic blood pressure not more than ninety millimeters of mercury on two separate occasions following twenty weeks of pregnancy, it requires the presence of proteinuria that exceeds 300 milligrams in twenty-four hours. Two percent to eight percent of pregnancies are affected by this condition, making it one of the primary reasons of maternal & newborn death & morbidity (Rao et al., 2022).

Preeclampsia is a significant obstetric issue for pregnancies in Upper Egypt, as noted through (Abbas et al. 2016) in Assiut, where it was the main reason of maternal death, representing 27.7 percent of all avoidable reasons.(Abbas et al., 2016) , (Ameen et al., 2023)

Pregnant females have infection with SARS-CoV-2 exhibited a significantly elevated possibility of developing preeclampsia compared to those uninfected (Conde-Agudelo & Romero, 2022). In regards with the guidelines published by the National Institute for Health & Care Excellence (NICE) in 2019, preeclampsia was categorized into the following risk factors: (1) females are at an elevated possibility of developing preeclampsia if they have a history of hypertensive disorders throughout an earlier pregnancy or a maternal illness like autoimmune diseases, diabetes, chronic kidney disease, or chronic hypertension. If a woman is nulliparous, exceeds the age of forty, has a body mass index (BMI) of at least thirty-five kilograms per square meter, has a family history of preeclampsia, has experienced a multifetal gestation, or has had a gestation interval of more than ten years, then she is considered to be at intermediate risk (Fox et al., 2019).

The Risk Factors for Pre-eclampsia

Pregnancy-Related Risk Factors

Previous Pregnancy with Pre-eclampsia

There is a lack of clarity regarding the reasons for the association between an earlier gestation with pre-eclampsia & the occurrence of a recurrence of pre-eclampsia in a later gestation. A number of causes, including genetics, the existence of other risk factors like obesity, or the fact that hypertensive gestation is a predictor of cardiovascular illness later in life, could be responsible for this (Bramham et al., 2011).

Multifetal Gestation

The updated two-stage model of pre-eclampsia causes recognizes that multifetal pregnancy needs a bigger placenta, which is connected to the "intrinsic cause" of the condition (Staff, 2019).

History of Small for Gestational Age (GA) or Adverse Outcome

Babies that are born with a weight that is lower than the 10th percentile for their age of gestation are classed as small for GA, or SGA for brief. There is a possibility that this is the result of growth restriction (IUGR) or other reasons. Sometimes, the terms IUGR and SGA are utilized interchangeably; nevertheless, there is a difference in the stage of that A fetus that is growth-restricted is referred to as IUGR, while a neonate with a birth weight that falls short than expected is referred to as SGA (Osuchukwu & Reed, 2024).

Age Extremes: Advanced Patient Age & Adolescent Pregnancy

Adverse pregnancy results, which include perinatal, neonatal, and maternal death, are crucial markers of health on a global, national, and regional scale. All pregnancies pose risks. On the other hand, females who are younger than nineteen years old, also known as adolescents, and those who are older than thirty-five years old, also known as advanced maternal age (AMA), have been related to a greater probability of adverse pregnancy results. These results include stillbirth, maternal mortality, neonatal, perinatal, baby, and under-five mortality. (Nove et al., 2014).

Parity

Nulliparity has historically been identified as a risk factor, potentially triple the likelihood of preeclampsia. Certain investigations have determined that nulliparous females exhibit a greater probability of preeclampsia relative to other groups (Mayrink et al., 2019).

Cytomegalovirus

The first stage in the development of this condition is impaired implantation, which is followed by

shallow trophoblastic invasion. (Molvarec et al., 2011) It is interesting to note that a number of studies have demonstrated that an infection with cytomegalovirus (CMV) might lead to improper placental function and implantation. (Leghmar et al., 2015) According to the findings of another research, it is plausible that preeclampsia is caused by a CMV infection; this is because of a rise in angiogenic factors. Prior investigations that investigated the correlation between anti-CMV antibodies in gestation & the progression of preeclampsia came to a number of contradictory conclusions. (Alvarado-Esquivel et al., 2017) For example, in the investigation conducted in Canada, the prevalence of CMV antibody seropositivity & anti-CMV IgG titers have been shown to be greater among females with preeclampsia compared to females who were considered to be normal pregnant controls. On the other hand, a different piece of research hasn't found any correlation between the presence of serological evidence of CMV infection and preeclampsia. The seroprevalence of cytomegalovirus antibody is prevalent in advancing countries, which is noticeable. (Shaiegan et al., 2015)

It is common knowledge that the immune response of the host to a CMV infection is driven mostly via cell-mediated immunity (CMI), & the presence of a cell-mediated immunity would reduce the likelihood of a cytomegalovirus infection becoming reactivated. It is not yet apparent if the reactivation or development of infection with CMV in preeclampsia is caused by an immunological deficit to CMV, a 1ry or 2ry infection with this organism, or a combination of these factors. The QuantiFERON-CMV (QF-CMV) test is an in vitro approach that can be used to detect cases who have CD8+ T-cells that are specific to CMV. In this particular assay, the specific interferon-gamma (IFN-γ) is evaluated. This interferon-gamma is largely produced by CD8+ T-cells that have been activated by CMV antigens. (Lochmanova et al., 2010)

Autoimmune Disease

Researchers believe that around five percent of the population in the United States is affected by autoimmune illnesses. There is a lack of understanding regarding the mechanisms that result in the progression of autoimmune diseases (Barak, 2006). An intriguing possibility that preeclampsia is an autoimmune illness that is triggered by gestation is brought to light by the research that has been discussed here. There is a lack of knowledge on the environmental & genetic factors that contribute to the progress of AT1-AA in preeclampsia. The adaptive immunological response to foreign antigens and/or the inflammatory response that occurs in combination with placental ischemia are possibly two of the most important factors that contribute to the production of AT1-AA. There is a possibility that each of these characteristics is responsible for the well-known fact that preeclampsia is more common in females who are carrying their first child. Additionally, preexisting illnesses that are correlated to immunological and/or inflammatory abnormalities are responsible for the increased risk of preeclampsia. Some examples of these conditions include diabetes mellitus and obesity that is dependent on insulin. (Xia & Kellems, 2009)

Assessment of Antenatal Health Care

Antenatal care, often known as ANC, is a comprehensive approach that encompasses monitoring for any complications that may arise in the fetus and the mother, as well as providing preventive treatments & services, advise and education programs, & help to women who are of childbearing age. ANC was totally neglected until lately. In a prospective cohort study at Qena University Hospital, Hany et al. (2018) reported that in high-risk pregnancies, the number of antenatal visits was strongly linked to complications in late pregnancy and after delivery. There are around 529,000 females who lose their lives annually as a result of risk factors related to pregnancy, delivery, & abortion, as stated by WHO. ANC services have grown more easily accessible over the course of the past few decades. The percentage of females in reproductive age who had at least one ANC session with a skilled practitioner was roughly eighty-five percent worldwide and approximately seventy-seven percent in developing countries during the years of 2010 and 2015. (Mgawadere, 2009), (Elsaman et al., 2023)

Association between hypertensive disorders & COVID- 19 through pregnancy

recognized from feces, secretions, respiratory droplets, & fomites & is pathogenic to the men. When an infected individual sneezes or coughs, respiratory droplets come into contact with the mucous

membranes of respiratory tract. This is the method by which this virus is transmitted from person to person through close contact. Fecal-oral transmission has also been identified as a possible mode of transmission. The incubation period for a virus typically lasts for four days, but it may last for as long as fourteen days (Zhu et al., 2020).

As COVID-19 spreads so quickly around the world, pregnant females and their unborn kids are at a significantly increased possibility of acquiring an infection throughout outbreaks of infectious diseases. Anatomical and physiological alterations, like a rise in the transverse diameter of thoracic cage & a raised level of the diaphragm, are additional factors that contribute to the elevated susceptibility of pregnant females to infection (Hui & Zumla, 2019).

It is possible for severe infection with SARS-COV-2 led to in clinical signs that are comparable to those of preeclampsia. These signs include hypertension, proteinuria, and elevated hepatic enzymes. Hypercoagulability, thrombocytopenia, endothelial damage, renal failure, arteriopathy, and the possibility of SARS-COV-2 being a pro-inflammatory condition that leads to reduced maternal vascular perfusion are all factors that should be considered. Therefore, a state similar to preeclampsia might occur, which will accelerate the progression of maternal morbidity & death & will make perinatal results worse (Liu et al., 2020).

In spite of the fact that asymptomatic cases are still at risk for developing preeclampsia, multiple investigations have demonstrated that preeclampsia-like syndrome begins to develop in cases who have severe infection with SARS-COV-2 & that it resolves following the enhancements of pneumonia (Mendoza et al., 2020).

Finally, an investigation about the treatment of pregnancies with COVID-19 in cases with hypertensive condition and their gestations, as well as those with preeclampsia-like clinical characteristics admitted to hospitals, with regard to the severity of cases, utilizing oxygen flow to maintain saturation levels above ninety-five percent, intravenous fluids to preserve antibiotics, hydration, steroids, prophylactic low-dose heparin following venous thromboembolism evaluation, antiviral drugs, & antihypertensive drugs Additionally, information regarding the status of the pregnancy, the manner of delivery, as well as the results for both the mother and the fetus, should be involved in surveillance systems for COVID-19 subjects who are pregnant (Wang et al., 2020).

The link between COVID-19 & preeclampsia

Pre-eclampsia, which affects between three and five percent of all pregnancies, is responsible for at least forty-two thousand maternal deaths annually. Following twenty weeks of gestation, the presence of proteinuria and hypertension, either at the beginning or the advancement of the condition, is indicative of pre-eclampsia. This condition can result in eclampsia, which is characterized by seizures and has the potential to be life-threatening. A complete understanding of the pathogenesis of pre-eclampsia hasnt yet been achieved. A number of theories have been proposed, some of which include placental ischemia & oxidative stress, excessive vascular inflammation, & endothelial dysfunction (Xing et al., 2023). These ideas, on the other hand, have not been able to provide a comprehensive explanation for the pathogenesis of pre-eclampsia.

There is an association between the presence of periodontal illness or other diseases throughout pregnancy and an increased probability of having pre-eclampsia, according to research that has been conducted. The presence of infections can result in decreased blood supply to the mother, ischemia of the placenta, and hypoxia. When this occurs, pre-eclampsia can be brought on by elevated concentrations of inflammatory markers as well as endothelial dysfunction syndrome. COVID-19. The worldwide pandemic in current years has been triggered through the viral respiratory illness transmitted by Severe Acute Respiratory Syndrome Corona Virus 2, recognized as SARS-CoV- (El-Sadr et al., 2023). It is still possible for pregnant females to become infected with SARS-CoV-2 because of the fact that vaccine effectiveness decreases over time, immune escape occurs as a result of viral variations, and immune protection is diminished (Feikin et al., 2022). Previous investigations have demonstrated that there is a causal association between the infection caused by COVID-19 & a higher probability of hypertensive illnesses occurring throughout pregnancy (Tan et al., 2021).

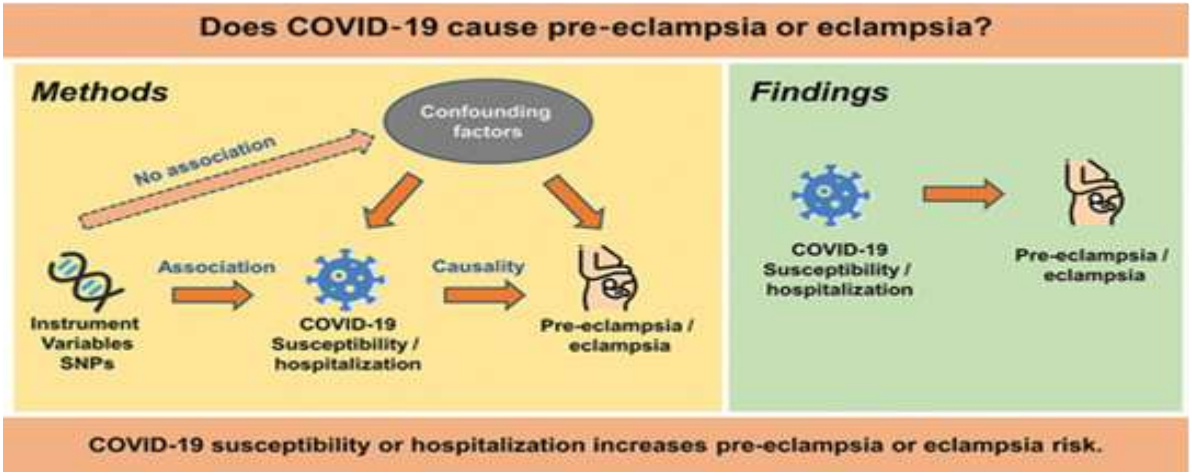

Figure 1: Investigation the probable causal association among COVID-19 & the possibility of pre-eclampsia/eclampsia (Xing et al., 2023)

Considering the Severity of COVID-19

According to the findings of a number of research, the severity of the COVID-19 virus is additionally related to an increased occurrence of PE. An investigation into the correlation among the degrees of infection withSARS-CoV-2 & the probability of progressing PE was carried out by Jonathan Lai et al. through the use of retrospective observational research. The pregnant females who were diagnosed with PE & COVID-19 have been divided into four distinct groups, each of which was determined by the degrees of the COVID-19 infection: moderate, asymptomatic, mild, & severe. The risks attained were 1.9 percent, 2.2 percent, 5.7%, & 11.1 percent correspondingly. There was a dose-response association between the severity of SARS-CoV-2 infection & the likelihood of getting PE, with the incidence of PE rising as the severity of COVID-19 rose. This was the primary conclusion that emerged from the study. In addition, they reported that the median interval between the commencement of infection of SARS-CoV-2 & the identification of PE was sixteen days, with the interquartile range ranging from seven to sixty-one days. This further strengthens the existence of a connection among the two illnesses (Lai et al., 2021).

COVID-19 Vaccine During Pregnancy & Perinatal Outcomes

The pandemic of the coronavirus disease 2019 (COVID-19) has been affecting a significant number of individuals all over the globe for the past two years. It has become the most significant public health concern, & it has compelled healthcare facilities to organize their medical units, especially those that deal with obstetrical and gynecologic procedures. (Franchi et al., 2020) In women who have severe acute infection with respiratory syndrome coronavirus 2 (SARS-CoV-2), pregnancy is thought to be an independent risk factor for adverse results. This is because pregnant females have elevated rates of maternal death & admissions to intensive care units in comparison with females who are not pregnant. Additionally, pregnant women have higher rates of preterm deliveries (both iatrogenic & spontaneous), cesarean sections, stillbirth, & other pregnancy-related diseases. (Oakes et al., 2021) A recent declaration was made by the ACOG, the Centers for Disease Control, & the Society for Maternal-Fetal Medicine & Prevention, declaring that vaccination should be administered to all pregnant females in order to minimize the rates of maternal & fetal-neonatal morbidity and death within the population. The COVID-19 vaccinations, which include booster doses, are safe & open to pregnant female, according to (Kalafat et al. 2022). nevertheless, despite the growing recognition that these programs are safe & open to pregnant female, it was observed by Zavala et al. (Zavala et al., 2022) that by September 2021, 17 percent of national policies still continued to recommend against the utilization of any COVID-19 vaccine throughout gestation. Of these, twenty-five percent were low- & middle-income countries. This was accomplished by considering the absence of clinical trials, as well as reproductive & developmental

toxicology information that involved pregnant female. Additionally, there are still reports of a low acceptance rate among this particular group of cases, primarily because to the concern that mothers have regarding the potential ramifications for the health of their fetus & newborn. (Mappa et al., 2022) In addition, although a significant amount of research has been conducted on the influences of SARS-CoV-2 infection on gestation & perinatal results, there is currently a lack of information regarding the effects of the SARS-CoV-2 vaccine. In pregnant women, preliminary findings on the immunization & safety capabilities of SARS-CoV-2 vaccines appear to be reassuring. These data addtionally show that neonates born to moms who have received vaccinations may have antibodies against SARS-CoV-2. (Gray et al., 2021) Additionally, the Centers for Disease Control & Prevention in the US & the National Health Service in the UK took int account the application of the Moderna or Pfzer-BioNTech vaccines to be safer. This was because of to the rapidity of mRNA disintegration. However, clinical trials that assessed other types of vaccines, like the J&J/Janssen COVID-19 vaccine, did not appear to have any adverse pregnancy-related results. (Shimabukuro et al., 2021)

The global dissemination of the SARSCoV-2 pandemic is occurring at an accelerated pace. It is imperative to identify and safeguard individuals who are most vulnerable in society as mortality rates increase. Previous epidemics of human coronaviruses, including SARSCoV-2 and MERS-CoV, have provided valuable insights into the heightened susceptibility of pregnant females and their fetuses to the detrimental consequences of infection (Wong et al., 2004),(Zhu et al., 2020) , (Ahmed et al., 2025) The clinical manifestations of COVID-19 in pregnant individuals have been shown to be similar to those observed in non-pregnant individuals with the virus. These symptoms included fever, congestion, myalgia, shortness of breath, and diarrhea. Consequently, the outcome of COVID-19 infection throughout pregnancy was adverse for both the fetal and maternal health. The health of the mother was adversely affected by a COVID-19 infection throughout pregnancy (Guan et al., 2020).

Lymphopenia, leukocytosis, reduced platelet counts, & elevated concentrations of transaminase, C-reactive protein, & D-dimer were commonly seen in the laboratory results of patients. The majority of chest CT pictures had imaging characteristics that are suggestive with COVID-19 pneumonia (Guan et al., 2020).

A systematic review was conducted, including a total of 230 women from 20 eligible studies. Among these women, there were 154 deliveries, 66 continuing pregnancies, & ten abortions. Additionally, 156 neonates from the same 20 valid researches have been involved in the review. A total of 34.62 percent of the cases involving pregnant persons were found to have obstetric problems, and among these instances, 59.05% of the individuals reported fever. A prevalence rate of 40.71 percent was observed for lymphopenia in the studied population. Mechanical ventilation was supplied to a proportion of 5.1% of the female population. A total of seven ladies were in a critical state. One female parent and two juvenile individuals died. Approximately 24.74 percent of newborns were born prematurely. All five infants who tested positive for SARSCoV-2 through throat swab testing were delivered through cesarean section. Among the babies who underwent throat swab testing, a total of three out of eight individuals had higher concentration of IgG and IgM antibodies targeting the SARS-CoV-2 virus (Chi et al., 2021).

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