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PREGNANCY COMPLICATIONS IN COVID-19: A RETROSPECTIVE REVIEW OF MEDICAL RECORDS

by
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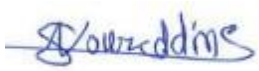

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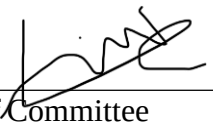

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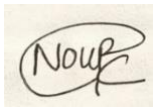

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ABSTRACT
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Nour Hussein Kassem for Master of Science in Nursing
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Title: Pregnancy Complications in COVID-19: A Retrospective Review of Medical Records

Background: The coronavirus 2019 (COVID 19) is a novel virus that led to a global public health emergency. Several case reports highlighted the severity of infection in pregnant women given their immunocompromised state. Nevertheless, the exact effect of COVID 19 on pregnancy and childbirth is unknown due to lack of sufficient studies and guidelines.

Aims: To evaluate the adverse effects and maternal-fetal outcomes that COVID-19 has on pregnancy in a sample of women who delivered at a tertiary medical center in 2021, compare the maternal and fetal outcomes of these women to a comparison group of healthy women matched by age and parity, and identify the predictors of select maternal and fetal outcomes.

Methods: This study used a retrospective descriptive comparative design. Data were collected through chart review on the maternal fetal outcomes of pregnant women that contracted COVID-19 throughout the course of their pregnancy, and delivered in the year of 2021 in Emirates Hospital Jumeirah, a tertiary healthcare center in Dubai, UAE and the comparison group. Women who contracted COVID-19 infection prior to their pregnancy were excluded from the study.

Results: From January to December 2021, 43 pregnant women contracted COVID-19 infection that were matched with 43 healthy pregnant women for a total sample of 86 with a mean age of 31 and parity 0.72. The incidence of preterm deliveries was significantly higher in the COVID-19 group, with a rate of 20.9% vs. 4.7% in the comparison group ($p = 0.049$). A higher number of premature rupture of membranes was notably observed with an incidence of 18.6% in the COVID-19 group versus none in the comparison group ($p = 0.005$). No significant difference was found in maternal outcomes; however, women who delivered prematurely were 46 times more likely to experience fetal distress (20.9% vs. 2.3%, $p=0.015$). While controlling for confounders, multivariable logistic regression showed that fetal distress was the only significant predictor of premature birth, whereas history of prior maternal complications and premature birth predicted fetal distress, with a positive trend for exposure to COVID-19.

Conclusion: The findings suggest that women who contract COVID-19 infection are more likely to deliver prematurely and experience fetal distress than those who do not. However, a limitation of the study was the small sample size that was recruited from one medical center. A comprehensive maternal-fetal assessment and monitoring is required in women exposed to COVID-19 until more evidence becomes available from rigorous studies.

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CHAPTER I

INTRODUCTION

Pregnancy is a critical period in a woman's life, and ensuring the health and wellbeing of both the mother and the fetus is of paramount importance. The physiological changes that occur during pregnancy make women more susceptible to infections (Mascio, et al., 2020), and the COVID-19 pandemic has brought new challenges and uncertainties to this population. The virus has affected people globally and has been shown to have a significant impact on different body systems and organs, including the respiratory and cardiovascular systems (Adhikari, et al., 2020). However, the impact of COVID-19 on pregnancy is less well understood, and there is a need to further investigate the effects of the virus on this vulnerable population (Capobianco, et al., 2020).

In Dubai, United Arab Emirates (UAE), the COVID-19 pandemic has had a significant impact on the healthcare system; however, its effects on pregnancy are not well known as indicated by the lack of studies in this area. Therefore, pregnant women and their fetuses faced unique challenges and uncertainties due to the pandemic. It is crucial to understand the effects of COVID-19 on pregnancy outcomes, in order to provide evidence-based guidance to healthcare providers and effective management to pregnant women. The purpose of this study was to assess the impact of COVID-19 infection on pregnancy outcomes in a tertiary healthcare center in Dubai, the United Arab Emirates (UAE).

Identifying the additional risk, if any, that an exposure to or infection with COVID-19 imposes during pregnancy is important to develop preventive measures to protect the mother

and fetus.

The results of this study will provide valuable insights into the effects of COVID-19 on pregnancy and inform healthcare providers and pregnant women about the potential risks and benefits of exposure to COVID-19 during pregnancy.

A. Background And Significance

The coronavirus 2019 (COVID-19) is a variant form of a previously known severe acute respiratory syndrome coronavirus (SARS-CoV). COVID-19 was first reported in Wuhan, China in December of 2019; however, it was only declared as a global pandemic in March of 2020 (World Health Organization [WHO], 2021). COVID-19 is a multisystem disease caused by a single-stranded RNA virus that is believed to be bat-borne, and has a wide array of clinical presentations, ranging from lack of symptoms to critical illness in patients who then require intensive medical care (Gorbalenya et al., 2020).

Generally, vulnerable patient populations are considered at high risk for complications from any given disease and its sequelae. Pregnancy, given the adaptations the body goes through, by default makes females a vulnerable population. Maternal susceptibility to infections is increased during pregnancy due to physiologic, mechanical, and immune changes that alter the body (Hammad et al., 2021). The immune changes the pregnant female goes through to avoid rejection of the fetus result in a state of relative immunosuppression (Hammad et al., 2021).

Furthermore, given the immunocompromised status during pregnancy, COVID-19 infection can increase the risk of pneumonia and its complications in pregnant women more than in those who are not pregnant (Capobianco et al., 2020). In a systematic review and

meta-analysis by Di Mascio et al. (2020), more than 90% of hospitalized pregnant women affected by a variant of the coronavirus, including COVID-19, had a diagnosis of pneumonia. One third (33.3%) of pregnant women with COVID-19 had preterm birth either at 34 or 37 weeks of gestation (Di Mascio et al., 2020). In another systematic review and meta-analysis by Kim et al. (2020), a 12.9% case fatality rate of pregnant women with COVID-19 infection was reported in those admitted to the intensive care unit or had passed away within one week of delivery. Moreover, 45% of pregnant women infected with COVID-19 showed pregnancy-related complications, including fetal abnormalities, premature rupture of membranes, and placenta praevia as documented in a systematic review of 13 observational studies in China (Capobianco et al., 2020).

On the other hand, some studies did not document an association between COVID-19 infection in pregnancy and adverse maternal or neonatal outcomes. In a large, single-institution cohort study of 252 pregnant women with COVID-19 infection, only 13 (5%) presented with or developed severe or critical illness, and no subsequent maternal deaths were reported (Adhikari et al., 2020). Also one systematic review of 132 studies of pregnant women with COVID-19 found the rates of stillbirths (0.99%) and neonatal death to be low (Dube & Kar, 2020).

Although physiologic theory and some empirical findings suggest a higher risk for adverse events in pregnant women with COVID-19, the evidence is not conclusive. Furthermore, many of the studies were performed in the early stages of the pandemic when the adverse outcomes of the disease and its sequelae were still not yet known to healthcare professionals. Moreover, most of the studies reported outcomes in pregnant women with COVID-19, but did not compare those to pregnant women who were not infected with

COVID-19. According to a report from the Center for Disease Control and Prevention (CDC) in June 2020, 31.5% of pregnant women were hospitalized due to COVID-19, compared to only 5.8% of nonpregnant women (Adhikari, et al., 2020). There was no published study found in the Middle East that examined maternal-fetal outcomes in pregnant women who had COVID-19 infection, except for one study in Iran that reported on case fatality rates. Among nine pregnant women with severe COVID-19 disease, 7 out of 9 died, resulting in a case fatality rate of 77.8% (Hantoushzadeh et al., 2020). Given the different ethnic and genetic background of Middle Eastern females, such a study may add distinct findings to the international literature. An in-depth study regarding maternal illness, placental pathology, and neonatal complications can inform future monitoring and treatment of pregnant women with COVID-19 infection. The proposed study will fill the gap in knowledge in the Middle East by identifying pregnancy outcomes in pregnant women with COVID-19 and comparing those to a group of women who were pregnant during the same period but did not contract COVID-19.

B. Literature Review

The outbreak of SARS-CoV-2 in December 2019 has caused a worldwide pandemic that impacted millions of individuals across the globe under the name of Covid-19.

Pregnant women were a particularly vulnerable group during the pandemic, and there are growing concerns about the potential effects of the virus on their health and that of their fetuses. Over the last two years, several studies have been conducted to assess the impact of SARS-CoV-2 on pregnancy outcomes. A literature review of the current understanding of the effects of SARS-CoV-2 on maternal morbidity and mortality, vertical transmission, and

fetal and neonatal outcomes is presented in the below sections.

Recent research on SARS-CoV-2 and pregnancy, including evaluation studies of management protocols for COVID-19 in pregnancy, as well as systematic reviews and meta-analyses of pregnancy outcomes, were reviewed. Furthermore, this review ends with a discussion of the implications of these findings for clinical practice, highlighting areas in need of future research, and the necessity of ongoing monitoring of the impact of SARS-CoV-2 on pregnancy outcomes.

A narrative review by Adhikari et al. (2021), showed that pregnant women with SARS-CoV-2 infections are at an increased risk of severe morbidity and mortality compared to pregnant women who are not infected with the virus. The review's results showed that pregnant women with SARS-CoV-2 infections had a higher prevalence of preterm birth, cesarean section, intensive care unit admission, and a higher likelihood of maternal death than non-infected pregnant women. A systematic review and meta-analysis by Capobianco et al. (2020) also reported that SARS-CoV-2 infection in pregnant women was associated with an increased risk of preterm birth, preeclampsia, and cesarean section. Additionally, a systematic review by Di Mascio et al. (2020) reported that the infection with COVID-19 is associated with a high risk of respiratory complications in pregnant women.

Furthermore, a systematic review and meta-analysis by Capobianco et al. (2020) documented that neonatal complications were more prevalent among infants born to mothers with SARS-CoV-2 infections. The findings of the review showed that infants born to infected mothers were more likely to be admitted to the neonatal intensive care unit and had a higher incidence of respiratory distress syndrome.

The above research findings had implications for clinical practice. For instance, Capobianco et al. (2020) recommended the use of maternal testing to identify SARS-CoV-2 infection in pregnant women as part of routine prenatal care. In addition, Dube and Kar (2020) recommended that neonatal care in COVID-19-positive mothers should include close monitoring and early intervention in case of complications. Fernandez (2021) highlighted the association between COVID-19 during pregnancy and preterm birth, which calls for increased monitoring of pregnant women with SARS-CoV-2 infections.

1. Effects Of COVID-19 On Mothers

Numerous studies have been conducted to examine the clinical presentations, outcomes, and impact of COVID-19 on pregnant women and their neonates. Yan and colleagues (2020) found that the average gestational age at hospital admission of pregnant women with COVID-19 was 38 weeks, with fever (51%) and cough (28%) being the most prevalent symptoms. Moreover, a narrative review of 13 articles was conducted on the effects of COVID-19 in pregnant women and their neonate (Panahi et al., 2020). The review studied a total of 37 pregnant mothers and 38 neonates, with the majority of mothers having a normal vaginal delivery in the third trimester and no preterm labour. The most common symptoms present in the mothers were fever, cough, and chest pain. Chest CT scans showed ground glass opacity with progressive consolidations in most of the patients, and no changes in the results before and after delivery in 35 of them (Panahi et al., 2020). All the neonates were tested for COVID-19 infection at birth; however, there was no evidence of intrauterine vertical transmission or congenital abnormalities. Thus, all the neonates who were diagnosed with COVID-19 were infected after birth, likely through contact with an infected individual

or environment. Symptoms in the affected infants appeared between 5 to 17 days after birth and included tachypnea, milk regurgitation, vomiting, cough, fever, pneumothorax, liver disorders, thrombocytopenia, and pulmonary changes observed on chest CT scans. All of the mothers had healthy babies with an average Apgar score of 8-10 (Panahi et al., 2020).

Most importantly, high risk of maternal death in pregnant women with COVID-19 was reported in a systematic review and meta-analysis by Kim and colleagues (2020). Out of 85 reported cases, 11 women died during pregnancy or within a week of delivery, resulting in a case fatality rate (CFR) of 12.9%. Of the 11 deaths, 7 were from a single report from Iran. If this study is excluded, the CFR would be 5.3%., Maternal death can result in significant emotional and psychological trauma for the family and can also result in loss of income and support for the children. Therefore, it is crucial to monitor and treat pregnant women with COVID-19 to prevent or reduce the risk of maternal death (Kim et al., 020).

a. Pneumonia And Its Complications in Pregnant Women with COVID-19

Pneumonia is one of the most common and severe consequences of COVID-19, and pregnant females undergoing physiologic adaptation are predisposed to more severe pneumonia. Di Mascio et al. (2020) conducted a systematic review and meta-analysis of nineteen studies, which included 79 hospitalized pregnant women. Their findings revealed that over 90% of pregnant women hospitalized with a variant of the coronavirus, including COVID-19, had received a diagnosis of pneumonia. Similarly, a study by Yan et al. (2020)

reported that out of 116 pregnant women with COVID-19, eight cases (6.9%) had severe pneumonia.

Moreover, out of 100 neonates tested for severe acute respiratory syndrome coronavirus 2 in the study by Yan et al. (2020), 86 had negative results. Among these 86 neonates, paired amniotic fluid and cord blood samples from ten neonates also tested negative for the virus. One fourth (23.3%) of women in the study presented without symptoms. The most common symptoms observed in the pregnant women with COVID-19 included fever (50.9%) and cough (28.4%), and abnormal radiologic findings were found in 96.3% of cases (Yan, et al., p. 2020).

Pregnant women with COVID-19 are also at an increased risk of developing severe and critical illness, which can result in respiratory failure, septicemia, and multiorgan dysfunction (DeBolt, et al., 2021). Given the higher risk for adverse events in pregnant women with COVID-19, it is important to monitor and treat these women carefully to prevent or reduce the risk of pneumonia and its complications.

b. Preterm Birth in Pregnant Women with COVID-19

Preterm birth is another serious consequence of COVID-19 in pregnant women, which can have a significant impact on both the mother and the fetus, including respiratory distress syndrome, hypoglycemia, and developmental delays. In the systematic review and meta-analysis by Di Mascio et al. (2020), one third (33.3%) of pregnant women with COVID-19 had preterm birth either at 34 or 37 weeks of gestation. Furthermore, preterm birth can also result in increased healthcare costs, and may even require admission to neonatal intensive care units (Karasek et al., 2021). Therefore, it is important to closely monitor and

manage pregnant women with COVID-19 to prevent or reduce the risk of preterm birth.

Yan and colleagues (2020) conducted a medical record review of 116 pregnant women with COVID-19 pneumonia, from 25 hospitals in China between January 20, 2020, and March 24, 2020. The women had a median gestational age of 38^{+0} weeks on admission. Out of the 116 cases, 8 women delivered before 24 weeks, with one case complicated by a missed spontaneous abortion. In addition, 99 women delivered during hospitalization, with 85.9% undergoing caesarean delivery and 14.1% having a vaginal delivery. The rate of preterm delivery before 37 weeks was 21.2%, with 28.6% of those resulting from preterm premature rupture of membranes. The rate of spontaneous preterm birth before 37 weeks was 6.1% (6 out of 99), and there were no reports of spontaneous preterm delivery before 34 weeks, nor fetal deaths. Out of the 100 neonates tested for severe acute respiratory syndrome coronavirus 2, 86 had negative results, and 47.0% of them were transferred to the neonatal intensive care unit (NICU). One case of severe neonatal asphyxia resulted in neonatal death. Additionally, paired amniotic fluid and cord blood samples from 10 neonates used to test for severe acute respiratory syndrome coronavirus had negative results, and there was no evidence of vertical transmission (Yan, et al., 2019). In a case report by Ronnje et al. (2020), a woman in the third trimester of pregnancy developed severe COVID-19, which resulted in an emergency caesarean section and preterm delivery at around 33 weeks of gestational age.

In a recent review by Smith et al. (2022), the association between COVID-19 infection during pregnancy and preterm delivery was evaluated in a large cohort of 14,264 pregnancies. The findings indicated that severe COVID-19 late in pregnancy may double or triple the probability of preterm delivery, with the risk being highest for those infected during the third trimester. The authors suggested that the increased risk in milder COVID-19 disease

states or earlier in pregnancy is likely minimal. The study compared three groups of pregnant individuals with symptomatic COVID-19 out of a total of 5,059. Of these groups, 89.7% were classified as moderate, 9.6% as mild, and 0.8% as severe. Among the completed pregnancies with mild COVID-19 before 37 weeks of gestation, there was no significant difference in the risk for preterm delivery compared to those who tested negative. The adjusted risks were 10.0% (95% confidence interval [CI] 7.8, 12.0) and 9.8% (9.1, 10.5), respectively. However, severe COVID-19 infection after 20 weeks of gestation was associated with a higher risk of preterm delivery compared to mild or moderate disease. For instance, at 35 weeks, the risk ratio for preterm delivery was 2.8 (95% CI 2.0, 4.0) for severe compared to mild/moderate COVID-19. Moreover, the risk ratios for medically indicated and spontaneous preterm delivery were 3.7 (95% CI 2.0, 7.0) and 2.3 (95% CI 1.2, 3.9), respectively. In terms of absolute risk, COVID-19 during pregnancy was associated with a higher likelihood of spontaneous preterm and indicated preterm delivery, relative to term birth. The adjusted absolute risks of preterm delivery varied by gestational age. Overall, this review by Smith and colleagues (2022) had a large sample size, with over 14,264 pregnancies and rigorous methodology, strengthening the validity and generalizability of the findings. However, there were some limitations, such as self-reported information, limited clinical measures, and loss to follow-up. Nevertheless, this investigation added to the growing body of literature on the effect of COVID-19 on pregnancy outcomes, highlighting the need for further research to elucidate the underlying mechanisms of the relationship between COVID-19 infection and preterm delivery.

c. Pregnancy-Related Complications in COVID-19

Pregnancy-related complications are another serious consequence of COVID-19 in pregnant women, which can have a significant impact on both the mother and the fetus. In the systematic review of 13 observational studies by Capobianco et al. (2020), 45% of pregnant women infected with COVID-19 showed pregnancy-related complications, including fetal abnormalities, premature rupture of membranes, and placenta previa. These complications can result in significant morbidity and mortality for both the mother and the fetus, as well as long-term consequences for the neonate. Additionally, pregnancy-related complications can also result in increased healthcare costs, and may require transfer to specialist care centers, or even early delivery.

Moreover, pregnant women with COVID-19 may also experience a range of psychological symptoms such as anxiety and depression, which can further complicate the pregnancy. Pregnant women with COVID-19 may also face difficulties accessing health services and support, due to the fear of infection, lack of resources, or lack of availability. This can result in lack of access to timely prenatal care and maternal-fetal monitoring, which can further increase the risk of maternal and fetal morbidity and mortality, although no published studies have addressed this issue.

In conclusion, the COVID-19 pandemic has resulted in significant consequences for pregnant women. Therefore, it is important to monitor and manage pregnant women with COVID-19 carefully to prevent or reduce the risk of adverse events. The ongoing COVID-19 pandemic, though the prevalence is reduced at the present time, highlights the need for

increased awareness and resources for maternal health, especially in low- and middle- income countries, where maternal mortality and morbidity are higher.

2. Mother-To-Child Transmission of COVID-19

It is important to understand the transmission of COVID-19 from mother to child as it can impact both maternal and fetal outcomes. Citu et al. (2021) analyzed maternal and fetal outcomes in a cohort of 76 pregnant women who tested positive for COVID-19 during their pregnancy compared to 813 pregnant women with no COVID-19 during the study period. Biological samples from both the mother and newborn, such as nasal swab, breast milk placental, serum, urine, feces and amniotic fluid were analyzed. The results showed that SARS-CoV-2 was detected in the placenta with a positivity rate of 7.53%, 2.92% in the umbilical cords but none in the amniotic fluid (0%). In the women, the highest positivity rate was in the nasal swabs (8.54%), followed by fecal samples (6.18%), then SARS-CoV-2 IgM serum tests at 4.38%. The positivity rate for urine samples was only 0.89%. The tests for the newborns revealed that the nasal swabs had the highest positivity rate at 5.4%, followed by fecal specimens at 4.05%, and serum samples at 1.35%. However, urine samples tested negative in all cases (Citu et al.,2021). The authors concluded that the risk for vertical transmission is low, although they reported a 1.01% positivity rate in the women's breast milk following delivery.

Another study by Garcia-Ruiz et al. (2021) provided evidence for the possibility of vertical transmission of COVID-19, with important implications for prenatal care and neonatal management. A total of 45 samples of placenta, amniotic fluid, and umbilical cord blood were obtained from 44 women with singleton pregnancies and one with a twin

pregnancy, with a median gestational age at diagnosis of 34.7 weeks (range 14-41.3 weeks) and a median interval between positive rapid test and delivery of 21.5 days (range 0-141 days). Among the women, 14 (33%) tested positive for SARS-CoV-2 at the time of delivery. Of particular concern is the finding of a positive RT-PCR in one singleton pregnancy with SARS-CoV-2 detected in the placenta, amniotic fluid, and umbilical cord blood, representing a rate of 2.2% (Garcia-Ruiz et al., 2021). This finding shows that the virus can cross the placental barrier and infect the fetus, consistent with previous reports of vertical transmission. Nevertheless, the negative results of nasopharyngeal aspiration in most neonates at birth suggest that transmission during delivery is not a major route of infection (Garcia-Ruiz et al,2021). Although the study was limited by the small sample size, time frame for follow up and lack of data on the severity of maternal COVID-19, the 38 neonates were tested after 24-48 hours and all came back negative again expect one neonate who had positive result, which highlights the need for close monitoring and testing of neonates born to mothers with COVID-19. The findings suggest the need for further research in this area to further our understanding of the risks and mechanisms of vertical transmission, and to inform best practices in prenatal care and neonatal management for mothers with COVID-19.

3. Effects on the Fetus

The below section outlines several studies that analyzed the impact of COVID-19 on fetuses, including fetal distress, fetal abnormalities, premature rupture of membranes, and placenta praevia.

a. Fetal Distress

Fetal distress refers to the condition in which the fetus experiences an insufficient supply of oxygen and nutrients, which can result in significant health concerns. In a recent systematic review, fetal distress emerged as the most frequent complication observed in fetuses born to mothers who tested positive for COVID-19, with a prevalence of 6.63% (Kyle et al., 2020). The symptoms displayed by infected neonates were mostly mild, and the neonatal outcomes were generally positive. However, it is important to approach these findings with caution, as the current evidence is limited and the need for larger, higher quality studies is imperative in order to fully comprehend the impact of maternal COVID- 19 on fetal health (Kyle et al., 2020).

The review of the evidence of mother-to-child transmission of SARS-CoV-2 and its impact on perinatal outcomes and congenital anomalies by Dube and Kar (2020) included a total of 1,408 neonates and 1,318 fetuses from 38 case reports and 34 cohort studies. The findings showed that 3.67% of neonates had positive nasopharyngeal swab test, while 7.1% had positive cord blood samples. The rate of preterm labor was 26.4%, and 59.9% of deliveries were via cesarean section. The most common neonatal symptom was breathing difficulty, and the stillbirth rate was 9.9 per 1000 total births in babies born to COVID-19 positive mothers (Dube et al., 2020).

b. Fetal Abnormalities and COVID-19

The International Registry of Coronavirus Exposure in Pregnancy enrolled 17,163 pregnant women who underwent the coronavirus test between June 2020 and July 2021 from 78 countries (Hernández-Díaz et al., 2022). The investigators compared the congenital

malformation in fetuses of pregnant women who were infected with COVID-19 to those of pregnant women who were not exposed. The analyses included only women with complete follow up, including 92 exposed and 292 non exposed women. The results showed 3.3% exposed versus 2.7% of the unexposed (RR 1.2; 95% CI 0.32–4.2) newborns had major congenital malformation, including fetal abnormalities such as absent pulmonary valve, aortic arch anomalies, and hypoplastic left heart syndrome (Hernández-Díaz et al., 2022). No specific pattern of malformations was observed. The investigators concluded that their findings do not provide evidence for large teratogenic effect of maternal COVID-19 infection during the first months of pregnancy and recommended larger studies (Hernández-Díaz et al., 2022).

A systematic review of COVID-19 in pregnancy documented the presence of SARS-CoV-2 protein in the placental cells, which was found in all the women that tested positive for COVID-19, as well as fibrin deposits and inflammatory infiltrates, causing poor vascular perfusion and growth restriction in the fetus (Sánchez-García et al., 2022). These factors such as fibrin deposits could result in premature delivery and disturb nutrient transport to the fetus. In that study, 98% of newborns born to COVID-19-positive mothers had a negative PCR result, with only 2% of them having pneumonia or dying from severe sepsis. A study of their placentas showed a similar phenomenon of premature rupture of the membranes, potentially leading to neurological repercussions in their lives (Sánchez-García et al., 2022). Consequently, although the children had a negative PCR result, they were affected by their mother.

c. Premature Rupture of Membranes, Placenta Previa, And COVID-19

The findings of a case control study of 55 COVID 19 infected women and 55 matched controls showed that pregnant women infected with COVID-19 had an increased risk of premature birth and two-fold greater risk of preterm labor (Tagghavi et al., 2021).

On the other hand, maternal and obstetric outcomes—neonatal in case groups—such as mode of delivery, premature rupture of membrane, postpartum hemorrhage, perineal resection rate, birth weight of neonates, Apgar score, and neonatal asphyxia rate were similar to pregnant women without COVID-19 (Taghavi et al.,2021). The authors recommended more case-control studies to ascertain their results (Taghavi et al.,2021).

One narrative review in China revealed that the incidence of placenta praevia was higher among pregnant women infected with COVID-19. Placenta praevia is a serious pregnancy complication that poses a threat to both the mother and the baby and can lead to severe bleeding and adverse outcomes (Wong et al., ,2021). The exact mechanisms underlying this relationship are not yet understood and more research is required to shed light on this matter. The immune response triggered by COVID-19 infection and its impact on the placenta could be one potential explanation for this relationship, but this needs to be further investigated (Wong et al., 2021).

d. Stillbirths and Neonatal Death in COVID-19

While some studies have reported low rates of stillbirths and neonatal death in pregnant women with COVID-19, the evidence is not conclusive. A systematic review of a total of 60 case report, cohort and case series, by Dube and Kar (2020) found low rates of

stillbirths (9.9 per 1000) and neonatal death (5.46 per 1000) in pregnant women with COVID-19, which according to the authors were low rates. The impact of COVID-19 on stillbirths and neonatal death in the Middle Eastern population has not been well studied. An in-depth study of maternal illness, placental pathology, and neonatal complications in this population can provide valuable information for future monitoring and treatment of pregnant women with COVID-19 (Beuskem, 2021).

4. Research in the Middle East

Unfortunately, there is a lack of studies in the Middle Eastern region that examine the maternal-fetal outcomes of pregnant women with COVID-19 infection. According to a systematic review of the literature, only one study in Iran reported on the case fatality rate of pregnant women with COVID-19 (Hantoushzadeh et al., 2020). This highlights the need for further research in the region to better understand the impact of COVID-19 on pregnant women and their fetuses. Given the different ethnic and genetic background of the Middle Eastern population, an in-depth study regarding maternal illness, placental pathology, and neonatal complications can add distinct findings to the international literature and guide future monitoring and treatment of pregnant women with COVID-19 infection in the region. Thus, the COVID-19 pandemic has highlighted the need for further research in the Middle Eastern region to better understand the impact of the disease on the pregnant population.

C. Summary

In summary, the novel coronavirus (COVID-19) is a major global pandemic that affects pregnant women differently due to their vulnerability to infections and physiologic,

mechanical, and immune changes. The literature suggests that COVID-19 in pregnancy can increase the risk of pneumonia and its complications, preterm birth, fetal abnormalities, premature rupture of membranes, and placenta previa, but research results are not consistent. The literature also shows a higher risk of maternal death, and pregnancy-related complications in pregnant women with COVID-19. To mitigate the risk and consequences of COVID-19 in pregnant women, it is important to monitor and treat these women carefully. However, there are limitations in existing studies, including sample size and selection bias, which could explain the inconsistent findings in some areas and these should be addressed in future research. Moreover, the importance of the role of the healthcare system in this area and lack of studies in the Middle Eastern region call for future studies.

To advance our understanding of the impact of COVID-19 on pregnant women and their fetuses, future research should focus on well-designed, multi-center studies with larger sample sizes and diverse populations. One aspect to consider is to compare outcomes of infected pregnant women to those of pregnant women who were not infected but presented for health care during the same period as the group of interest. This consideration was taken in designing the proposed study.

CHAPTER II

STUDY AIM AND THEORATICAL FRAMEWORK

The purpose of this study is to examine the effects of COVID-19 on pregnancy outcomes, specifically in a tertiary healthcare center in Dubai, UAE. The main objective of the study is to compare the pregnancy outcomes of women who have been exposed to COVID-19 to those who have not been exposed. This will provide a clear understanding of how COVID-19 exposure can impact the health of the mother and fetus. The study will also examine the maternal-fetal outcomes, including possible complications and the likelihood of hospital admissions.

The results of this study will provide crucial information to healthcare providers, policymakers, and the general public regarding the impact of COVID-19 on pregnancy outcomes. It will also contribute to the body of literature on the subject and help guide future research and policies related to maternal-fetal health during the COVID-19 pandemic. Thus, the findings may provide insight into the management and care of pregnant women during the pandemic.

A. Theoretical Framework

The theoretical framework for this study is a fundamental aspect of laying the foundation for the methodology, including the study design, selected variables, and interpretation of results. The framework describes the relationship between physiological changes during pregnancy and the impact of COVID-19 on pregnant women. This framework

considers the significant cardiovascular and respiratory system changes in pregnant women and how these changes interact with COVID-19's pathophysiology to lead to adverse outcomes for both the mother and her newborn. Furthermore, the theoretical framework is informed by the most recent research and understanding of the physiological changes that occur during pregnancy and the mechanisms by which COVID-19 can impact pregnancy outcomes.

During pregnancy, the female undergoes substantial anatomical and physiological changes to be able to nurture and accommodate the developing fetus. Multiple organ systems get significantly altered, which therefore makes pregnant women a high-risk population. The adaptability of women to these physiologic changes varies significantly from one person to the other. The most significant change in the pregnant woman's body is

the increase in plasma volume that progressively occurs over the period of pregnancy. Plasma volume increases by approximately 50% and is proportional to the weight of the fetus (Soma-Pillay et al., 2016). This increase in plasma volume over time results in marked haemodilution, which is reflected by decreased hemoglobin concentration and red blood cell count. Furthermore, a progressive fall in platelet count also occurs throughout the course of pregnancy, but is not a cause for concern unless the levels reach below 100×10^9 cells/L (Soma-Pillay et al., 2016). Furthermore, pregnancy produces a hypercoagulable state whereby pregnant females are prone to thrombus formation. In preparation for hemostasis post-delivery, the body increases the production of clotting factors, including fibrinogen, and decreases that of anticoagulation factors such as protein S and antithrombin (Ramsay, 2010).

Cardiac changes are the most significant changes that occur physiologically in the pregnant female. Cardiac output increases by approximately 40% throughout 40 weeks of

gestation to compensate for the marked peripheral vasodilation that occurs. An increase in 10-20 beats per minute in heart rate occurs to compensate for the increased cardiac output. With the progression of pregnancy until reaching term, the uterus grows large enough to affect venous return depending on the mother's position. Lying supine causes pressure on the inferior vena cava and decreases venous return, which would in turn decrease uterine blood flow and compromise the pregnancy (Soma-Pillay et al., 2016).

Respiratory changes that occur during pregnancy include a vast increase in oxygen demand and consumption, in tidal volume, and hyperventilation. Pregnant females may be in a state of mild compensated respiratory alkalosis in order to adapt to the body's increase in metabolic rate and need for oxygen (Soma-Pillay et al., 2016). Other physiologic changes include a shift in glucose metabolism. Insulin-secreting pancreatic beta-cells hyperplasia occur and result in increased insulin secretion and sensitivity in early pregnancy, but progress into insulin resistance later on. The surge of hormones makes the pregnant woman susceptible to fluctuations in insulin resistance and possible development of gestational diabetes. (Soma-Pillay et al., 2016).

Understanding the pathophysiology of the COVID-19 virus has been quite a struggle initially. In the first couple of months of the pandemic, there was general confusion and ambiguity towards the constellation of symptoms that a patient who may have contracted the virus would present with. Symptoms of infected patients may range from minimal to severe disease leading to multisystem organ failure (Yuki et al., 2020). The disease progresses from the incubation phase into the symptomatic phase until it reaches the pulmonary phase. Patients are most infectious during the late incubation/pre- symptomatic phase where the virus exhibits the highest viral load (Marik et al., 2021). This is where the virus infects the

ciliated epithelium of the nasopharynx and the airways. The presence of aberrant RNA is detected in infected cells by recognition receptors, which in turn activate a cascade of transcription of multiple proteins that trigger the host's defenses, including inflammatory cytokines and chemokines. The rate of expression of these inflammatory markers depends on the severity of disease and in turn, these chemo and cytokines increase the involvement of macrophages, T cells, and mast cells in the defence response (Marik et al., 2021). Progression into the pulmonary phase depends on the entry of the viral inoculum into the lungs and infecting type II pneumocytes and alveolar macrophages. Reaching severe COVID-19 disease involves the accumulation of activated macrophages in the lungs and inflammation of the endothelial tissue of the vascular system that leads to multiorgan immuno-thromboses (Marik et al., 2021). Injury of the endothelial tissue results in the activation of clotting factors, and given the extensive injury that occurs in COVID-19 infection, the increased activation of clotting factors puts the body in a hypercoagulable state, which results in a higher tendency to develop thrombi (Marik et al., 2021).

Pregnancy coupled with COVID-19 infection puts the pregnant female in a high- risk situation whereby acute decompensation is exceedingly likely. The pregnant female's physiological changes alongside the pathology of COVID-19 infection may lead to severe multiorgan dysfunctions and complications. The pregnant female is at higher risk of developing pulmonary embolism, deep vein thrombosis, stroke, myocardial infarction, placental thrombosis, moderate to severe pneumonia and fetal demise. Below is an illustration representing the physiologic changes of pregnancy coupled with the pathophysiology of COVID that will result in the increased risk of complications.

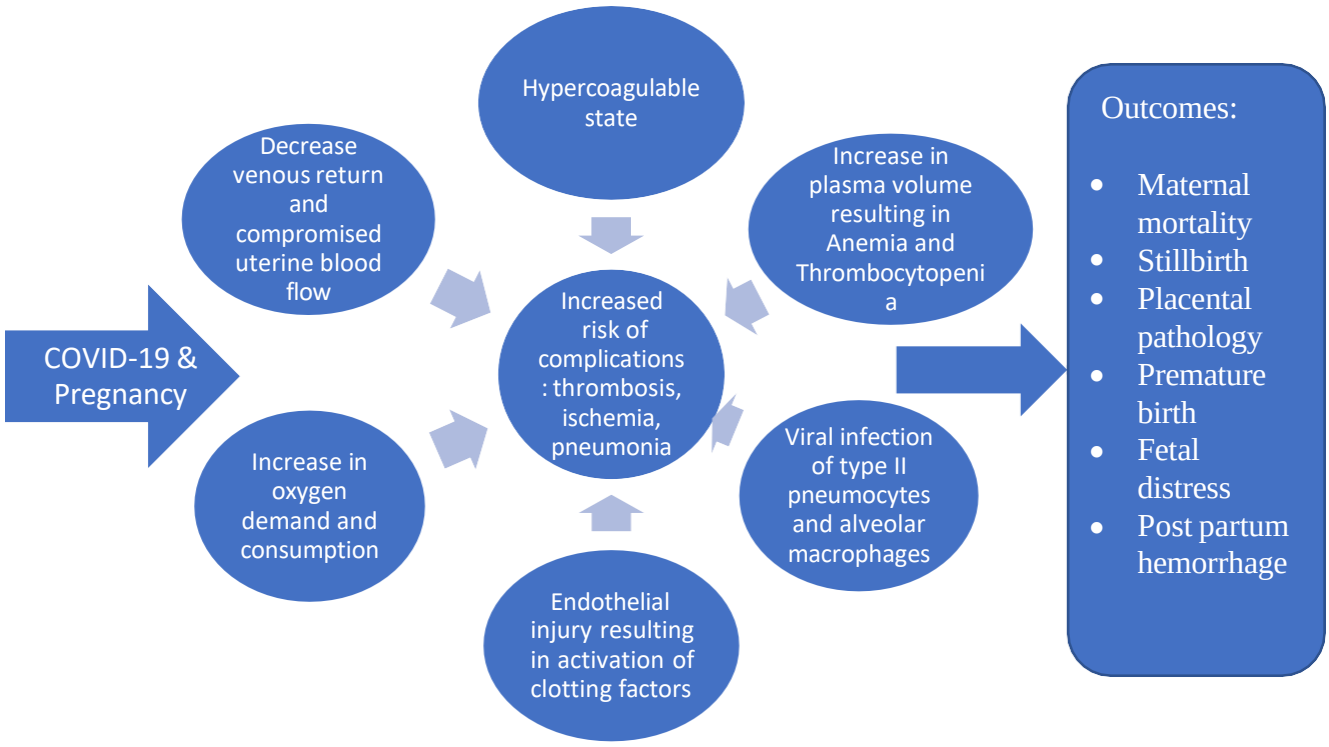

Figure 1. Theoretical Framework of the pathophysiology of COVID19 and its impact on pregnancy outcomes.

By taking into account the above various factors, the theoretical framework provides a comprehensive understanding of the impact of COVID-19 on pregnancy outcomes and assists in predicting COVID-19 exposure outcomes in pregnant women. The outcomes that will be examined include mortality, preterm/still births, placental problems, eclampsia/preeclampsia, postpartum hemorrhage. Predictor variables include: age, para, gravida, history of maternal complications and history of respiratory, hematologic, metabolic or cardiovascular disease.

B. Specific Aims of the Study

1. To evaluate adverse maternal and fetal outcomes of COVID-19 infection in pregnant females presenting to the Emirates Hospital Jumeirah (EHJ) during the year 2021

(January 1 to December 31).

2. To compare the outcomes of the pregnant women with COVID-19 to those of a sample of pregnant women not exposed to COVID-19 matched by age and parity during the same time.

- The following hypothesis will be tested:

Pregnant women who are exposed to COVID-19 will experience more adverse outcomes and have higher rates of hospital admissions compared to those who have not been exposed.

3. To describe the course of hospitalization in women admitted to labor and delivery who tested positive for COVID19, including the method of delivery, placental pathology, and neonatal outcomes, compared to a sample of women with negative PCR matched by age who delivered around the same time.
4. To identify the predictors of maternal and neonatal mortality, post-partum hemorrhage, fetal distress, placental pathology, still births, premature births.

CHAPTER III

METHODS

A. Study Setting and Design

The study was conducted using a retrospective descriptive comparative design and data were collected through chart review of patients who presented to EHJ, which is a reputable tertiary healthcare center and leading hospital in obstetrics and gynecology in the city of Dubai, UAE. EHJ is a private hospital that consists of 60 inpatient beds, multiple specialty outpatient department, labor and delivery department, intensive care units, and operating theatre. The patient population consists of middle to high income people, mostly having private insurance, but also significantly self-paying due to the high touristic nature of the city. A retrospective comparative design for this study was considered to facilitate collection of a significant amount of medical record data in what was considered a worldwide peak in the year of 2021. A prospective study was not considered as COVID cases have considerably decreased all around the world due to multiple factors such as vaccination, unwillingness to test, and scarcity of cases to provide significant data.

B. Sample

All female patients who were pregnant, tested positive for COVID-19, either during pregnancy or upon delivery, and who delivered at EHJ between January 1 and December 31 of 2021. An average of 800 patients were seen over the course of the year, as such the sample

of women was matched by age and parity in a 1:1 ratio, those who did not have COVID-19 and delivered at the institution within one month of the COVID-19 group were compared for the same outcomes. All patients who met the study's inclusion criteria were enrolled in the study. Patients who had a history of COVID-19 infection prior to pregnancy were excluded from the study.

C. Data Collection

The study underwent a rigorous and thorough ethical review process to ensure the protection of patients' rights for privacy and confidentiality and compliance with ethical principles pertinent to human subjects' research. The Institutional Review Board (IRB) of the American University of Beirut reviewed and approved the study proposal. In addition, the Institutional Review Board and EHJ administration approval was taken for the use of electronic medical records for the study.

A standardized data collection sheet was used to extract the relevant information from the electronic medical records. The data collection sheet was designed to ensure that all relevant information is collected in a consistent and standardized manner, to minimize the risk of bias and to increase the accuracy of the data (Appendix).

The data collected included patient characteristics such as age, and medical history, as well as information on the course of hospital admission. In addition, data on maternal-fetal adverse outcomes, placental pathology, and neonatal conditions, such as prematurity, still births, etc… were also collected.

The data were used to determine the frequency of maternal-fetal adverse outcomes in the study sample and to identify any risk factors that may be associated with these outcomes.

Furthermore, to ensure the quality and accuracy of the data being collected, strict protocols were set in place to ensure that the data are collected in a consistent, reliable manner. Data collection involved a thorough review, where all inconsistencies or inaccuracies were identified and corrected.

D. Statistical Analysis

The study used the Statistical Package for Social Sciences (SPSS) version 28, and a two-tailed alpha of 0.05 was used to indicate statistical significance.

Descriptive statistics such as means and standard deviation were used to describe the continuous variables and frequencies and percent were used to describe the categorical variables of the sample and the two groups of women (Aim 1).

To answer aims 2 and 3 and test the hypothesis that pregnant women exposed to COVID-19 will have more adverse maternal-fetal outcomes and higher rates of hospital admissions compared to those who have not been exposed, inferential statistics were used. Furthermore, student t-tests were used to compare the two groups on continuous variables such as gestational age at delivery between the COVID-19 and non-COVID-19 groups. Chi Squared and Fisher Exact tests were used to compare the two groups on categorical variables such as incidence of pre-eclampsia.

Binary logistic regression analyses were used to identify the predictors of maternal-fetal adverse outcomes, fetal distress, etc... in the sample (Aim 4). This statistical technique was used because the target dependent variables were dichotomous, i.e. presence or absence of the outcome. The regression analysis also allowed for control of confounding variables and identified the independent effects of COVID-19 exposure on maternal-fetal outcomes.

In preparation for the regression, Fisher exact tests were conducted between each outcome and the presence of comorbidities, timing or mode of delivery and the remaining dicotomous variables. In addition, t tests were conducted to compare the group with the outcome to its counterpart on the number of pregnancies, abortions, and comorbidities.

CHAPTER IV

RESULTS

From January to December of 2021, a total of 840 women delivered in EHJ. Of these patients, 43 fit the criteria of contracting COVID-19 during their pregnancy. These patients were subsequently matched to an equal number of healthy patients, by age and parity who delivered within one month of the COVID19 group, for a total sample size of 86 patients for this study, with a mean age of 31 years, and a mean parity of 0.72 (Table 1). A significantly higher number of comorbidities were reported in the COVID positive group, than in the healthy group with a mean of 0.60 in the COVID-19 positive group vs 0.25 in the non-COVID-19 group, p=.007. The most common comorbidity in both groups was anemia at 27.9% (Table 1). History of coagulopathy was more in the COVID19 group than the healthy group (9.3% vs. 0%, p = .116). Furthermore, the incidence of preterm deliveries was significantly higher in the COVID-19 group, with a rate of 20.9%, compared to the non-COVID-19 group, which exhibited a lower rate of 4.7%, p = .049.

Table 1. Sample Characteristics (N = 86).

Variables	Total (N=86)		COVID Group (N=43)		Comparison group (N=43)	
Age (Mean, standard deviation)	31.19 ±3.47		31.19 ±3.47		31.19 ±3.47	
Para (Mean, standard deviation)	.72±.73		.72±.73		.72±.73	
Gravida (Mean, standard deviation)	2.02± 1.39		2.11± 1.76		1.93± .88	
Number of comorbidities*(Mean, Standard deviation	.43 ± .60		.60± .69		.26± .44	
Comorbidities	**Frequency**	**Percent**	**Frequency**	**Percent**	**Frequency**	**Percent**
History of anemia	18	20.9	12	27.9	6	14.0
History of thyroid problems	10	11.6	5	11.6	5	11.6
History of hypertension	2	2.3	2	4.7	0	0
History of diabetes mellitus	1	1.2	1	2.3	0	0
History of coagulopathy	4	4.7	4	9.3	0	0
History of asthma or hyperactive airway disease	2	2.3	2	4.7	0	0
Time of Delivery*						
Full Term Delivery	75	87.2	34	79.1	41	95.3
Preterm Delivery	11	12.8	9	20.9	2	4.7
Normal Vaginal Delivery	50	58.1	27	62.8	23	53.5
C-Section	36	41.9	16	37.2	20	46.5
History of previous maternal complications	16	18.6	8	18.6	8	18.6

***Indicates significant difference between the COVID-19 and the comparison group**

Table 2 Shows the frequency of symptoms in the COVID-19 group. Two thirds of the COVID-19 group (59.3%) reported no symptoms. The most common reported symptoms related to the disease were fever, cough, and shortness of breath (30.2% each), (Table 2). Anosmia was not reported by any of the patients that tested positive for COVID-19. Only one patient out of the 43 was hospitalized for COVID-19 infection prior to delivery. The mean gestational age at the time of PCR testing was 36.86 weeks.

Table 2. Disease Attributes of the COVID19 group (n=43).

Variable	Frequency	Percent
Fever	13	30.2
Cough	13	30.2
Shortness of breath	13	30.2
Sore throat	5	11.6
Rhinorrhea	6	14.0
Loss of taste	3	7.0
Anosmia	0	0.0
Covid hospitalization	1	2.3
Gestational age at the time of PCR testing (mean, standard deviation)	36.86± 3.1	

Comparison of Maternal and Fetal Outcomes of the two Groups

Table 3 shows results of the differences in maternal and fetal outcomes between the COVID-19 and the comparison group. The maternal-fetal outcomes in the COVID-19 group demonstrated distinct differences when compared to the non-COVID-19 control group. Notably, the COVID-19 group exhibited a higher incidence of some of the adverse outcomes for both mothers and fetuses. A higher number of premature rupture of membranes was notably observed with an incidence of 18.6% in the COVID-19 group vs. none in the comparison group, p = .005. There were no differences in the incidence of preeclampsia

symptoms in both groups. Gestational diabetes was a notable finding in the sample of the study, with higher prevalence in the COVID-19 group (23.3% vs. 4.7%, p = .026). Fetal distress was also more frequent in the COVID-19 group (20.9% vs. 2.3%, p = .015).

Table 3. Comparison of COVID-19 group and comparison group on maternal and fetal outcomes.

Variable	Covid group (n=43)		Comparison group (n=43)		P value
Placenta previa	1	2.3	0	0	1.000
Placenta abruptio	0	0	0	0	-
Premature rupture of membranes	8	18.6	0	0	.005
Postpartum hemorrhage	0	0	0	0	-
Eclampsia	0	0	0	0	-
Preeclampsia	4	9.3	4	9.3	1.000
Gestational diabetes	10	23.3	2	4.7	.026
Stillbirth	0	0	0	0	-
Fetal distress	9	20.9	1	2.3	.015

A. Predictors of maternal and fetal outcomes

To answer aim 4, a logistic regression analysis was conducted with those variables correlated at the bivariate level with p value < 0.1 for the selected maternal and fetal outcomes. Starting with maternal adverse outcomes, maternal mortality, placenta previa and placental abruption, eclampsia and pre-eclampsia, stillbirths and postpartum hemorrhage were not analyzed due to the very few (if any) cases that had these outcomes. The only outcomes that were analyzed were premature birth and fetal distress. The number of predictors entered was limited given the small sample size of 86. For logistic regression, a minimum sample size of at least 100 is needed, with 50 participants per predictor (Bujang et al., 2018). Table 4 shows the results for the regression analysis of premature birth. The variables entered were the grouping variable (COVID-19 versus comparison), gestational diabetes, and fetal distress. Although the variable premature rupture of membranes was significantly associated with premature birth, it was not included as it was strongly correlated with fetal distress, thus causing collinearity in the regression analysis. The Hosmer Lemeshow test was non-significant (p=.817), indicating that the model fit the data and it explained 35% of the variance in premature birth. The model was able to correctly classify 54.5% of the women with premature birth and 96% of women who delivered full term, with an overall 90.7% accurate classification. The only significant predictor was fetal distress, such that presence of fetal distress was associated with 16 times more likelihood of having premature birth.

Table 4. Regression Analysis to Predict Premature Birth.

Predictor	B	SE of B	Wald	P value	Odds ratio	95% CI lower bound	95% CI upper bound
COVID-19	.824	.931	.783	.376	2.280	.367	14.149
Gestational diabetes	.825	.941	.768	.381	2.281	.361	14.423
Fetal distress	2.792	.853	10.901	.001	16.313	3.062	86.898
Constant	-3.274	.762	18.442	<.001	.038		

Legend: CI = confidence interval

A similar analysis was done for fetal distress as the outcome, starting with bivariate analyses using Fisher Exact test and t tests. Variables with p value < 0.1 in the bivariate analysis were then entered into the logistic regression model, namely the grouping variable for COVID 19, premature rupture of membrane, history of prior maternal complications, gravida and premature birth. However, there was collinearity between premature birth and premature rupture of membranes, and between gravida and history of maternal complications, so we excluded premature rupture of membranes and gravida from the analysis. In the 3-variable model, the Hosmer Lemeshow was non-significant (p=.940), indicating that the model fit the data. The model classified correctly 60% of those who had fetal distress and 96.1% of those who did not, with an overall correct classification of 91.9% of the sample. The model explained 52% of the variance in fetal distress. The significant predictors were premature birth and history of prior maternal complications, with having COVID-19 approaching significance with p value between 0.05 and 0.1. The results indicated that women who delivered prematurely were 46 times more likely to experience fetal distress and those with prior maternal complications were 18 times more likely to experience fetal distress; there was also a tendency for women with COVID-19 to have higher risk for fetal

distress. Table 5 shows these results.

Table 5. Regression Analysis to Predict Fetal Distress.

Predictor	B	SE of B	Wald	P value	Odds ratio	95% CI lower bound	95% CI upper bound
COVID-19	2.026	1.163	3.031	.082	7.580	.775	74.116
Premature birth	3.865	1.212	10.103	.001	45.623	4.326	481.131
History of prior maternal complications	2.865	1.212	5.585	.018	17.553	1.631	188.940
Constant	-5.482	1.414	15.032	<.001	.004		

CHAPTER V

DISCUSSION AND CONCLUSION

A. Discussion

This study aimed at examining maternal and fetal outcomes in women who delivered in EHJ in 2021, comparing those who contracted COVID-19 to those who did not throughout their pregnancy. The main results showed that women who contracted COVID- 19 infection during pregnancy were more likely to undergo premature delivery, possibly due to fetal distress. No significant differences were found in maternal adverse outcomes except for premature rupture of membranes, gestational diabetes and fetal distress, which may not necessarily related to COVID-19, as the population of women were young adults in the 3rd decade of life. Most of the women had mild disease, one patient required hospitalization to a regular unit, none of the patients reached the need for intensive care or monitoring. The multivariable analyses showed fetal distress to predict premature birth, whereas fetal distress was predicted by history of prior maternal complications and premature birth.

The sample in this study was in the third decade of life and relatively healthy, as evidenced by the limited frequency of chronic health conditions. Despite reports by the CDC for increased likelihood of hospitalization of pregnant women with COVID-19 infection, only 1 out of the 43 women in our study who contracted COVID 19 required hospitalization but without the need for intensive care. Most women got exposed in the third trimester (mean gestational age of 37 weeks), similar to Yan et al. (2020) study who reported average

gestational age of 38 weeks. In terms of symptoms, 59% had no symptoms as opposed to 23.3% in the study by Panahi et al. (2020). The most frequent symptoms in this study were fever, cough and shortness of breath (each at 30%), in line with Yan et al. (2020). No maternal mortality was reported. To note that EHJ is renowned and highly regarded as private tertiary care center with competent physicians who provide high quality care. Ensuring adequate and timely care impacts the progression of the disease and its effect on the pregnant woman.

Gestational diabetes and anemia were more notable in the COVID-19 group than the control group but the difference was not statistically significant. Additionally, 9.3% of the COVID-19 group had history of coagulopathy versus none in the comparison group but again the difference was not significant. Coagulopathy, coupled with the pathophysiology of COVID-19 and the hypercoagulable state of both the disease and pregnancy in itself, such findings may be correlated, based on the theoretical framework of the study, to the increased incidence of fetal distress and premature birth.

Smith et al. (2022) reported that COVID-19 during pregnancy was associated with a higher likelihood of spontaneous preterm and indicated preterm delivery, relative to term birth. Our study revealed a higher frequency of preterm birth (20.9 vs. 4.7) in our sample of pregnant women exposed to COVID 19, with a rate of premature rupture of membranes significantly higher than the comparison group p=0.005. The rate of preterm birth was lower than what was reported by Di Mascio et al. (2020) and Dube and Kar, who reported rate of 33.3% and 26.4%, respectively. The rate of C section was 37.2% in the COVID 19 and group, which is lower than the rates reported by others; 85.9% by Yan et al. (2020) and 59.9% by Dube and Kar (2020). There are many reasons for these differences, both physiologic and cultural that are beyond the scope of this study; it is worth noting that the rates in this sample

did not differ between the COVID 19 and comparison group. In terms of placental pathology in the COVID-19 group, these were minimal, with only one case of placenta previa, no abruptio and no postpartum hemorrhage. Other maternal complications included 9.3% preeclampsia and 23.3% gestational diabetes.

In terms of fetal outcomes, there was no stillbirth in this sample, whereas Dube and Kar reported a rate of 9.9 per 1000 births. The Apgar score and birth weight could not be retrieved at the time of the study. Fetal distress present in 20.9% of the group of women with COVID 19, which is higher than what was reported by Kyle et al. (2020). Preterm neonates are more susceptible to intrauterine demise due to the hypercoagulable state that COVID-19 and pregnancy poses on the woman's body.

Comparing the maternal and fetal outcomes between the two groups, premature birth, premature rupture of membranes, gestational diabetes and fetal distress were significantly more frequent in the COVID 19 group versus the comparison group. However, these group differences did not hold in the multivariable analyses. The only predictor of premature birth was fetal distress, whereas exposure to COVID-19 was not significant. On the other hand, the predictors of fetal distress were history of previous maternal complications and premature birth, with a trend for a possible association with exposure to COVID 19 ($p = 0.082$). Fetuses of pregnant women who delivered prematurely were 46 times more likely to suffer from intrauterine distress and those with prior maternal complications 18 times more likely to experience fetal distress; also, there seems to have an 8 times higher risk of premature birth in women exposed to COVID 19 than the comparison group, when controlling the other predictors. There were no studies that reported comparisons between exposed and non-exposed women to COVID-19 on maternal and fetal outcomes to refer to. One possible

explanation for the lack of significant effect of exposure to COVID-19 is the mild nature of disease in this sample. Overall, the sample was not sufficient to test our theoretical framework as it was biased to a small mild COVID-19 group (n=43). A larger group with more heterogeneity in COVID-19 status could provide different results, which need to be substantiated with physiologic measures like inflammatory and coagulation markers.

Limitations of the study include the small sample size of women who contracted COVID-19. Given that the sample was restricted to a single institution, and specific special patient population during a time where a lockdown was in place, limited the access to a large pool of patients. To note, given the strict directives by the health authorities during the COVID crisis, and the limited number of critical beds in EHJ, those with severe COVID disease were transferred to governmental hospitals for management. This may have affected the results of our study findings. Furthermore, lack of data available on the electronic medical records of the pregnant women such as neonatal birth weight, Apgar score, etc…, and not controlling for the BMI levels of the pregnant women restricted the predictors of adverse outcomes that could have been examined. Additionally, lack of adequate testing due to fear of contracting the virus while being in a high-risk state may have affected the ability to accurately detect the true incidence of COVID-19 infection in this population. Furthermore, the absence of a significant number of COVID-19 hospitalizations limit the knowledge of disease progression and expectation of adverse outcomes from the progression of the disease.

B. Conclusion

In conclusion, understanding the impact of COVID-19 infection on pregnancy outcomes is of utmost importance in ensuring the health and well-being of both the mother

and the baby. The intersection of COVID-19 and pregnancy has been a subject of intense scrutiny and research in aims of improving our understanding of the implications of this disease on the pregnant female. With the seasonal effects of COVID-19, although reported as less severe now, it is crucial to consider those who contract the disease as high-risk women and to manage and care for them accordingly. Despite the limitation to one center and use of a retrospective design, it is hoped that the significance of the incidence of fetal distress and premature birth guides clinicians into a more intense level of care towards the end of the third trimester. Despite the fact that pregnant women are considered a special patient population, contracting COVID-19 puts them in a more intense, critical, and delicate state. Further studies of large cohort groups are needed to provide a clearer picture on adverse maternal and fetal outcomes that are to be expected when contracting the disease with set clinical guidelines that can be benchmarked globally. There is a big need for more comprehensive research on the topic to provide clear guidance for healthcare providers and patients, and to ensure the best possible outcomes for both mother and baby. With the continued presence of COVID-19 cases globally, it is imperative to understand the implications of the disease on pregnancy outcomes, to ensure that proper treatment protocols are developed and used, and to raise awareness of the possible complications during the course of illness.

APPENDIX

PATIENT DATA COLLECTION SHEET

Age:

Marital status: ☐ Married ☐ Divorced/Separated Para:
Gravida:

Co-morbidities: ☐ Anemia ☐ Thyroid Disease ☐ HTN ☐ DM
☐ Coagulopathy ☐ Asthma/Hyperactive Airway ☐ Other

History of Prior Maternal Complications:

Gestational age at the time of positive PCR test:

Symptoms at the time of positive PCR test: ☐ Fever ☐ Cough ☐ SOB
☐ Sore throat ☐ Rhinorrhea ☐ Loss of taste ☐ Anosmia

Hospitalization for COVID19: Yes/No. If yes length of hospital stays

Regular floor or ICU admission: Yes/No; if yes, how many times during pregnancy

Intubation/mechanical ventilation: Yes/No

Delivery: Term/Preterm. If preterm, gestational age at delivery Mode of delivery: Normal Vaginal Delivery/C-section

Labor problems: ☐ Placenta previa ☐ Placental abruption
☐ Premature Rupture of Membranes ☐ Postpartum hemorrhage

Maternal complications: ☐ Eclampsia ☐ Preeclampsia ☐ Gestational diabetes

Fetal/neonatal complications: ☐ Still birth ☐ Fetal distress

Apgar score at delivery:

Birth weight:

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