
| RESEARCH ARTICLE

COVID-19 Exposure: A Possible Association with Congenital Anomalies and Adverse Neonatal Outcomes

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| ABSTRACT

The impact of COVID-19 exposure on neonatal outcomes has not yet been fully evaluated. This article aimed to find whether COVID-19 exposure was linked to congenital anomalies, and other adverse neonatal outcomes. This was achieved through predetermined criteria which were used to search the Google Scholar database for published literature. Eleven full-length articles, which evaluated neonates born to COVID-19 positive mothers, were included, of which there were review articles, observational studies, one case report, and one case series. Positive reports of congenital anomalies were seen in four of the included articles. However, the other studies reported no congenital anomalies, low risk of congenital anomalies, or did not mention congenital anomalies. It is possible that the included positive reports were unrelated to the presence of COVID-19. Other adverse neonatal outcomes which were reported in the articles included preterm birth, perinatal death, dyspnea, fever, fetal distress, and pregnancy losses. While further research is needed to further ascertain the relationship, current evidence suggests no risk or low risk of congenital anomalies with the presence of COVID-19.

| KEYWORDS

Congenital Abnormalities, Abnormalities, Multiple, Abnormalities, Severe Teratoid, Cardiovascular Abnormalities, Heart Defects, Congenital, Hernias, Diaphragmatic, Congenital, Fetal Anomalies, Deformities, Birth Defects, Congenital, Hereditary, and Neonatal Diseases and Abnormalities

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1. Introduction

A new viral illness emerged in late 2019, which became known as COVID-19 or Coronavirus Disease 2019. The virus proved to be a source of acute respiratory illness (Hu et al., 2020). Early observations revealed that the pandemic has resulted in a decrease of crude birth rates in 18 of 22 countries evaluated (Aassve et al., 2021). It has also been noted that there have been a reduced number of admissions to the neonatal intensive care unit (Liu et al., 2022) and a reduction in preterm births (Leibovitch et al., 2021). The rate of neonatal mortality has increased by 8.7% during this period (Liu et al., 2022).

The World Health Organization has estimated that worldwide, congenital anomalies may result in the death of approximately 240,000 neonates annually. They note that these congenital anomalies are of multi-factorial origin and may include genetic disorders, nutritional deficiencies, environmental factors, and infectious causes (World Health Organization, 2020). Khan et al. (2020) has expressed concern that coronaviruses have been known to cause congenital anomalies and has stressed the importance of collaboration and pooling of knowledge to monitor and prevent these adverse outcomes (Khan et al., 2020).

The occurrence of the COVID-19 pandemic has led to many problems. However, we do not yet fully understand to what extent the exposure to this virus has had an impact on neonatal outcomes. In this review, our primary aim is to evaluate the published literature to determine if COVID-19 infection in mothers leads to an increased occurrence of congenital anomalies. Our secondary aim is to evaluate these articles for other adverse outcomes related to COVID-19.

2. Method and Search Strategy

The Google Scholar database was utilized to obtain the articles which were included in this review. Keywords were identified including "congenital defects" and "covid-19". These were combined with the Boolean operator "AND" to generate a list of articles. The articles underwent title screening, followed by abstract screening to determine relevance. Only articles relevant to the research topic, already published and peer-reviewed, available in the English language, or with an English translation, within the last 5 years were included. Due to the novelty of the COVID-19 virus, all articles obtained were published from 2020 to 2021. The search took place on May 3rd, 2022. A total of eleven articles were after evaluating the first ten pages of search results.

3. Results and Discussion

3.1 Included studies

From the database, eleven articles were identified for inclusion, of which there were three systematic reviews with meta-analysis, three traditional reviews, one case report, three retrospective studies, and one case series.

TABLE 1: Summary of included studies

Author, Year	Participants/Studies	Method	Congenital anomalies	Adverse outcomes reported
(Çakırca et al., 2021)	75 pregnant women	Retrospective single center study	No congenital malformations.	No neonatal mortality, no mother to child transmission.
Di Mascio et al., 2020	19 studies: 79 hospitalized women	Systematic review and meta-analysis of Medline, Clinicaltrials.gov, Cinahl, and Embase.	Not reported.	Preterm birth 41.1% of cases, perinatal death 7.0%
(Fernandes et al., 2022)	-	Traditional review	COVID-19 may be associated with thromboembolism, limb/digit ischemia, as well as placental abnormalities.	-
(Goldshtroum et al., 2020)	7 neonates	Case series	6 infants with congenital heart disease and 1 with congenital diaphragmatic hernia	-
(Iqbal et al., 2020)	-	Traditional review	-	Risk of vertical transmission is low, however other effects such as maternal mental health and stress can lead to effects on fetal brain development
Izewski et al., 2021	515 pregnant women, no neonates tested positive	Retrospective analysis of collected data	Not reported.	No significant differences noted.

Neef et al., 2020	32 studies: 261 neonates	Systematic review and meta-analysis of PubMed/Medline, Google Scholar, and Web of Science	Not reported.	Dyspnea in 42.3%, fever in 19.1%
Papapanou et al., 2021	39 studies, neonates tested positive 1.6-10%	Systematic review and meta-analysis of PubMed, Scopus, and the Cochrane Database of Systematic Reviews	Not reported.	Preterm deliveries 14.3-63.8%. Fetal distress 7.8%-61.1%
Perveen et al., 2020	1 patient	Case report	33-week preterm neonate with purpuric lesions on the left upper limb with nil spontaneous movement, which progressed to necrotic plaques.	-
Salem et al., 2020	-	Traditional review of Medline, Google Scholar.	Current data does not suggest a high risk.	Cannot confirm an association between COVID-19 and risk of maternal, fetal, or neonatal complications.
Woodworth et al., 2020	5,252 pregnant women with 4,442 known outcomes, and 4527 fetuses and infants.	Retrospective study	Not reported.	32 pregnancy losses, 12.9% born preterm

3.2 Is there a connection between COVID-19 exposure and the presence of congenital anomalies?

In our analysis, we sought to find out whether there was a correlation between the presence of congenital anomalies in neonates who were born to mothers who were COVID-19 positive. All the mothers included in the articles were found to be COVID-19 positive when tested. Most of the studies did not routinely test the neonatal population. Papapanou et al. notes that 1.6-10% of the neonatal population in their review tested positive (Papapanou et al., 2021).

Through our search of the medical literature, we were able to find both original and review articles which evaluated the neonatal outcomes. Of the articles found, most did not mention the presence of congenital anomalies within their study populations and thus were not able to aid in answering our primary aim (Di Mascio et al., 2020) (Neef et al., 2020) (Izewski et al., 2021) (Papapanou et al., 2021) (Woodworth et al., 2020). Çakırca et al. reported that no malformations were seen within their study population (Çakırca et al., 2021) while Salem suggested that their data did not indicate a high risk of congenital anomalies (Salem et al., 2020).

There were isolated reports of congenital anomalies. Perveen reported a case of a preterm neonate born with purpuric lesions of the left upper limb, progressing to necrotic plaques, and requiring amputation (Perveen et al., 2020) and Goldshtrom reported a case series of infants born to COVID-19 positive mothers, of which six infants were born with heart disease and one infant was born with a congenital diaphragmatic hernia (Goldshtrom et al., 2020). However, since these congenital anomalies were not detected by the larger studies, it is fair to assume that these occurred independently of COVID-19 exposure.

Iqbal suggested that even though there was a low rate of mother-to-child transmission, other factors may influence neonatal outcomes, including decreased maternal mental health, and subsequent stress, leading to effects on fetal brain development (Iqbal et al., 2020). However, during our perusal of the literature as indicated above, we did not find studies to substantiate Iqbal's claim.

3.3 Other adverse neonatal outcomes

A review of the above articles also lead to possible associations of adverse neonatal and fetal outcomes including preterm birth, perinatal death, dyspnea, fever, fetal distress, pregnancy losses (Di Mascio et al., 2020) (Neef et al., 2020) (Papapanou et al., 2021) (Woodworth 2020). Salem et al. (2020) however, reported that their data cannot be conclusively linked with adverse maternal, fetal, or neonatal outcomes (Salem et al., 2020), while another study reported that among their population of 75 mothers, there were no neonatal mortality outcomes to report, with no noted mother to child transmission (Çakırca et al., 2021).

4. Conclusions

The impact of COVID-19 exposure on neonatal outcomes has not been fully evaluated. This article sought to find whether COVID-19 exposure was linked to congenital anomalies, and other adverse neonatal outcomes. This was achieved using predetermined search criteria of the Google Scholar database. Positive reports of congenital anomalies were seen amongst four included studies. However, the other studies reported no congenital anomalies, low risk of congenital anomalies, or did not mention congenital anomalies. It is possible that the included positive reports were unrelated to the presence of COVID-19. Other adverse neonatal outcomes included preterm birth, perinatal death, dyspnea, fever, fetal distress, and pregnancy losses. While further research is needed to further ascertain the relationship, current evidence suggests no risk, or a low risk of congenital anomalies with the presence of COVID-19.

4.1 Aims and further prospects

While there were a few reported congenital anomalies such as limb abnormality, congenital diaphragmatic hernia, and congenital heart disease, the impact of COVID-19 leading to congenital abnormalities remains inconclusive. While it is possible that these birth defects were not related to COVID-19, it is also true that many studies, including systematic reviews and meta-analyses did not include congenital abnormalities within the scope of their study, so the primary aim could not be conclusively determined. Thus, it would be useful for future studies to focus on evaluating COVID-19 exposure to determine if there is a link between COVID-19 and congenital abnormalities. We were able to determine through our review, that there were other adverse neonatal outcomes related to COVID-19 exposure such as preterm birth, perinatal death, dyspnea, fever, fetal distress, and pregnancy loss.

4.2 Limitations

Some limitations existed in writing this paper. These included the limitation of articles to those that have been published, peer-reviewed, in the English language, and not including more databases. Due to the novelty of the COVID-19 infection, many possible defects may not have been published yet or thought to be possibly linked to the virus. Of the articles, some did not make any comment on congenital anomalies.

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