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Effects of COVID-19 Virus Infection on Pregnancy Outcomes: a Systematic Review and Meta-analysis

Upendra Pandit,[1] Niki Shrestha,[2] Gayatri khanal[3]

[1]Department of Obstetrics and Gynecology, Chitwan Medical College, Chitwan, Nepal,[2]Department of Community Medicine, Chitwan Medical College, Chitwan, Nepal, [3]School of Public Health and Community Medicine, Chitwan Medical College, Chitwan, Nepal.

ABSTRACT

Background: Pregnant mothers are more susceptible to Corona Virus Diseases 2019 (COVID-19) during pandemic. Our aim was to find out the effects of the COVID-19 infection on pregnancy outcomes compared to mothers without COVID-19 diseases.

Methods: The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) and obtained number of the Centre for review and Dissemination (CRD42021272321). The observational studies from September 1st to October 31, 2021 were searched with Medical Subject Heading (MeSH) term in the databases. A Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline was followed. Certainty of the evidence were assessed using Grading of Recommendations Assessment Development and Evaluation (GRADEpro) approach.

Results: Pregnant women with Polymerase Chain Reaction (PCR) positive group for COVID-19 were likely to have preeclampsia/eclampsia of Relative Risk (RR) and Confidence Interval (CI) (RR, 1.52; 95% CI, 1.14-2.02) respectively. Likewise, foetal distress (RR, 1.56; 95% CI, 1.31- 1.85, caesarean section (RR, 1.25; 95% CI, 1.10-1.42), postpartum haemorrhage (RR, 1.37; 95%CI, 1.00-1.88), moderate certainty of the evidence in ICU/high-dependency unit admission (RR, 4.92; 95% CI, 3.28- 7.38), preterm births (RR, 2.12; 95% CI, 1.10-4.08) and perinatal death (RR, 2.55; 95% CI, 1.64-3.95). Very wide CI on maternal death rate (RR 9.87; 95% CI, 3.10- 31.45) was observed compared to COVID-19 negative group.

Conclusions: Pregnant mothers with COVID-19 positive diseases have a moderate certainty of the effect of admission to ICU/high-dependency unit, Preterm birth and perinatal death.

Keywords: Childbirth; complications; COVID-19; maternal; neonates

INTRODUCTION

The World Health Organization declared a pandemic due to the contagious spread of COVID-19 diseases in March 2020. Since then, the world still has been responding against COVID-19. Maternal mortality ratio has increased from 13.19% to 22.93% due to the COVID-19 diseases and its complications in the index pregnancy.[1,2] The new variants of COVID-19 "Delta" and "Omicron" had hit hard.

Pregnant mothers were more susceptible to COVID-19 infection primarily because pregnancy is an immune-suppressive state where various hormonal changes predispose to COVID-19 infection.[3,4] Physiological changes and immunological response can increases the risk to acquire more severe diseases from respiratory diseases like SARS-CoV-2 virus infection in the pandemic.[5] COVID-19 diseases have scaled up the obstetric challenges and adverse effects on pregnancy outcomes especially in low resource settings following the pandemic.

There have been very few studies as well as inconclusive outcome data reflecting the quality of the evidence in pregnancy, which would be applicable in clinical practice. The objective of this review was to find out the effects of the COVID-19 diseases on pregnancy outcomes compared to mothers without COVID-19 irrespective of

Correspondence: Dr Upendra Pandit, Department of Obstetrics and Gynecology, Chitwan Medical College, Chitwan, Nepal. Email address: drupandit@gmail.com,Phone: +9779848032739.

the severity of the symptoms and diseases, following the pandemic.

METHODS

This was a systematic review and meta-analysis of observational studies searched in the databases: PubMed/MEDLINE, Google Scholar, Embase and CINAHL from September 1, 2021 to October 31, 2021. PRISMA guideline was followed throughout the review and Meta-Analysis.

Protocol Registration

The review protocol was registered in PROSPERO on 11 August 2021, and is available online at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021272321,

Inclusion Criteria

We included observational studies (comparative, case control and cohort studies) published in the English language for the assessment of effects on pregnancy outcomes following exposure to COVID-19 diseases. Those observed articles to have at least one pregnancy outcome with comparative data were included for review and meta-analysis.

Study participants

All pregnant mothers with a PCR result of COVID-19 infection concurrently at gestational age 20 weeks to full term (42 weeks) or neonatal cases of age range from birth to one month during admission in the hospital or health centre in a specific time period following pandemic.

Exclusion Criteria

Non pregnant women, paediatric population, case reports, previous systematic reviews, articles included in other systematic reviews, articles with lack of comparable data were excluded in this review and Meta-Analysis.

Search strategy

The advance searches were conducted by UP and GK using medical subject heading terms and keywords such as COVID-19 infection, SARS-CoV-2 infection, pregnancy, gestation, childbirth, maternal, outcomes, neonates, vertical transmission, maternal to foetal transmission and delivery in databases (PubMed/MEDLINE, Google Scholar, Embase and CINAHL) from September 1, 2021 to October 31, 2021. The detail of the search history is shown in the search history (Supplementary file 1).

Study selection

Twenty-two thousand studies were retrieved from the searched databases for screening. Studies were screened for title, abstract, duplicates and imported in Zotero software. Problems and discrepancies were resolved with mutual consent obtained among authors. The detailed of selected studies, including the country of the study, study design, sample size, population, exposure, comparison and outcomes were noted.

Data extraction and analysis

Comparative data of COVID-19 positive group and negative group of all maternal, foetal, and neonatal outcomes including co-morbidities during the management of antenatal, intra-natal and postnatal period of the late pregnancy were included. The respective data were retrieved using Review Manager (version 5.4.1). The comparative data and measurement of at least one outcome in maternal, foetal or neonatal outcome was obtained for the statistical analysis. Quantitative meta-analysis was done for an outcome if more than one study presented the comparative data. A random-effect estimate of the pooled risk ratio was calculated using Mantel-Haenszel method and presented in forest plots including risk of bias showing individual study.

Risk of bias assessment

Methodological quality and risk of bias was assessed using the ROBINS-I tool for non-randomized studies composite of seven domains given in the Review Manager (version 5.4.1) (supplementary file 2). We calculated the pooled risk ratio (RR) in random effects models for meta-analysis of maternal comorbidities, maternal outcomes and neonatal outcomes. The certainties of the evidences were assessed using GRADE pro.

RESULTS

A total of 132 full text articles were reviewed with title and abstract, and outcomes comprising comparative data. Out of those, 18 articles met the inclusion criteria.[6-23] One hundred thirteen articles were excluded because 16 were systematic reviews, 72 were without comparative data, and 25 were without the outcome of interest (Figure 1).

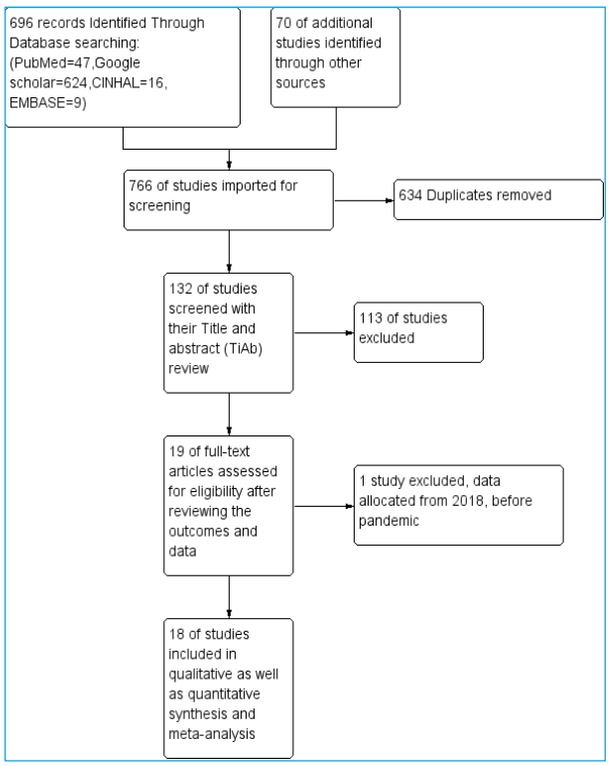

Figure 1. PRISMA flowchart

Out of the 18 studies, 7 were observational with comparative data, two studies were case - control and 9 prospective/retrospective cohorts; including one multinational study. There were 15 studies comparing pregnancy outcomes between positive vs. negative for COVID-19 infection. Three studies included study population comprised of neonates born from COVID-19 positive or negative pregnant mothers. The characteristics of the studies are presented in supplementary files (supplementary file 3). The methodological quality and bias of included studies are presented elsewhere.

Pregnant women with PCR positive for COVID-19 had an increased risk but low certainty of the evidences in co-morbidity of obesity (RR 1.74; 95% CI, 0.86 to 3.53) based on the pooled data of 4 studies, preeclampsia/eclampsia (RR, 1.52; 95% CI, 1.14-2.02), gestational diabetes (RR, 1.13; 95% CI, 0.97- 1.31) and hypertensive disorders (RR, 1.07; 95% CI, 0.82 - 1.39) (Table 1).

Pregnant women had an increased risk but low certainty of the evidence was observed for foetal distress (RR, 1.56; 95% CI, 1.31- 1.85), caesarean section (RR, 1.25; 95% CI, 1.10-1.42) (Figure 2), and postpartum haemorrhage (RR, 1.37; 95%CI, 1.00-1.88) with PCR positive compared to the PCR negative group (Table 1)

Moderate certainty of the evidence was observed in COVID positive group who had an increased risk of admission to ICU/high-dependency unit (RR, 4.92; 95% CI, 3.28- 7.38), preterm births (RR, 2.12; 95% CI, 1.10-4.08) and perinatal death (RR, 2.55; 95% CI, 1.64-3.95) compared to COVID-19 negative group (Figure 5). A very wide confidence interval was observed in maternal death (RR 9.87; 95% CI, 3.10- 31.45) (Figure 3)

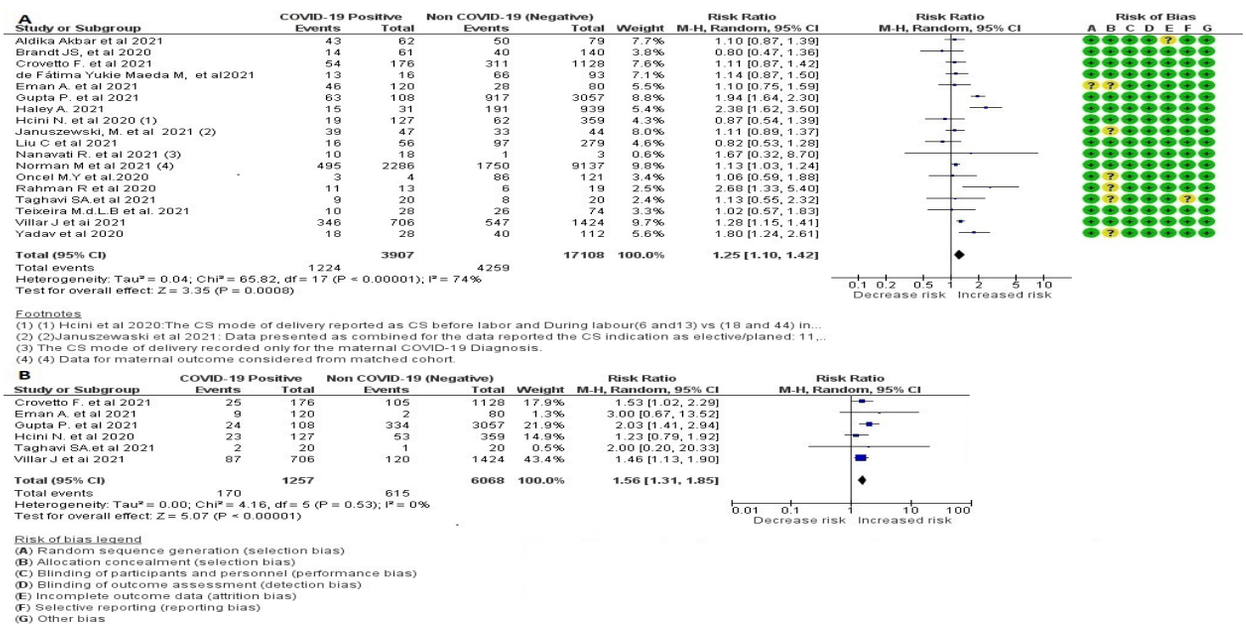

Figure 2. Forest plot showing maternal outcome. (A) Caesarean Section (B) Foetal distress.

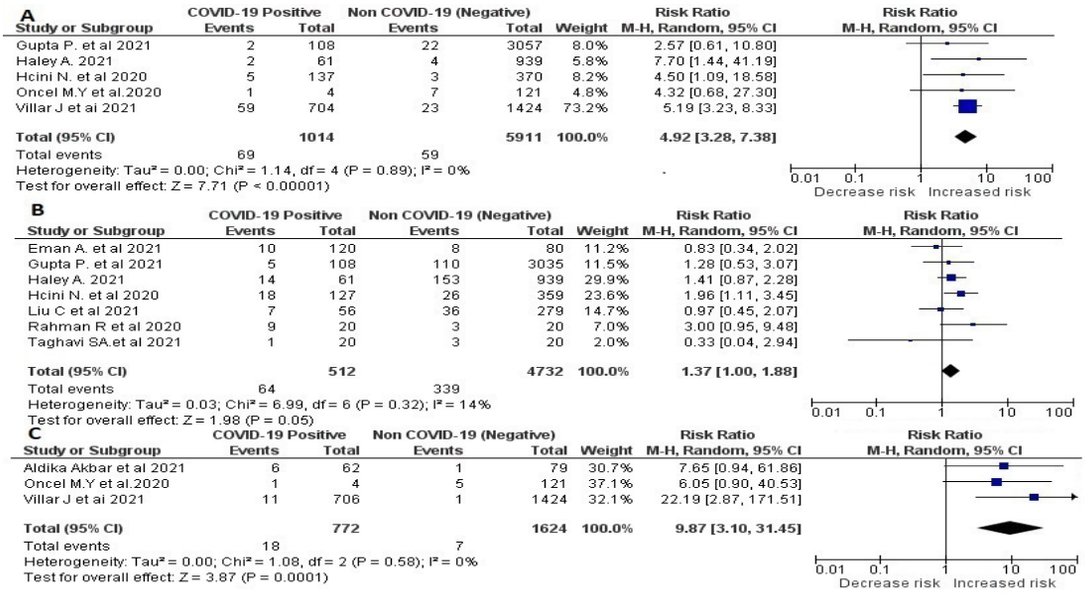

Figure 3. Forest plot showing maternal outcomes. (A) Mother admitted to ICU (B) Postpartum haemorrhage (C) Maternal death.

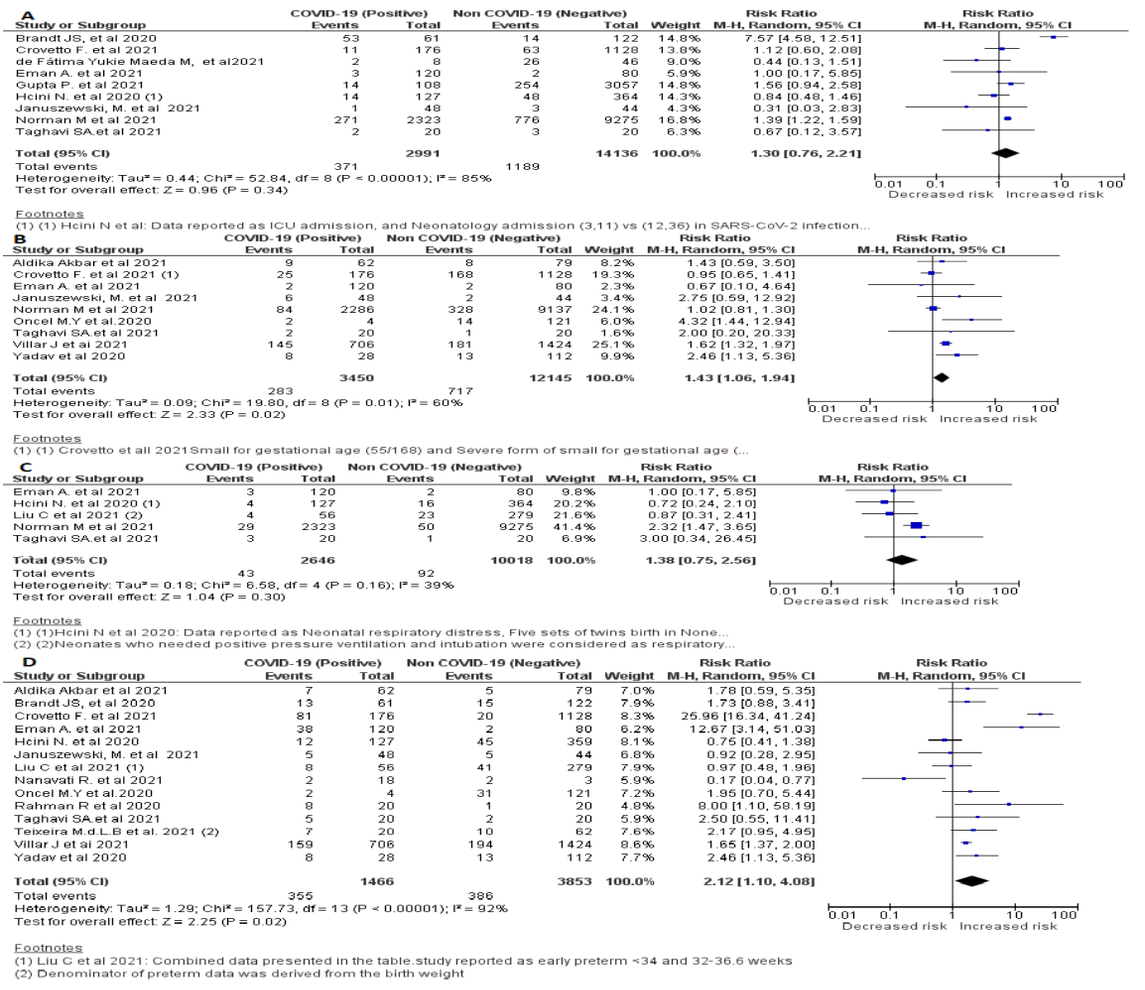

Figure 4. Forest plot showing neonatal outcomes. (A) NICU admission (B) low birth weight (C) Neonatal respiratory distress (D) Premature birth.

Mother with COVID-19 positive diagnosis had an increased risk of their neonates having a birth Apgar Score <7 in one minute (RR, 1.19; 95% CI, 0.73-1.94) and having an Apgar Score <7 in 5 minutes (RR, 1.41; 95% CI, 1.09-1.82) (Table 1).

Further analysis of the other variables regarding maternal and neonatal outcomes are presented in supplementary files (Supplementary file 4). The comprehensive data of outcomes, no of participants/studies, the certainty of the evidence, relative effect, risk with COVID-19 negative and risk difference with COVID-19 positive are presented in Table 1.

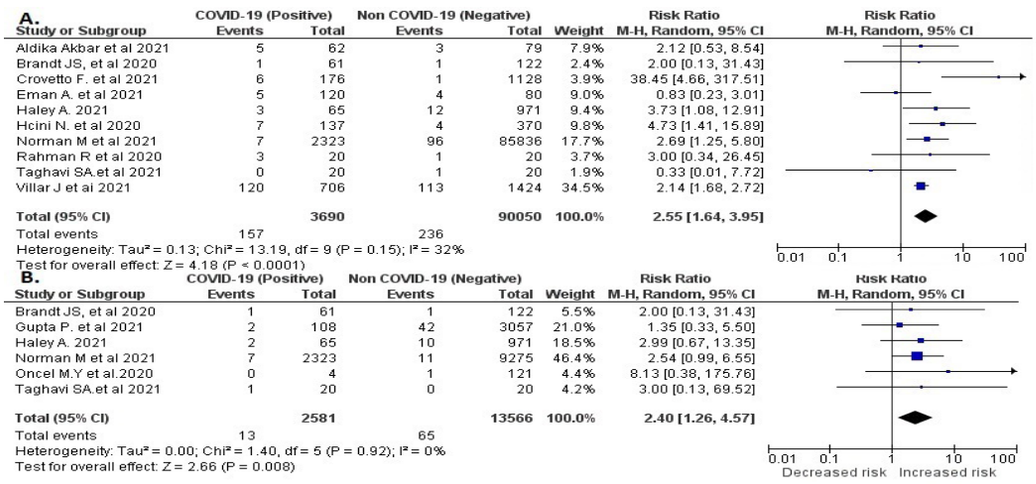

Figure 5. Forest plot of neonatal outcomes. (A) Perinatal death (B) Neonatal death.

Table 1. Showing summary of pooled results using random effect models and certainty of the evidence.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with COVID-19 /SARS-COV-2 Positive Negative	Risk difference with COVID-19 /SARS-COV-2
Pregnancy Induced Hypertension (PIH)	2270 (2 observational studies)	Low	**RR 1.46** (1.07 to 2.01)	52 per 1,000	**24 more per 1,000** (4 more to 53 more)
Hypertensive Disorders	4949 (6 observational studies)	Low	**RR 1.07** (0.82 to 1.39)	159 per 1,000	**6 more per 1,000** (38 fewer to 67 more)
Preeclampsia/ Eclampsia	5406 (9 observational studies)	Low	**RR 1.52** (1.14 to 2.02)	81 per 1,000	**42 more per 1,000** (11 more to 83 more)
Gestation Diabetes (GDM)	15172(5 observational studies)	Low	**RR 1.13** (0.97 to 1.31)	78 per 1,000	**10 more per 1,000** (2 fewer to 24 more)
Prelabour Rupture of Membrane (PROM)	3170 (3 observational studies)	Low	**RR 1.23** (0.62 to 2.43)	146 per 1,000	**34 more per 1,000** (55 fewer to 209 more)
Abnormal Foetal Growth in 20-24 weeks	1504 (2 observational studies)	Low	**RR 0.83** (0.20 to 3.45)	7 per 1,000	**1 fewer per 1,000** (5 fewer to 16 more)
Foetal Distress/ AbnormalFoetal Heart Rate (Intrapartum)	7325 (6 observational studies)	Low	**RR 1.56** (1.31 to 1.85)	101 per 1,000	**57 more per 1,000** (31 more to 86 more)
Preterm Labor	4500 (3 observational studies)	Low	**RR 3.34** (0.12 to 91.70)	30 per 1,000	**71 more per 1,000** (27 fewer to 2,758 more)

Corioamnionitis	1183 (2 observational studies)	Low	**RR 1.29** (0.41 to 4.04)	30 per 1,000	**9 more per 1,000** (18 fewer to 92 more)
Surgical Intervention/ (C.Section) for Delivery	21015 (18observational studies)	Low	**RR 1.25** (1.10 to 1.42)	249 per 1,000	**62 more per 1,000** (25 more to 105 more)
Postpartum haemorrhage (PPH)	5244 (7 observational studies)	Low	**RR 1.37** (1.00 to 1.88)	72 per 1,000	**27 more per 1,000** (0 fewer to 63 more)
Mother Admission to ICU/HDU	6925 (5 observational studies)	Moderate	**RR 4.92** (3.28 to 7.38)	10 per 1,000	**39 more per 1,000** (23 more to 64 more)
#Maternal Death	2396(3 observational studies)	High	**RR 9.87** (3.10 to 31.45)	4 per 1,000	**38 more per 1,000** (9 more to 131 more)
Apgar Score abnormality (<7) in One minutes of Birth	772 (3 observational studies)	Low	**RR 1.19** (0.73 to 1.94)	79 per 1,000	**15 more per 1,000** (21 fewer to 75 more)
Apgar Score abnormality (<7) in Five Minutes of Birth	15314 (6 observational studies)	Low	**RR 1.41** (1.09 to 1.82)	22 per 1,000	**9 more per 1,000** (2 more to 18 more)
Preterm Birth/ Premature delivery <37 weeks	5319 (14 observational studies)	Moderate	**RR 2.12** (1.10 to 4.08)	100 per 1,000	**112 more per 1,000** (10 more to 309 more)
Neonatal Respiatoy Distress/Ashyxia	12664 (5 observational studies)	Low	**RR 1.38** (0.75 to 2.56)	9 per 1,000	**3 more per 1,000** (2 fewer to 14 more)
Neonates Admission in HDU/NICU	17127 (9 observational studies)	Low	**RR 1.30** (0.76 to 2.21)	84 per 1,000	**25 more per 1,000** (20 fewer to 102 more)
Small baby for gestational age (IUGR)/ Low birth weight	15595 (9 observational studies)	Low	**RR 1.43** (1.06 to 1.94)	59 per 1,000	**25 more per 1,000** (4 more to 55 more)
Neonatal PCR Positive within 24-72 hours of Delivery	14948 (4 observational studies)	Low	**RR 5.45** (0.29 to 103.49)	0 per 1,000	**1 more per 1,000** (0 fewer to 25 more)
Neonatal Sepsis	12634 (2 observational studies)	Low	**RR 1.44** (0.52 to 3.98)	4 per 1,000	**2 more per 1,000** (2 fewer to 13 more)
Perinatal Death /IUFD	93740 (10 observational studies)	Moderate	**RR 2.55** (1.64 to 3.95)	3 per 1,000	**4 more per 1,000** (2 more to 8 more)
Neonatal Death	16147 (6 observational studies)	Moderate	**RR 2.40** (1.26 to 4.57)	5 per 1,000	**7 more per 1,000** (1 more to 17 more)

**The risk in the PCR positive group (and its 95% confidence interval) is based on the assumed risk in the PCR negative group and the relative effect of the exposure (and its 95% CI). # Maternal Death with very high Confidence interval indicates few information available for the comments. CI: confidence interval; RR: risk ratio*

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

DISCUSSION

In the review, it demonstrated that pregnant women with COVID-19 positive were at significant risk of adverse pregnancy outcomes and complications, including caesarean section. It indicates an increased risk of pregnancy complications in this group compared to negative test result of COVID-19.[24] The other adverse effects were the abnormal foetal heart rate or foetal distress, postpartum haemorrhage and increased risk for admission of mothers to intensive care unit or high dependency unit.

Notably, pregnant women with COVID-19 positive had pre-existing co- morbidities such as hypertensive disorders, preeclampsia, gestational diabetes and obesity.[25] These conditions put them into high risk to acquired severe diseases and could be accountable for the pregnancy complications. These co-morbidities contribute to compromise in kidney functions in COVID-19 positive mothers. The COVID-19, itself is a systemic inflammatory responsive disease which leads to vascular changes in placenta at foetal-maternal interface that ultimately predisposes to preeclampsia [26-28] like features, low birth weight and abnormal foetal heart pattern in neonates. The COVID positive group had an increased risk of preterm birth compared to the negative group. However, a systematic review done by Chmielewska[29] indicated that the preterm birth before the pandemic versus during the pandemic did not change globally.

The maternal mortality rate was observed to be very high in the group of pregnant women with COVID-19.[30,31] The death rates were perhaps increased in the countries which have limited resources and lack of preparedness to deal with obstetrics emergencies during the pandemic. Thus, unavailability of extensive intensive care services may be the indirect but avoidable cause of maternal mortality in these countries. But, wide range of confidence interval indicates the needs further information regarding effects of maternal death.

The risk of neonatal complications includes low Apgar Score <7 in 1 and 5 minutes, neonatal respiratory distress, neonatal admission in neonatal intensive care unit or high dependency unit and neonatal PCR Positive within 24-72 hours of delivery.[32,33] Perinatal death and neonatal death were also substantially higher in the group of pregnant women with COVID-19 positive group. Our overall results were consistent with the findings in a recent systematic review.[34- 36]

Implications for clinical practice

Out of all pregnancy outcomes, maternal death due to COVID-19 infection in pregnancy has wide confidence interval and high certainty of the evidence.[34] The antenatal care promotion including vaccination, is necessary to identify those co-morbidities beforehand and institute preventive strategies for severe illness and its transmission.[37-40] But further information is needed regarding wide range of confidence interval in the effect of maternal death.

There is moderate certainty that an infected mother gets admission in an intensive care unit and risk for preterm delivery. The adequate number of intensive care units with the provision of foetal surveillance and intensive neonatal care incubators for very sick neonates is required for quality care particularly in low resource setting countries. Similarly, promotion and protection of life saving intervention such as Kangaroo Care Method (KCM).[41, 42] Knowledge of infection prevention practices to prevent mother to child transmission of COVID-19 virus horizontally or vertically should be imparted to stakeholders and service providers in relevant institution.[43] Vaccination against COVID-19 for premature and low birth weight babies would be the subject for future research.

Although very wide confidence interval indicates very few statistical information was observed in maternal death, moderate certainty of the evidence in perinatal death require comprehensive maternal and neonatal care provision to scale down the death risk under one window at primary health care level rather than frequent referral and transfer of the infected patient.[44,45]

CONCLUSIONS

Pregnant mothers with COVID-19 positive diseases have a moderate certainty of the effect of admission to ICU/ high-dependency unit, Preterm birth and perinatal death. We have observed very high range of confidence interval on the effects of maternal death that indicates insufficient data coverage.

Significant statistical heterogeneity and clinical heterogeneity was observed in most of the pooled effects of the outcomes. However, subgroup or sub-sets analysis of pregnancy population and neonates is beyond the scope of this review.[46-48] Likewise, very few studies and inconsistent outcomes were available for the funnel plot in this meta-analysis.[49,50] Although the GRADE is recommended for its use in intervention effect, for the first time probably the GRADE has been used in pregnancy and childbirth domain for this review of COVID-19 pandemic.[51]

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DECLARATIONS OF INTEREST

Authors declared that there is no conflict of interest in this review process.

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