Clinical Manifestation and Maternal Complications and Neonatal outcomes in Pregnant Women with COVID 19: An Update a Systematic Review and Meta-analysis

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Abstract

Background Existing evidence indicates that the risk of obstetric and perinatal outcomes is higher in women with coronavirus infection. outbreaks suggest that pregnant women and their fetuses are particularly susceptible to poor outcomes. However, there is little known about pregnancy related complications and co-morbidity in this group of women. Therefore, this, systematic review and meta-analysis performed in order to find out whether COVID-19 may cause different manifestations and outcomes in antepartum and postpartum period or not.

Methods We searched databases, including Medline (PubMed), Embase, Scopus, Web of sciences, Cochrane library, Ovid and CINHAL to retrieve all articles reporting the prevalence of maternal and neonatal complications, in addition clinical manifestations, in pregnant women with COVID 19 that published with English language from January to April 2020. Results 11 studies with total 177 pregnant women included in this systematic review.

Results show that the pooled prevalence of neonatal mortality, lower birth weight, stillbirth, premature birth, and intrauterine fetal distress in women with COVID 19 were 4% (95% CI: 1 - 9%), 21% (95% CI: 11 – 31%), 2% (95% CI: 1 - 6%), 28% (95% CI: 12 - 44%), and 15% (95% CI: 4 - 26%); respectively. Also the pooled prevalence of fever, cough, diarrhea and dyspnea were 56% (95% CI: 30 - 83%), 30% (95% CI: 21 - 39%), 9% (95% CI: 2 - 16%), and 3% (95% CI: 1 - 6%) in the pregnant women with COVID-19.

Conclusion According to this systematic review and meta-analysis, the pregnant women with COVID-19 with or without pneumonia, are at a higher risk of pre-eclampsia, preterm birth, miscarriage and cesarean delivery. Furthermore, the risk of LBW and intrauterine fetal distress seems increased in neonates.

Introduction

The global pandemic due to coronavirus has become a major burden in the world infecting over a million patients (1). There are six different CoV strains in humans of which, severe respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory Syndrome (MERS-CoV) are the most known types (2). Coronavirus is an enveloped and single-strained ribonucleic acid having 9–12 nm-long surface spikes. One of the four major proteins on the envelope binds to angiotensin converting enzyme2 (ACE2) receptor for entering the host cell (3, 4). It was first reported in Wuhan, China, in December 2019, causing a spectrum of symptoms from asymptomatic to death which are mostly nonspecific. Respiratory signs and symptoms accompanied with some other manifestations such as fever, sore throat, cough, diarrhea, nausea, vomiting are the common symptoms of COVID-19 (5, 6). In blood test assay, patients might have lower blood cell counts (Lymphopenia, thrombocytopenia,(and increased C-reactive protein level, erythrocyte sedimentation rate, lactate dehydrogenase, creatinine, and a prolonged prothrombin time (7, 8). It can be transmitted through human-to-human contacts mainly by respiratory droplets (9).

According to the knowledge currently available in the literature about the susceptibility of pregnant women to SARS-CoV and MERS-CoV, it seems that there should be a great attention to the coronavirus

infection in pregnancy (10). There are several physiological changes during pregnancy which can make the mother more susceptible to severe infections (11). The converted function of cardiorespiratory and immune system, physiologic dyspnea due to increased maternal oxygen demands, the alteration in pulmonary demands can put pregnant women at the risk of severe infection and hypoxic compromise as well as misdiagnosis and mismanagement of routine upper respiratory tract symptoms (12, 13). Since there is a great amount of ACE2 receptor expressed in the placenta, the scientists are concerned about the possibility of vertical transmission (14, 15).

In this article, we have evaluated several factors such as maternal and neonatal complications, therapeutic managements, signs and symptoms in pregnant women in a systematic review and meta-analysis in order to find out whether COVID-19 may have a different manifestation and outcome in antepartum and postpartum period or not.

Methods

This systematic review and meta-analysis was performed according to the Meta-Analyses of Observational Studies in Epidemiology (MOOSE) and Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for reviews of analytical observational studies (16, 17).

Search Strategy and Screening

All original published articles were searched in international databases, including Medline (PubMed), Embase, Scopus, Web of science, Cochrane library, Ovid and CINHAL to retrieve all articles reporting the prevalence of maternal and neonatal complications, therapeutic managements, signs and symptoms in pregnant women with COVID 19. Researchers performed a search of these databases, with hand searching through the reference lists and grey literature. We searched in these search engines without language limitations from January to April 2020. The search protocol developed based on four main roots of “Maternal Complications”, “Neonatal Complications”, “Signs” and “Therapeutic Management”. All related components to these keywords were “Maternal Complications” (“Preeclampsia”, “Preterm Labor”, “Gestational Diabetes”, “Infections”, “Hypertension”, “Fetal Distress”, “Cesarean”, “Vaginal Delivery”, and “Stillbirth”), “Neonatal Complications” (“Lower Birth Weight”, “C Reactive Protein”, “Liver Function Test”, “Intrauterine Fetal Distress”, “Premature Birth”, “Neonatal Mortality”, and Lymphopenia), “Signs” (“Fever”, “Caught”, “Malaise”, “Dyspnea”, “Myalgia”, “Sore Throat”, and “Diarrhea”) and “Therapeutic Management” added to searched queries based on scientific Mesh terms, EMTREE. Reference Manager bibliographic software was used to manage searched citations. Duplicate entries were searched by considering the title of the published papers, authors, the year of publication, and specifications of the sources types. In questionable records, the texts were compared. We reviewed the primary search results, and after reviewing each article by title and available abstract, some of the articles were eliminated. The evaluation of the papers under consideration was based on the inclusion and exclusion criteria by the two researchers, separately (YM, MS).

Eligibility Criteria

We included all observational studies which assessed the prevalence of maternal and neonatal complications, therapeutic managements, signs and symptoms in pregnant women with COVID 19. We excluded duplicate citations non-peer-reviewed, articles that the abstract and full text was not available, and other languages.

Data Extraction

After three steps of assessment for titles, abstracts and full texts, the full text of each selected article was retrieved for detailed analysis. Data were extracted using a checklist recording authors, publication year, type of study, total of sample, gestational age, cesarean, vaginal delivery, chronic illness, indicators of cesarean, complications of pregnancy, Signs and symptoms (fever on admission, cough, malaise, dyspnea, myalgia, sore Throat, diarrhea, nausea and vomiting, fetal movement, fetal heart rate, vaginal bleeding, premature rupture of membrane, antepartum, post-partum), laboratory tests, imaging, treatment and other parameters (abnormal Laboratory test, imaging, Bio Physical Profile, maternal mortality, maternal ICU admission, neonatal mortality, intrauterine fetal death, vertical transmission, treatments), and infant characteristics (birth weight, low birth weight, premature birth, Apgar score, intrauterine fetal distress, severe neonatal asphyxia, neonatal death, fetal death or stillbirth). All processes from systematic search to final data extraction were followed independently by two research experts (YM, MS) (Kappa statistic for agreement for quality assessment; 0.97). Probable discrepancies were resolved by the main investigator.

Risk of Bias

Qualitative evaluation of studies based on the Newcastle-Ottawa Quality Assessment Scale (NOS) (18) was performed by two of the authors (YM and MS). This scale is designed to evaluate the qualitative evaluation of observational studies. NOS examines each study by six items in three groups; selection, comparability, and exposure. Stars are given to each item and the maximum score is 9. In case of differences in the score assigned to the published articles, the external discussion method will be used. Finally, the articles were categorized as low, moderate and high risk. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist was also completed for all articles (19, 20).

Statistical analysis

The random effects model was applied to calculate the pooled prevalence with 95% confidence interval (95%CI) with Metaprop order. Heterogeneity across studies was evaluated using I2 value and reported as a percentage (%) to determine the extent of variation between-studies. A forest plot was used to schematically present the meta-analysis results. The Egger’s test and funnel plot were used for evaluating the publication bias. In addition, a subgroup analysis was done to identify different sources of heterogeneity. Statistical analysis was performed using STATA 16.0 (Stata Corp, College Station, TX, USA), and statistical significance was considered P-Value < 0.05.

Results

Study characteristics

306 articles were initially retrieved on the basis of the search strategies in the online databases. Among these articles, 97 duplicate publications were identified and removed. The remained ones were screened according to the titles and abstracts. 11 articles were selected as the final papers to be analyzed (Figure 1). The characteristics of 11 selected studies were demonstrated in Table 1. A total number of 177 pregnant women with COVID-19 were evaluated all in 2020 through 8 retrospectives, 1 case control, and 2 case report studies. The factors assessed in these studies involve gestational age, cesarean, vaginal delivery, chronic illness, indicators of cesarean, complications of pregnancy, signs and symptoms (fever on admission, cough, malaise, dyspnea, myalgia, sore throat, diarrhea, nausea and vomiting, fetal movement, fetal heart rate, vaginal bleeding, premature rupture of membrane, antepartum, post-partum), laboratory tests, imaging, treatment and other parameters (abnormal laboratory test, imaging, Bio Physical Profile, maternal mortality, maternal ICU admission, neonatal mortality, intrauterine fetal death, vertical transmission, treatments), and infant characteristics (birth weight, low birth weight, premature birth, Apgar score, intrauterine fetal distress, severe neonatal asphyxia, neonatal death, fetal death or stillbirth) (Table 1). Some studies had not reported the method of treatment. The studies which have reported the therapies applied for the patients have used both antibiotics and antivirals such as Oseltamiovir, Ganciclovir, Azithromycin and Ceftazidime. Two studies have used corticosteroids and two studies have used Chinese traditional medications which both of them had not explained about any benefits for the patients.

Quantitative analysis

Pooled prevalence of signs and symptoms in pregnant women with COVID 19

The least reported prevalence of fever in pregnant women with COVID 19 was 17% (95% CI: 2 - 33%) in the study by Wang X. et al. and the highest fever as prevalence was recorded 86% (95% CI: 60- 98%) in the retrospective study by Yu. et al. In total, the pooled prevalence of fever has been estimated as 56% (95% CI: 30 - 83%; I^2= 92.02%; P -Value < 0.01) (Figure 2 and Table 2). The Meta Regression was used to explore relationship of independent variables (age and gestational age) with the pooled prevalence of primary outcomes. The results of Meta regression showed that the prevalence of fever has not any relationship with age (coefficient: 0.029, P: 0.293, 95% CI: -0.026, 0.032), and gestational age of pregnant women with COVID 19 (coefficient: 0.023, P: 0.451, 95% CI: -0.021, 0.026).

The pooled prevalence of cough has been estimated as 30% (95% CI: 21 - 39%; I^2= 0.0%; P -Value = 0.37) (Figure 3 and Table 2). The least reported prevalence of cough in pregnant women with COVID 19 was 14% (95% CI: 12 - 40%) in the study by Yu. et al. and the highest prevalence was recorded 55% (95% CI: 25- 84%) in the retrospective study by Liu. et al (Figure 3). The results of Meta regression showed that the prevalence of cough has relationship with age (coefficient: 0.08, P: 0.001, 95% CI: 0.005, 0.010), and gestational age of pregnant women with COVID 19 (coefficient: 0.007, P: 0.001, 95% CI: 0.006, 0.011).

Also the pooled prevalence of dyspnea has been estimated as 3% (95% CI: 1 - 6%; I^2= 0.0%; P -Value = 0.76) (Figure 3 and Table 2). The least and highest reported prevalence of dyspnea in pregnant women with COVID 19 was 2% (95% CI: 2 - 5%) and 50% (95% CI: 19 - 95%), respectively (Figure 4 and Table 2). The results of Meta regression showed that the prevalence of dyspnea has relationship with age (coefficient: -0.0178, P: 0.046, 95% CI: -0.035, -0.000), and gestational age of pregnant women with COVID 19 (coefficient: -0.099, P: 0.326, 95% CI: -0.298, 0.099).

The pooled prevalence of myalgia, sore throat, and diarrhea in pregnant women with COVID 19 were 18% (95% CI: 1 - 35%, I^2= 49.84%; P -Value = 0.14), 7% (95% CI: 1 - 13%, I^2= 0.0%; P -Value = 0.55), and 9% (95% CI: 2 - 16%, I^2= 0.0%; P -Value = 0.97), respectively (Table 2). The results of Meta regression showed that the prevalence of myalgia, sore throat, and diarrhea have not any relationship with age and gestational age of pregnant women with COVID 19.

Pooled prevalence of infant characteristics in pregnant women with COVID 19

The least reported prevalence of premature birth in pregnant women with COVID 19 was 8% (95% CI: 1 - 16%) in the study by Schwartz. et al. and the highest premature birth as prevalence was recorded 50% (95% CI: 19 - 81%) in the retrospective study by Guo. et al. In total, the pooled prevalence of premature birth has been estimated as 28% (95% CI: 13 - 43%; I^2= 81.57%; P -Value = 0.00) (Figure 5 and Table 3). The results of Meta regression showed that the prevalence of premature birth has not relationship with age (coefficient: -0.014, P: 0.343, 95% CI: -0.044, 0.015), and gestational age of pregnant women with COVID 19 (coefficient: -0.055, P: 0.239, 95% CI: -0.147, 0.036).

The pooled prevalence of intrauterine fetal distress has been estimated as 15% (95% CI: 4 - 26%; I^2= 62.09%; P -Value = 0.04) (Figure 6 and Table 2). The least reported prevalence of intrauterine fetal distress in pregnant women with COVID 19 was 4% (95% CI: 4 - 13%) in the study by Wang X. et al. and the highest intrauterine fetal distress as prevalence was recorded 30% (95% CI: 2- 58%) in the retrospective study by Guo. et al (Figure 6 and Table 3). The results of Meta regression showed that the prevalence of intrauterine fetal distress has relationship with age (coefficient: 0.018, P: 0.003, 95% CI: 0.006, 0.030), but has not relationship with gestational age of pregnant women with COVID 19 (coefficient: -0.018, P: 0.851, 95% CI: -0.206, 0.170).

The pooled prevalence of neonatal mortality and lower birth weight in women with COVID 19 were 4% (95% CI: 1 - 9%; I^2= 0.0%; P -Value = 0.52) and 21% (95% CI: 11 - 31%; I^2= 0.0%; P -Value = 0.97), respectively. Also the pooled prevalence of stillbirth was 2% (95% CI: 1 - 6%; I2= 0.0%; P -Value = 0.40). The Lymphopenia prevalence in in women with COVID 19 were 37% (95% CI: 17 - 56%; I^2= 85.17%; P -Value = 0.00) (Table 3). The results of Meta regression showed that the prevalence of Lymphopenia has not relationship with age (coefficient: 0.029, P: 0.085, 95% CI: -0.004, 0.638), and gestational age of pregnant women with COVID 19 (coefficient: 0.053, P: 0.500, 95% CI: -0.102, 0.209).

Pooled prevalence of Laboratory tests in pregnant women with COVID 19

The pooled prevalence of increase CRP and LFT in women with COVID 19 were 58% (95% CI: 40 - 75%; I^2= 14.13%; P -Value = 0.13) and 32% (95% CI: 11 - 52%; I^2= 0.0%; P -Value = 0.88), respectively (Table 3). The results of Meta regression showed that the prevalence of increase CRP has not relationship with age (coefficient: 0.013, P: 0.440, 95% CI: -0.020, 0.047), and gestational age of pregnant women with COVID 19 (coefficient: -0.052, P: 0.672, 95% CI: -0.293, 0.189).

Pooled prevalence of complications in pregnancy and Cesarean indications in pregnant women with COVID 19

Results of this meta-analysis show that the pooled estimate of preeclampsia and fetal distress in women with COVID 19 were 26% (95% CI: 3 - 54%; I^2= 89.13%; P -Value = 0.00) (Table 4).

Publication Bias Assessment

The results of Egger's test show no significant bias occurred in the publication of the results (Egger's test = 1.15, SE: 0.480, P = 0.216).

Discussion

A total number of 177 pregnant women with COVID-19 were evaluated all in 2020 through 8 retrospective (21-28), 1 case control (29), and 2 case report studies (30, 31). The purpose of this systematic review and meta-analysis was to investigate the prevalence and relationship of several factors associated with COVID-19 in pregnancy and the effect of these factors on the maternal and neonatal outcome. Although a meta-analysis has been already published (32), we tried to have an update on this subject because of the fast rate of publications about the new data on COVID-19. We attempted to find out the severity of COVID-19 in pregnancy for providing optimum and on time diagnosis to prevent side effects and poor outcomes. In some cases, which the data was completely presented, we could carry out the meta-analysis.

The results of this paper demonstrate that the common signs and symptoms in pregnant women are fever, myalgia, increased CRP, increased LFT and Lymphopenia. As it was mentioned in results, the prevalence of fever, myalgia, sore throat and diarrhea was not related to age and gestational age of pregnant women, while cough and dyspnea had relationship with age and gestational age. About the neonatal factors, the prevalence of premature birth and fetal distress were not correlated with age and gestational age. Among laboratory tests also, Lymphopenia and increased CRP had not any correlation with age and gestational age. All the pregnant women admitted to the hospital had radiological features of COVID-19 pneumonia in CT scan or CXR. Their signs and symptoms were all similar to the non-pregnant population. The prevalence of preterm birth was 28% which is a high rate in comparison with healthy pregnancies. The rate of preeclampsia and cesarean section was more than the general population. The most common adverse perinatal outcome was fetal distress (26%) accompanied with a low rate of fetal death or stillbirth (2%) and neonatal death (4%). We investigated that there is not any clinical evidence of vertical transmission in the newborns, but previous evaluations caused by similar

viruses such as SARS and MERS were indicative of vertical transmission (33). Other studies on three newborns showed elevated SARS-CoV IgM antibodies. But the reported nasopharyngeal samples were negative (32, 34). Yang X et al reported an asymptomatic COVID-19 pregnant woman in the late period of pregnancy. They did not find any intrauterine infection caused by vertical transmission (35). But another study which has evaluated seven pregnant women with severe SARS-CoV-2, has demonstrated that the vertical transmission of COVID-19 infection from mothers during the last days of pregnancy is possible. The method of delivery in this study was C-section. So they concluded that the route of infection was trans-placental. Therefore, there cannot be any advantage for C-section compared to vaginal delivery (36). Rose et al also reported another case of severe COVID-19 during pregnancy. They believe there is a concern for vertical transmission and suggest an exact care for pregnant women as a high risk group (30). So we believe that the possibility of maternal-fetal transmission could not be ruled out completely.

In our systematic review, women suffering from COVID-19 had higher rates of preeclampsia and preterm birth. The fetuses had higher rates of fetal distress and the babies had higher rates of LBW. These data are retrieved from the women in the third trimester of pregnancy. The underlying diseases in pregnant women were gestational hypertension, diabetes and hypothyroidism. One patient needed mechanical ventilation which was not related to any underlying disease. One patient had multi organ dysfunction syndrome (MODS) leading to one stillbirth. One baby had severe neonatal asphyxia. Apgar score was in the normal range in all neonates (except one stillbirth and one asphyxia). Three women had voluntary termination. Two studies had twins, so 4 out of 13 LBW babies were due to twin delivery. But they all had normal infant characteristics without any evidence of COVID-19.

There is a study that has reported two cases of maternal ICU admissions. But these cases had underlying risk factors (high BMI>35) and complicated medical history (37). This can be a confirmation that COVID-19 alone cannot increase the risk maternal and neonatal morbidity. Some other studies have applied C-section for the majority of cases and reported that fetal distress was the major cause of decision for C-section (21, 38). Since fetal distress in our study has not any relationship with age and gestational age of pregnancy, so COVID-19 cannot be a cause of pregnancy termination by C-section.

There is a lack of data about the COVID-19 infection in the first and second trimester (32). On the basis of the results of this systematic review, there should be a multidisciplinary team of gynecologists, obstetricians, infection disease specialists and neonatologist to decide about the method of delivery (C-section or vaginal delivery). The indications should be evaluated more carefully.

Strengths

This is a comprehensive meta-analysis involving 11 valid publications and evaluating 177 pregnant women on this topic. Most of studies had an appropriate study population. The possibility that some patients were included in more than one report was low. The number of case reports in our assay was low. This leads to a lower risk of publication bias which increases the level of the evidence about our findings.

Limitations

The major limitations of this systematic review were the poor reports about the exact indications of C-section. We believe that most of C-sections were not necessary. Furthermore, the reported data about the pregnant women whose pregnancy was not terminated during the admission was limited. There was not a clear data about the neonates admitted in NICU. This can cause overestimation or underestimation of the risk of COVID-19 in pregnancy.

Conclusion

According to this systematic review and meta-analysis, the pregnant women with COVID-19 with or without pneumonia, are at a higher risk of preeclampsia, preterm birth, stillbirth and unnecessary cesarean delivery. Furthermore, the babies are at increased risk of LBW and intrauterine fetal distress. Although there cannot be any vertical transmission between mother and the fetus, the evidences show that it is still controversy. Hence, it is recommended to perform complete and exact evaluation of COVID-19 for the pregnant women at the time of admission. Chest CT-scan and RT-PCR testing seems to be necessary in these cases in order to prevent antenatal and postnatal complications and have a better outcome. Since the evidences are increasing, there may be several updates in a soon future.

Abbreviations

CI
Confidence Interval
EMBASE
Excerpta Medica dataBASE
NOS
Newcastle-Ottawa Scale
MOOSE
The Meta-Analyses of Observational Studies in Epidemiology
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-analyses
STROBE
The Strengthening the Reporting of Observational studies in Epidemiology
LBW
Lower Birth Weight
ICU
Intensive Care Units
RT-PCR
Reverse Transcription Polymerase Chain Reaction
COVID-19
Coronavirus Disease 2019

MODS
Multi Organ Dysfunction Syndrome
BMI
Body Mass Index
MERS
Middle East Respiratory Syndrome
SARS
Severe Acute Respiratory Syndrome
CRP
C-Reactive Protein
LFT
Liver Function Test
ACE2
Angiotensin-converting enzyme 2

Declarations

Ethics approval and consent to participate

Not applicable because no primary data were collected.

Consent for Publication

Not applicable.

Availability of data and material

Data is available and it can be accessed from the corresponding author with reasonable inquiry.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YM conceptualized the idea for this review, formulated the review question, and objectives, assisted with the development of the final search strategy, contributed to the data analysis/ interpretation, and writing the manuscript. MM, HRB, GM and MM contributed to the writing the manuscript. All authors contributed equally to the formulation of the review question/objectives, development of the search strategy,

conducting the searches, data extraction, data analysis/interpretation, and writing the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1: Patient characteristics, Maternal outcomes and complications, Signs and symptoms Laboratory tests, imaging, treatment and other parameters and Infant characteristics

Authors	Type of study	Total number of patient (Age)	Gestational age (weeks + days)	Maternal outcomes and complications	Signs and symptoms	Laboratory tests, imaging, treatment and other parameters	Infant characteristics
Chen H et al 2020	Retrospective	9 (26-44)	36 - 39 + 4	Cesarean section = 9 Vaginal delivery = 0 Gestational hypertension = 1 Pre-eclampsia = 1 Fetal distress = 2 Severe elevated LFT = 1 COVID pneumonia = 9 Pre-eclampsia = 1 Fetal distress = 2 History of still birth = 1 PROM = 2	Fever on admission = 7 Cough = 4 Malaise = 2 Dyspnea = 1 Myalgia = 3 Sore Throat = 2 Diarrhea = 1 Nausea and vomiting = 0 Fetal movement = NR FHR = NR VB = 0 PROM = 2	Lymphopenia = 5 Leukopenia = 7 CRP = 6 LFT = 3 Imaging = CT Scan BPP = NR Maternal mortality = 0 Maternal ICU admission = 0 Neonatal mortality = 0 Intrauterine fetal death = 0 Vertical transmission = 0 Treatment (AB = 9, AV= 6)	Birth weight (g) = 1880-3820 Low birth weight (<2500 g) (n) = 2 Premature birth (n) = 4 Apgar score (1 min, 5 min) = 9, 10 Intrauterine fetal distress (n) = 2 Severe neonatal asphyxia = 0 Neonatal death = 0 Fetal death or stillbirth = 0
Chen S et al 2020	Retrospective	5 (25-31)	38 - 41	Cesarean section = 2 Vaginal delivery = 3 Diabetes = 2 Pre-eclampsia=1	Fever on admission = 1 Cough = 2 Malaise = 0 Dyspnea = 0 Myalgia = 0 Sore Throat = 0 Diarrhea = 0 Nausea and vomiting = 0 Fetal movement = NR FHR = 1 VB = 0 PROM = 0	Lymphopenia = 12 Leukopenia = NR CRP = NR LFT = NR ↑ALK-P = 4 ↑LDH = 1 Alb = 5 ↑WBC=3 ↑Neutrophil=4 Imaging = CT Scan BPP = NR Maternal mortality = 0 Maternal ICU admission = 0 Neonatal mortality = 0 Intrauterine fetal death = 0 Vertical transmission = Highly probable	Birth weight (g) = 3235-4050 Low birth weight (<2500 g) (n) = 0 Premature birth (n) = 0 Apgar score (1 min, 5 min) = 10, 10 Intrauterine fetal distress (n) = 0 Severe neonatal asphyxia = 0 Neonatal death = 0 Fetal death or stillbirth = 0
Dashraath et al	Retrospective	55 (23-40)	26 - 41	Mechanical ventilation=1	Fever on admission =	↑WBC=21 Lymphopenia=12	Birth weight (g) = NR

2020				Vaginal delivery = 0	46 Cough = 15 Malaise = 0 Dyspnea = 10 Myalgia = 0 Sore Throat = 0 Diarrhea = 0 Nausea and vomiting = 0 Fetal movement = NR FHR = 0 VB = 0 PROM = 0	↓PLT=7 Imaging = CT Scan BPP = NR Maternal mortality = 0 Maternal ICU admission = 2 Neonatal mortality = 2 Intrauterine fetal death = 0 Vertical transmission = Highly probable	Low birth weight (<2500 g) (n) = NR Premature birth (n) = 24 Apgar score (1 min, 5 min) = NR Intrauterine fetal distress (n) = NR Severe neonatal asphyxia = 0 Neonatal death = 1 Fetal death or stillbirth = 1
Wang S et al 2020	Case report	2 (29-34)	36 - 37	Cesarean section = 2 Vaginal delivery = 0	Fever on admission = 2 Cough = 0 Malaise = 0 Dyspnea = 0 Myalgia = 0 Sore Throat = 1 Diarrhea = 0 Nausea and vomiting = 0 Fetal movement = NR FHR = 0 VB = 1 PROM = 0	Lymphopenia=1 Imaging = CT Scan BPP = NR Maternal mortality = 0 Maternal ICU admission = 0 Neonatal mortality = 0 Intrauterine fetal death = 0 Vertical transmission = NO	Birth weight (g) = 2890-3400 Low birth weight (<2500 g) (n) = 0 Premature birth (n) = 0 Apgar score (1 min, 5 min) = 9, 10 Intrauterine fetal distress (n) = 0 Severe neonatal asphyxia = 0 Neonatal death = 0 Fetal death or stillbirth = 0
Jihyun et al 2020	Case report	1 (28)	37 + 6	Cesarean section = 1 Vaginal delivery = 0	Fever on admission = 1 Cough = 1 Malaise = 0 Dyspnea = 0	↑ESR = 1 Imaging = CT Scan BPP = NR Maternal mortality = 0 Maternal ICU admission = 0 Neonatal mortality = 0 Intrauterine fetal death = 0	Birth weight (g) = 3130 Low birth weight (<2500 g) (n) = 0 Premature birth (n) = 0

					Myalgia = 0 Sore Throat = 1 Diarrhea = 0 Nausea and vomiting = 0 Fetal movement = NL FHR = NL VB = 0 PROM = 0	Vertical transmission = NR	Apgar score (1 min, 5 min) = 9, 10 Intrauterine fetal distress (n) = 0 Severe neonatal asphyxia = 0 Neonatal death = 0 Fetal death or stillbirth = 0
Yang et al 2020	Case-control	16 (30.9 ± 3.2)	38 ± 0.2	Cesarean section = 14 Vaginal delivery = 2	Fever on admission = 4 Cough = 0 Malaise = 0 Dyspnea = 0 Myalgia = 0 Sore Throat = 0 Diarrhea = 0 Nausea and vomiting = 0 Fetal movement = NL FHR = NL VB = 0 PROM = 0	Lymphopenia=2 ↑CRP=5 Imaging = CT Scan BPP = NR Maternal mortality = 0 Maternal ICU admission = 0 Neonatal mortality = 0 Intrauterine fetal death = 0 Vertical transmission = NO Treatment (AB = 16, AV= 1)	Birth weight (g) = 3078.2 Low birth weight (<2500 g) (n) = 3 Premature birth (n) = 4 Apgar score (1 min, 5 min) = 9.6, 10 Intrauterine fetal distress (n) = 1 Severe neonatal asphyxia = 0 Neonatal death = 0 Fetal death or stillbirth = 0
Liu et al 2020	Retrospective	11 (23-40)	34 - 38	Cesarean section = 10 Vaginal delivery = 1	Fever on admission = 9 Cough = 6 Malaise = 3 Dyspnea = 0 Myalgia = 3 Sore Throat = 1	Lymphopenia = 9 ↑CRP = 7 Imaging = CT Scan BPP = NR Maternal mortality = 0 Maternal ICU admission = 0 Neonatal mortality = 0 Intrauterine fetal death = 0 Vertical transmission = NO	Birth weight (g) = NR Low birth weight (<2500 g) (n) = NR Premature birth (n) = 0 Apgar score (1 min, 5 min) = 8, 9 Intrauterine fetal distress

					Diarrhea = 1 Nausea and vomiting = 0 Fetal movement = NL FHR = NL VB = 0 PROM = 0	Treatment (AB = 11, AV= 11)	(n) = 0 Severe neonatal asphyxia = 0 Neonatal death = 0 Fetal death or stillbirth = 0
Guo et al 2020	Retrospective	10 (22-36)	33 - 38	Cesarean section = 10 Vaginal delivery = 10 Fetal distress = 3 PROM = 1 Stillbirth = 1	Fever on admission = 10 Cough = 0 Malaise = 10 Dyspnea = 3 Myalgia = 0 Sore Throat = 1 Diarrhea = 0 Nausea and vomiting = 0 Fetal movement = NL FHR = NL VB = 0 PROM = 1	Imaging = CT Scan BPP = NR Maternal mortality = 0 Maternal ICU admission = 1 Neonatal mortality = 1 Intrauterine fetal death = 0 Vertical transmission = NR	Birth weight (g) = NR Low birth weight (<2500 g) (n) = NR Premature birth (n) = 5 Apgar score (1 min, 5 min) = 10, 10 Intrauterine fetal distress (n) = 3 Severe neonatal asphyxia = 0 Neonatal death = 0 Fetal death or stillbirth = 1
Schwartz et al 2020	Retrospective	38 (24-40)	31 - 41	Cesarean section = 35 Vaginal delivery = 3 Hypothyroid = 1 Gestational hypertension = 1 Pre-eclampsia = 2 Fetal distress = 10 GDM = 4 Scarred uterus oligo = 1 Placenta accrete = 1	Fever on admission = 38 Cough = 38 Malaise = 2 Dyspnea = 0 Myalgia = 3 Sore Throat = 2 Diarrhea = 3 Nausea and vomiting = 0	Lymphopenia = 5 ↑CRP = 6 ↑LFT = 3 Imaging = CT Scan BPP = NR Maternal mortality = 0 Maternal ICU admission = 0 Neonatal mortality = 1 Intrauterine fetal death = 0 Vertical transmission = NR	Birth weight (g) = 1520 - 3820 Low birth weight (<2500 g) (n) = 8 Premature birth (n) = 3 Apgar score (1 min, 5 min) = 8, 9 Intrauterine fetal distress (n) = 0 Severe neonatal

				Placenta Previa = 1	Fetal movement = 2 ↓ FHR = 2 ↓ VB = 1 PROM = 5		asphyxia = 0 Neonatal death = 0 Fetal death or stillbirth = 0
Wang X et al	Retrospective	23 (29)	≥ 28 ≤ 12	Cesarean section = 18 Vaginal delivery = 5	Fever on admission = 4 Cough = 6 Malaise = 0 Dyspnea = 0 Myalgia = 0 Sore Throat = 0 Diarrhea = 0 Nausea and vomiting = 0 Fetal movement = NR FHR = NR VB = 3 PROM = 3	Imaging = CT Scan BPP = NR Maternal mortality = 0 Maternal ICU admission = 0 Neonatal mortality = 0 Intrauterine fetal death = 0 Vertical transmission = NO	Birth weight (g) = NR Low birth weight (<2500 g) (n) = NR Premature birth (n) = 3 Apgar score (1 min, 5 min) = 9, 10 Intrauterine fetal distress (n) = 1 Severe neonatal asphyxia = 0 Neonatal death = 0 Fetal death or stillbirth = 0
Yu et al	Retrospective	7 (29-34)	39	Cesarean section = 7 Vaginal delivery = 0 Hypothyroidism = 1 PCO = 3	Fever on admission = 6 Cough = 1 Malaise = 0 Dyspnea = 1 Myalgia = 0 Sore Throat = 0 Diarrhea = 1 Nausea and vomiting = 0 Fetal movement = 1↓ FHR = NR	↑Neutrophil = 5 Lymphopenia = 2 ↓PLT = 2 ↑ESR = 4 Imaging = CT Scan BPP = NR Maternal mortality = 0 Maternal ICU admission = 0 Neonatal mortality = 0 Intrauterine fetal death = 0 Vertical transmission = Low Probable	Birth weight (g) = 3000 - 3500 Low birth weight (<2500 g) (n) = 0 Premature birth (n) = 0 Apgar score (1 min, 5 min) = 8, 10 Intrauterine fetal distress (n) = 0 Severe neonatal asphyxia = 0 Neonatal death = 0 Fetal death or stillbirth = 0

					VB = 0 PROM = 0		

Abbreviations:

LFT: liver function tests, PROM: premature rupture of membrane, MODS: multiple organ dysfunction syndrome, NR: not reported, FHR: fetal heart rate, VB: vaginal bleeding, PROM: premature rupture of membrane, AP: antepartum, PP: post-partum, NR: not reported, NL: normal, AB: antibiotic, AV: antivirus, CT scan: computed tomography scan, CXR: chest X ray, CRP: C-reactive protein, LFT: liver function tests, WBC: white blood cells, ALK-P: alkaline phosphatase, LDH: lactate dehydrogenase, Alb: albumin, PLT: platelet, ESR: estimated sediment rate, AP: antepartum, PP: post-partum, BPP: Bio Physical profile.

Table 2: Meta-analysis of prevalence of Signs and Symptoms COVID 19 in pregnant women by Random Effect Model (REM)

Outcomes	No. of Studies (Sample Size)	Pooled Prevalence (%)	95% Confidence Interval	Heterogeneity Assessment (%)		
				I2	Q test	P value
Fever	7 (126)	56 %	30 - 83	92.02 %	75.22	0.00
Cough	6 (110)	30 %	21 - 39	7.86 %	5.43	0.37
Malaise	3 (58)	13 %	1 - 28	45.58 %	3.68	0.16
Dyspnea	10 (176)	3 %	1 - 6	0.0 %	5.85	0.76
Myalgia	3 (58)	18 %	1 - 35	49.84 %	3.99	0.14
Sore Throat	5 (70)	7 %	1 - 13	0.0 %	3.06	0.55
Diarrhea	4 (65)	9 %	2 - 16	0.0 %	0.26	0.97
Increase CRP	5 (51)	58 %	40 – 75 %	14.13 %	7.16	0.13
Increase LFT	2 (19)	32 %	11 – 52 %	0.0 %	0.02	0.88
Lymphopenia	7 (126)	37 %	17 – 56 %	85.17 %	40.46	0.00

Table 3: Meta-analysis of prevalence of Laboratory tests and infant characteristics in pregnant women with COVID 19 by Random Effect Model (REM)

Outcomes	No. of Studies (Sample Size)	Pooled Prevalence (%)	95% Confidence Interval	Heterogeneity Assessment (%)		
				I2	Q test	P value
Neonatal Mortality	2 (65)	4 %	1 – 9 %	0.0 %	0.42	0.52
LBW	3 (63)	21 %	11 – 31 %	0.0 %	0.05	0.97
Premature Birth	6 (151)	28 %	12 – 44 %	81.57 %	27.12	0.00
Intrauterine Fetal Distress	5 (96)	14 %	4 – 25 %	60.06 %	10.01	0.04
Fetal Death or Stillbirth	2 (65)	2 %	1 – 6 %	0.0 %	0.72	0.40

Table 4: Meta-analysis of prevalence of complications in pregnancy and Cesarean indications in pregnant women with COVID 19 by Random Effect Model (REM)

Outcomes	No. of Studies (Sample Size)	Pooled Prevalence (%)	95% Confidence Interval	Heterogeneity Assessment (%)		
				I2	Q test	P value
Preeclampsia	4 (68)	26 %	3 – 54	89.13 %	27.59	0.00
Fetal Distress	3 (57)	26 %	15 – 38	0.00 %	0.15	0.93
Cesarean	5 (94)	86 %	75 – 95	43.48 %	7.08	0.13
Vaginal Delivery	5 (94)	14 %	5 – 24	43.48 %	7.08	0.13

Figures

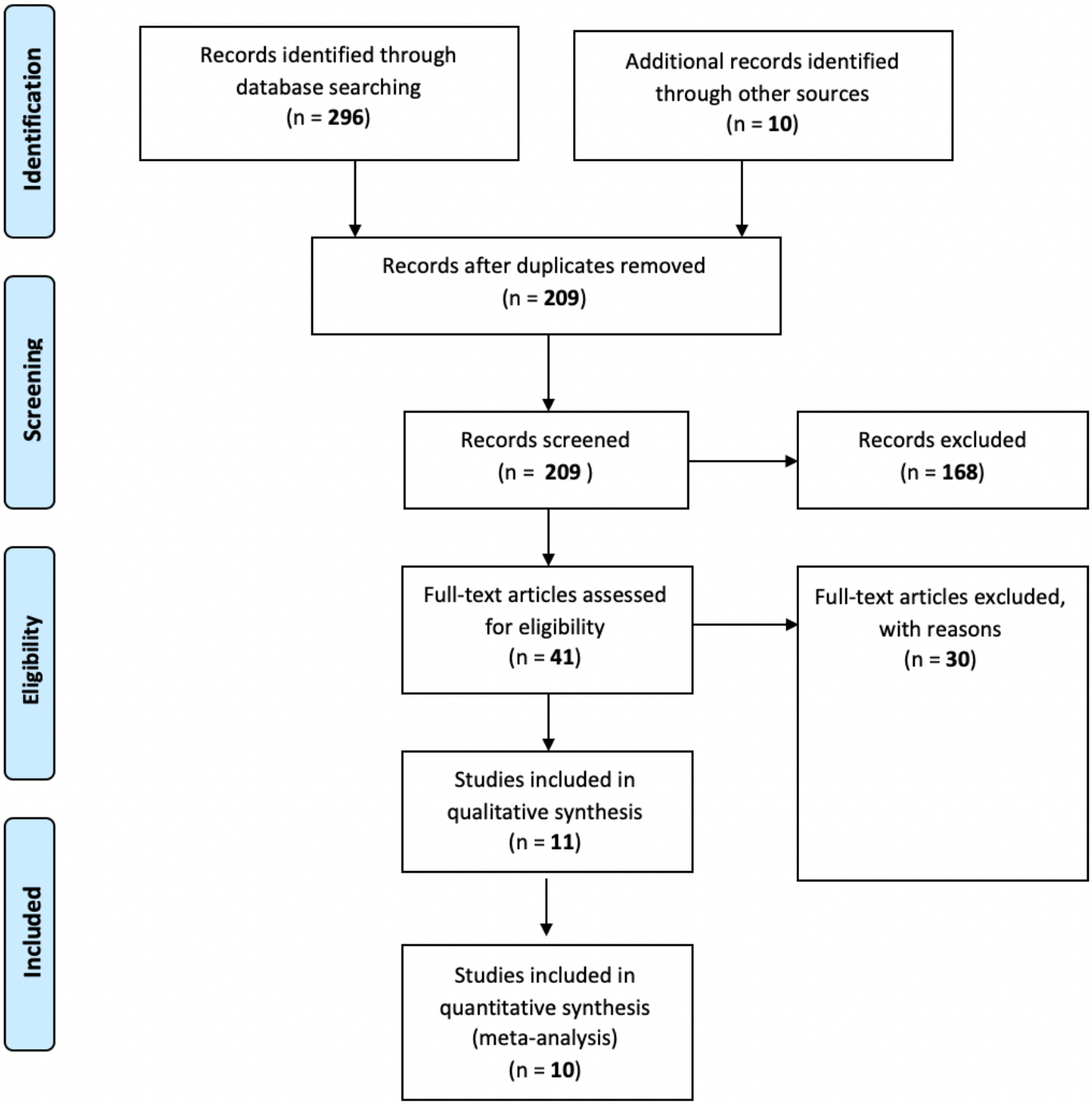

Figure 1

The Flowchart of Search Strategy and Syntax

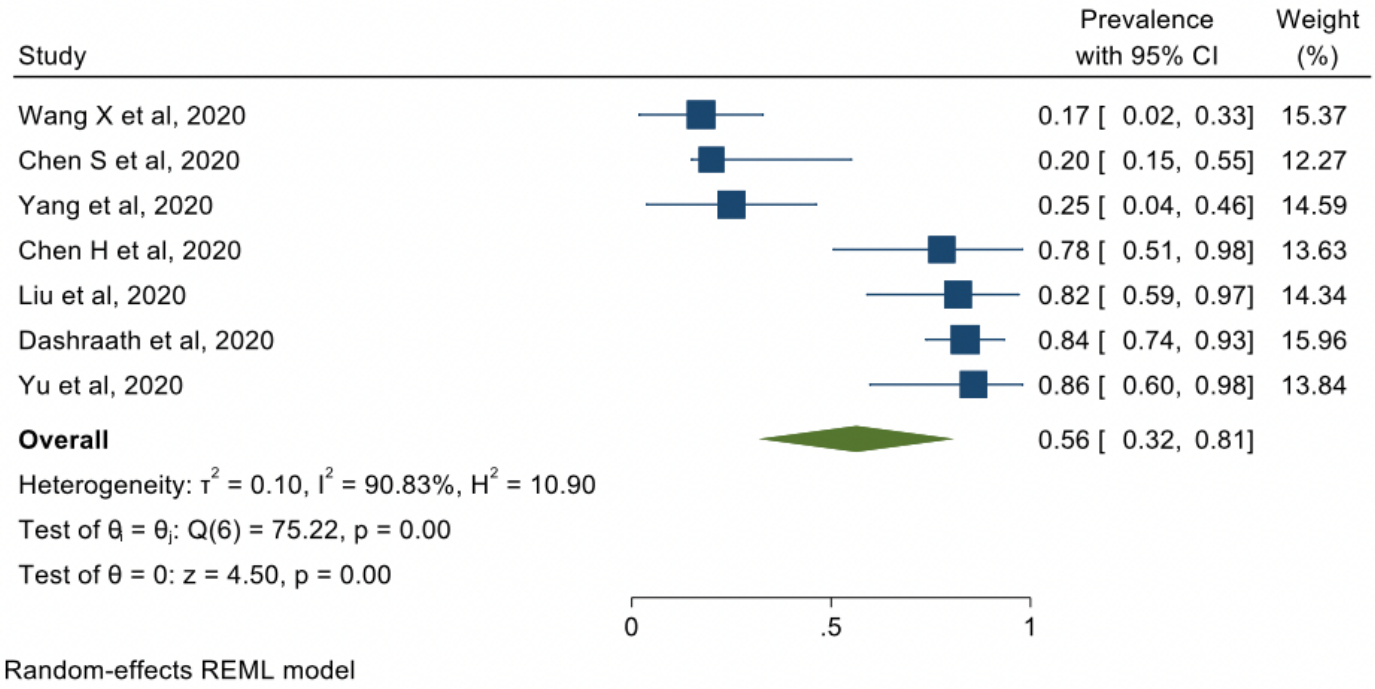

Figure 2

The pooled prevalence of Fever in pregnant women with COVID 19

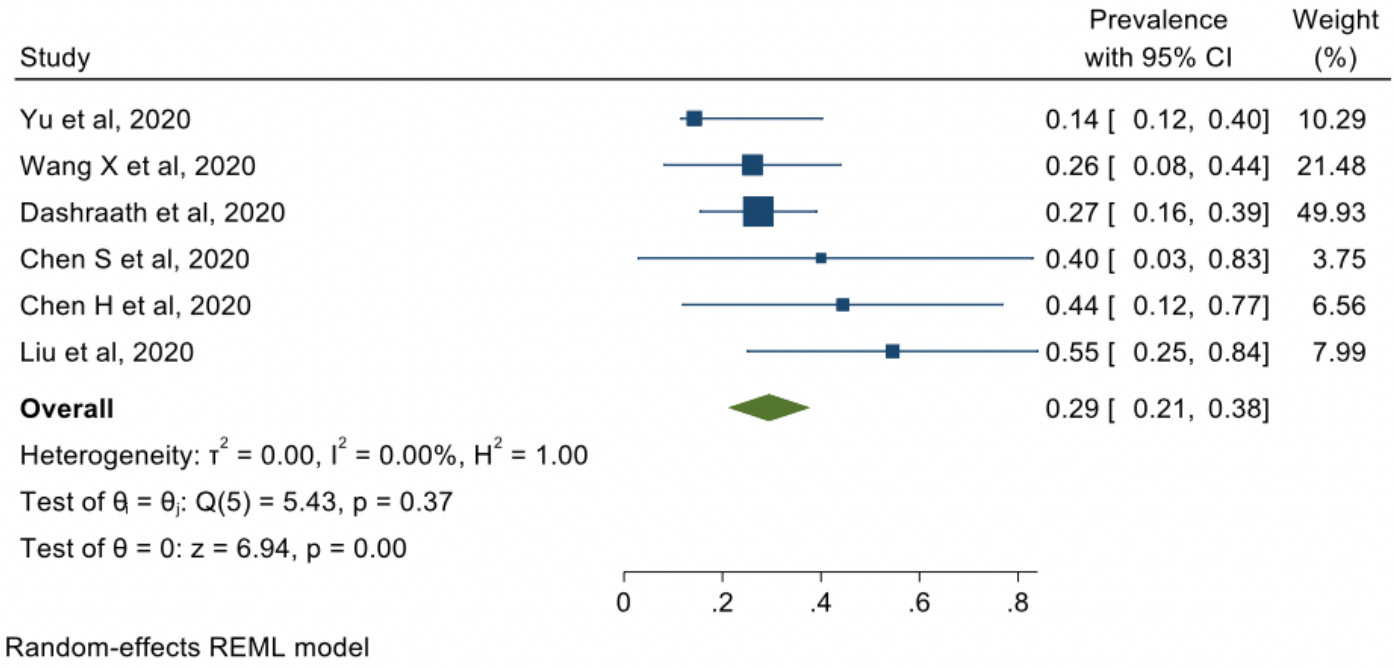

Figure 3

The pooled prevalence of caught in pregnant women with COVID 19

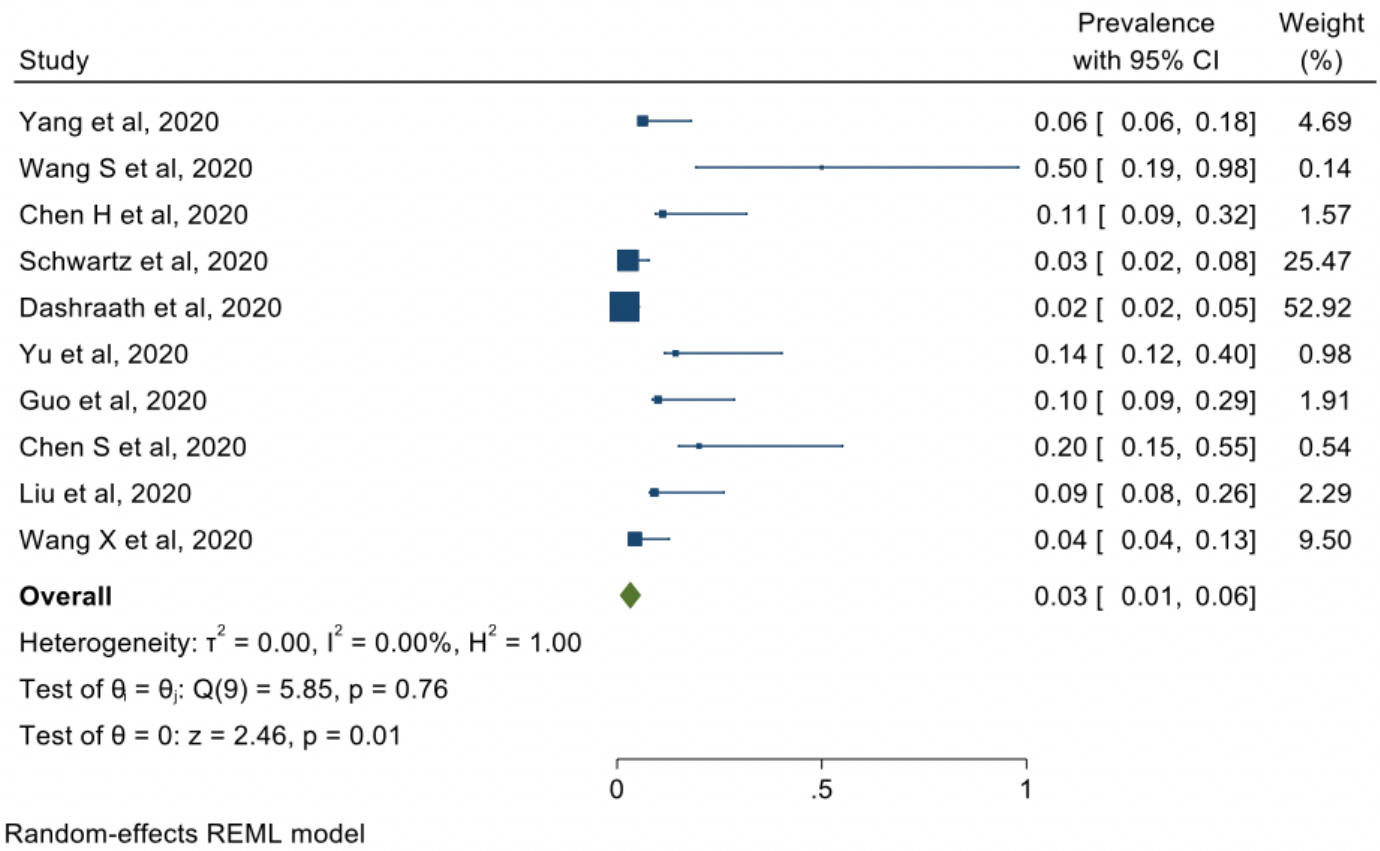

Figure 4

The pooled prevalence of Dyspnea in pregnant women with COVID 19

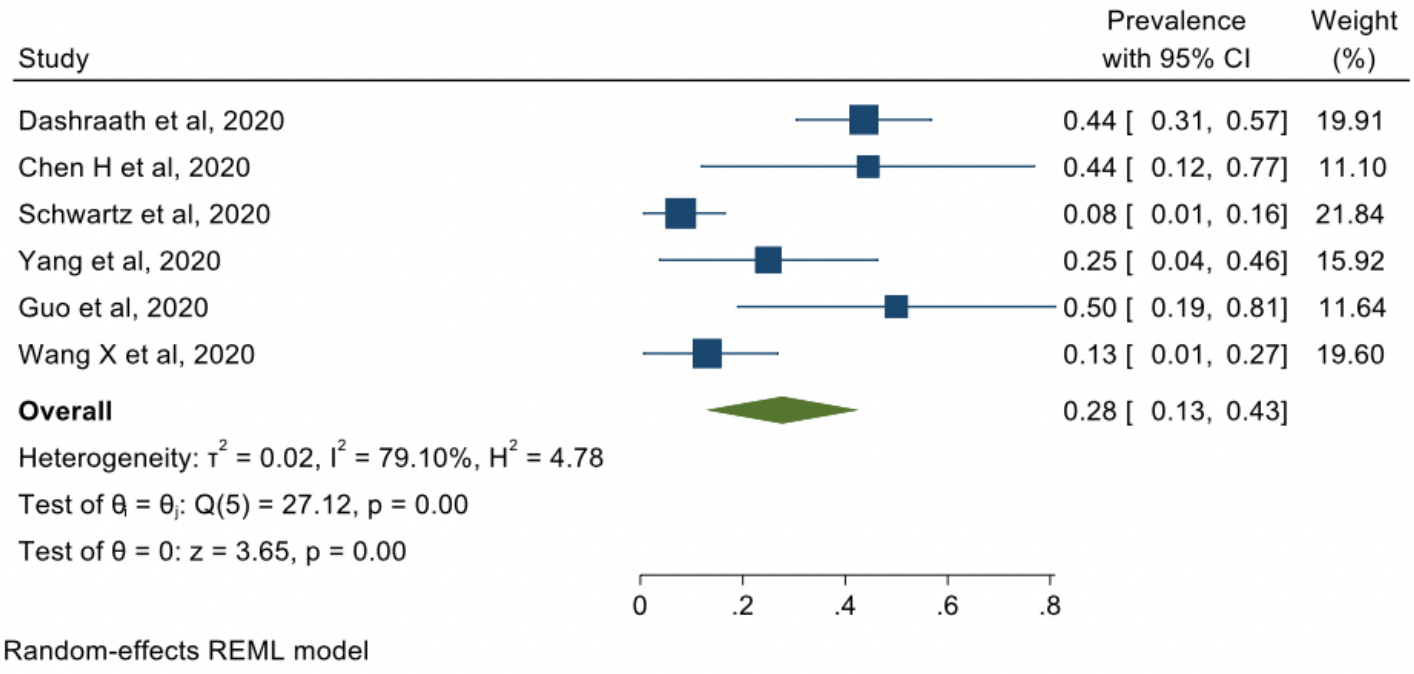

Figure 5

The pooled prevalence of premature birth in pregnant women with COVID 19

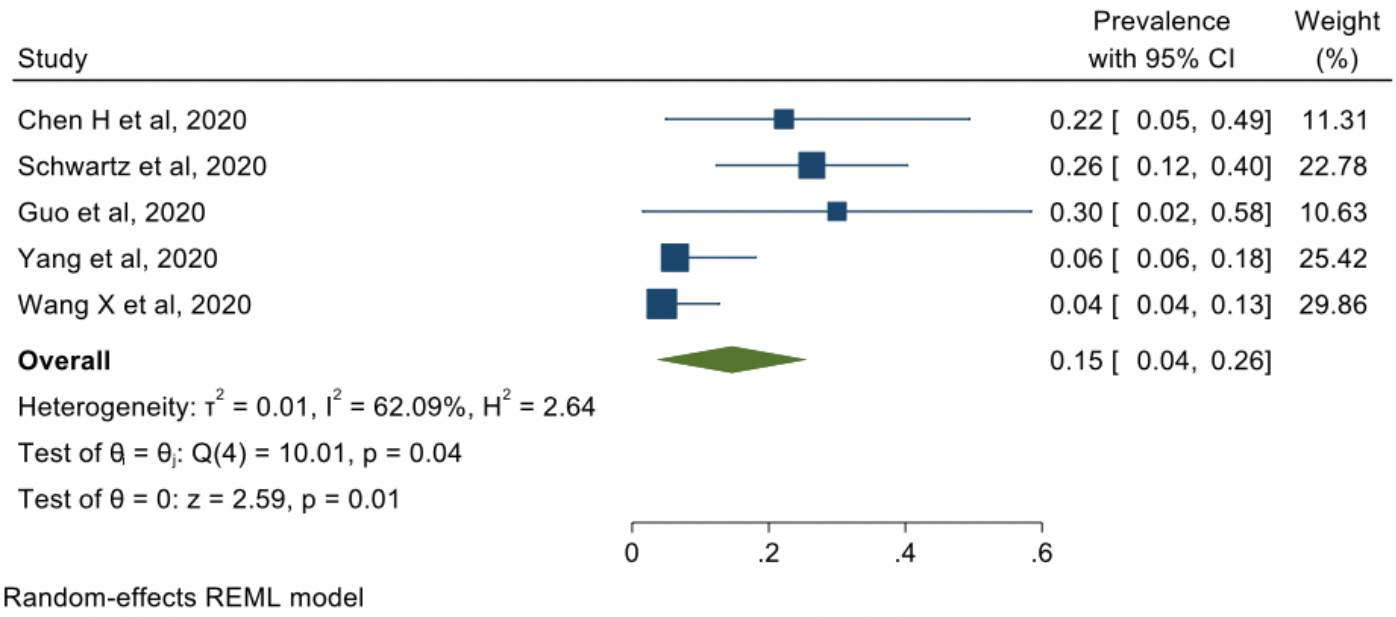

Figure 6

The pooled prevalence of Intrauterine fetal distress in pregnant women with COVID 19