COVID-19 infection in pregnant women, preterm delivery, birth weight, and vertical transmission: a systematic review and meta-analysis

COVID-19 em gestantes, parto prematuro, peso ao nascer e transmissão vertical: uma revisão sistemática e metanálise

Infección por COVID-19 en mujeres embarazadas, parto pretérmino, peso al nacer y transmisión vertical: una revisión sistemática y metaanálisis

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Abstract

In less than four months, the total of confirmed cases of COVID-19 was 1,684,833 worldwide. Outcomes among the public of pregnant women with COVID-19 are still unclear. We performed a systematic review and meta-analysis to analyze whether COVID-19 in pregnant women is related to premature birth and birth weight, and to summarize the diagnostic results of neonates born to mothers with COVID-19 for investigating the possibility of vertical transmission. Searches were performed in PubMed, Scopus, LILACS, Web of Science, Google Scholar, Preprints, bioRxiv, and medRxiv. We used the odds ratio (OR) and mean difference (MD) as measure of analysis. Summary estimates were calculated using random effects models. 38 studies were included; data from 279 women were analyzed; 60 patients were diagnosed with COVID-19. The meta-analysis showed no significant association between COVID-19 and preterm delivery (OR = 2.25; 95%CI: 0.96, 5.31; p = 0.06; I² = 0%). No significant relationship was found between birth weight and COVID-19 (MD = -124.16; 95%CI: -260.54, 12.22; p = 0.07; I² = 0%). Among 432 newborns, 10 were reported with positive results for early SARS-CoV-2. Due to the characteristics of the studies, the level of evidence of this meta-analysis was considered very low. COVID-19 in pregnant women may not be associated with the occurrence of preterm deliveries or the birth weight of the newborn children, however the evidence to date is very uncertain. A few reports suggest vertical transmission of SARS-CoV-2 to newborn is possible, but evidence is still uncertain.

COVID-19; Pregnancy; Vertical Infectious Disease Transmission

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Introduction

In December 2019, cases of pneumonia related to coronavirus disease 2019 (COVID-19) infection were reported in the city of Wuhan and soon spread to other locations in China and other countries [1]. In March 2020, the World Health Organization (WHO) declared a pandemic due to the global spread and the calamity reached by the infection [2]. As of April 24, 2020, the total number of confirmed cases of COVID-19 infection was 2,790,986 worldwide, with 195,920 deaths in 185 regions. Current scenarios with the highest number of confirmed cases are the United States and Spain, which have a total of 890,524 and 219,764, respectively [3].

Efforts to prevent the transmission of the etiological agent, which occurs mainly through aspiration or contact with respiratory secretions of infected patients, are being adopted worldwide, with an emphasis on the social isolation of the population through the blocking of services considered non-essential [4], including the restriction or closing of elective clinical services, bars, hotels, shopping malls, shows, restaurants, schools, universities, ports, airports, and highways.

Studies have described clinical and epidemiological features of COVID-19 infection in varied groups and demonstrated greater risks for the development of pneumonia as a serious form of infection among the group of elderly people and with chronic comorbidities, especially systemic arterial hypertension, diabetes mellitus and immunosuppression [5,6,7]. Furthermore, an official information from China demonstrated that 8% of pregnant women with COVID-19 were severe cases and may also be particularly vulnerable to infection [8]. However, results among the public of pregnant women and newborns require more detailed analysis.

There is no clear evidence regarding optimal delivery timing, the safety of vaginal delivery, or whether cesarean delivery prevents transmission to the newborn at the time of delivery [9,10,11,12,13]. Studies describing the prevalence of maternal and neonatal complications [9,14,15] and a brief narrative review suggest a possible increased risk of preterm delivery in pregnant women with COVID-19 [16], however there is no meta-analysis comparing the maternal and perinatal outcomes of pregnant women with COVID-19 with those without the infection. In addition, there are some recent isolated case studies reporting the occurrence of COVID-19 infection in neonates, which raises the importance of an analysis of essential information about the conditions in which the childbirth occurred and on the diagnostic methods used to investigate whether these infections are occurring in the neonatal or intrauterine period.

Thus, we performed a systematic review and meta-analysis to analyze whether the COVID-19 infection in pregnant women is related to premature birth and birth weight, and to summarize the diagnostic results of neonates born to mothers with COVID-19 infection for investigating the possibility of vertical transmission.

Methods

This study was conducted following the *Meta-Analysis of Observational Studies in Epidemiology* (MOOSE) statement [17]. Institutional review board approval and informed consent were not required for this systematic review and meta-analysis.

Research question and eligibility criteria

The first phase of this study focused on the following question: Is there a relationship between COVID-19 in pregnant women, preterm delivery and birth weight? Studies were considered eligible if they satisfied the following criteria: (i) they were a case-control or cohort (either prospective or retrospective) study, or nested design and considered pregnant women without COVID-19 as a control group; (ii) they provided data on COVID-19 diagnoses in pregnant women, delivery, and birth weight of the newborn; (iii) COVID-19 was ascertained by laboratory analyses positive in reverse transcription polymerase chain reaction (RT-PCR) tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or by radiological findings compatible with the disease; (iv) preterm delivery was

defined as the delivery that occurs before the complete 37 weeks of pregnancy; and (v) sufficient unadjusted or adjusted data were provided to evaluate the relationship between the described factors.

The second phase of this study focused on the following question: what are the postpartum diagnostic results for SARS-CoV-2 of neonates born to women with COVID-19? Studies were considered eligible if they satisfied the following criteria: (i) they were a cross-sectional study, case-control, cohort (either prospective or retrospective), nested design, case report, or case series and (ii) they provided data on diagnostic results of neonates born to women with COVID-19.

Search strategy

A systematic search using the PubMed, Scopus, LILACS, Web of Science databases and popular public preprint servers (bioRxiv, medRxiv and Preprints) was performed to identify studies that evaluated the relationship between COVID-19 in pregnant women, preterm delivery, birth weight, and results of neonates born to mothers with COVID-19 infection. A gray-literature search was conducted using Google Scholar. Publications were identified using the terms "SARS-CoV-2", "COVID-19", "pregnancy", "neonates", and related terms. Search was performed on May 4, 2020 without language restrictions. The reference lists of all eligible studies and reviews were manually scanned to identify additional studies for inclusion. The full electronic search strategy is illustrated in the Supplementary Material (Table S1. http://cadernos.ensp.fiocruz.br/static/arquivo/suppl-csp-0873-20_4342.pdf).

Study selection

Two independent investigators (G.C.M. and K.C.G.M.A.) screened the searched studies based on each paper's title and abstract. Relevant studies were read in full text and selected according to the eligibility criteria.

Data extraction and risk of bias assessment

Two independent investigators (G.C.M. and K.C.G.M.A.) extracted data from the published reports using a predefined protocol. Information about the study design, eligible population, age distribution, inclusion and exclusion criteria, diagnosis of COVID-19, laboratory analyses, clinical features of the pregnant women with COVID-19 infection, outcome, and diagnostic results of neonates were checked. Outcome data included crude estimates, means, and standard deviations (SD). Crude data refers to the number of pregnant women who had preterm delivery and of neonates with diagnostic results. Mean/SD refers of birth weight in the following groups: pregnant women with positive and negative COVID-19 infection, and neonates born to COVID-19 positive and negative woman.

The risk of bias for individual studies was assessed by two independent reviewers using the *Newcastle-Ottawa Scale* (NOS) [18]. The level of evidence of the outcomes of the meta-analysis (premature delivery, birth weight, and vertical transmission) was assessed by the *Grading of Recommendations, Assessment, Development, and Evaluations* (GRADE) by two independent reviewers.

Data analysis

The odds ratio (OR) was used as the measure of association between COVID-19 in pregnant women and preterm delivery. The OR was pooled using the random effects model assuming that the true value of the effect size of each study is sampled from a probability distribution rather than being identical. The results of birth weight were expressed as mean difference (MD); birth weight below 2,500g and a difference of 1,000g of birth weight between the groups were considered clinically important for this study [19]. Data on possible cases of vertical transmission were described.

Forest plots were used to present graphically the pooled ORs and the 95%CI (95% confidence interval) for results of preterm delivery and to present the estimates the results of birth weight in graphical form. P-values lower than 0.05 were statistically significant. Heterogeneity was investigated using the Cochran Q test with a cut-off of 10% for significance [19] and quantified using the I^2 index

[100% x (Q-df)/Q] [20]. Sensitivity analysis was performed to assess the robustness of the results related to the different case groups (pregnant women diagnosed only by RT-PCR – case group 1 – and pregnant women diagnosed by RT-PCR and imaging – case group 2) with the different control groups that one of the included studies [21] analyzed (pregnant women without COVID-19 admitted in the same period of pregnant women with COVID-19 – control group 1 – and pregnant women without COVID-19 admitted in 2019 – control group 2). Analyses were performed using Cochrane RevMan version 5.3 software (https://review-manager.software.informer.com/5.3/).

Results

Study selection

The initial search identified 1,720 reports, 173 of which were collected from PubMed, 31 from Web of Science, 103 from Scopus, 11 from LILACS, 1,320 from Google Scholar, two from Preprint database, 66 from medRxiv and 14 from bioRxiv. 38 studies were included in this systematic review: three studies [21,22,23] satisfied the eligibility criteria of the first research question and all 38 studies satisfied the eligibility criteria of the second research question (Supplementary Material – Figure S1. http://cadernos.ensp.fiocruz.br/static/arquivo/suppl-csp-0873-20_4342.pdf) [9,11,21,22,23,24,25,26,27,28,29,30,31, 32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56].

Study characteristics

Studies included for analysis of the first research question [21,22,23] were conducted in China and are of the case-control type. Data related to participants were extracted from medical records and in one study the data were reviewed independently by two investigators. All pregnant women included in the studies were in the third trimester of pregnancy and were admitted to the institutions in the same period, between January and March 2020. Gestational weeks of the women ranged from 33 to 41 weeks. None of the two included studies presented analysis for adjusted variables.

Data from 279 pregnant women were analyzed in this systematic review and meta-analysis. 60 patients were diagnosed with COVID-19 infection by RT-PCR or radiography; of these, 12 had vaginal delivery because neither presented any respiratory symptoms when admitted for full-term labor. Only one of the pregnant women in the studies had a severe clinical form of infection and there were no significant differences regarding neonatal complications in the groups. The median age of pregnant women in the studies was 30 years. Table 1 shows the main characteristics of the studies included by the criteria of the first research question and findings related to outcomes (delivery and birth weight).

Among the studies included based on the criteria of the second research question, four were case-control, 11 were case report, ten were series report, 11 were cross-sectional and two were cohort. Studies (38) described cases of neonates born in the United States (3), Peru (1), Iran (1), Portugal (1), Italy (1), South Korea (1), India (1) and China (29). 432 newborns were described as born to mothers diagnosed with COVID-19 infection before delivery and were tested for SARS-COV-2.

All studies described the test method used to investigate SARS-CoV-2 infection shortly after the birth of newborns, and most of them briefly reported the care taken by the health team to prevent the virus for the neonate, such as the use of masks by the mother and health professionals, isolation, and presence of negative pressure ward. Research for SARS-CoV-2 was investigated by collecting samples of throat (n = 405), amniotic fluid (n = 45), placenta (n = 26), umbilical cord blood (n = 28), serum (n = 3), feces (n = 26), urine (n = 27), bronchoalveolar secretion (n = 1), breast milk (n = 44), vaginal (n = 4), and cervical (n = 1) secretion from the mother. The main characteristics of the studies included are shown in Table 2.

Table 1

Main characteristics of the studies included in the analysis of the outcomes of premature birth and birth weight.

Study	Local and pregnant COVID-19 +/ COVID-19 - (n/n)	Inclusion criteria	Control group	Comorbidities	Type of delivery	Symptoms and complications	Key findings
Li et al. [21]	Maternal and Child Health Hospital of Hubei Province, China (17/121)	Pregnant women who were admitted into the hospital during January 24 to February 29, 2020. Throat swabs were collected from all these patients and realized computed tomography imaging.	Pregnant women without pneumonia during the same period randomly selected from the medical records. Only those aged 25-35 years were selected to match the age range of cases. Considering the potential adverse effects of mental stress caused by city lockdown and severe epidemics, we also included the second control group of 121 women admitted during January 24 – February 11, 2019 (control 2019 group). For this meta-analysis we considered the 2020 group.	Two confirmed cases (12.5%) had chronic conditions of hypertension and polycystic ovary syndrome. Around 31% of the case group had other maternal complications, significantly higher than the control. All these complications were developed before diagnosis of COVID-19.	There were 12 patients who took emergency cesarean section because of active labor at the time of admission, and three had scheduled cesarean section. Two patients had vaginal delivery because neither presented any respiratory symptoms when admitted for full-term labor.	Four cases were admitted with fever for investigation and eight developed fever after childbirth. None presented other respiratory symptoms on admission nor during hospital stay. Seven had typical image of pneumonia in both lungs and eight in single lung. None were admitted into the intensive care unit because of COVID-19 or severe maternal complications	Among three confirmed cases COVID-19 with preterm delivery, two were caused by premature rupture of membranes, and one by placental bleeding. There were 23.5% preterm delivery among the newborns born to mothers with COVID-19 infection, significantly higher than from the control. Low birth weight also occurred more often in infants of case group (17.6%) than in control group (2.5%). However, neonates from the case and control showed no significant differences in key neonatal indicators. No events of deaths and vertical transmission occurred in these newborns.

(continues)

Table 1 (continued)

Study	Local and pregnant COVID-19 +/ COVID-19 - (n/n)	Inclusion criteria	Control group	Comorbidities	Type of delivery	Symptoms and complications	Key findings
Liao et al. [23]	Zhongnan Hospital of Wuhan University, China (10/53)	Pregnant women who delivered vaginally during January 20 to March 2, 2020.	Pregnant women without COVID-19 delivered vaginally on the same period.	No comorbidities were reported.	The delivery methods of the two groups of pregnant women were all by vaginal.	Five women had low fever a few days before the onset of labor; four patients had mild respiratory symptoms, and one patient did not complain of particular discomfort. Data showed nine women had a low lymphocyte ratio. All patients had a chest CT scan that showed typical findings of multiple patchy ground-glass shadows.	There was no statistically difference in premature rupture of membranes, premature delivery, neonatal asphyxia, amniotic fluid pollution, postpartum hemorrhage, or perineal lateral resection rate between the two groups. Three neonates were self-discharged from the hospital owing to family refusal of neonatal treatment. Throat swab tests SARS-CoV-2 performed twice (24 hours apart) in each of the seven neonates were all negative.
Lu et al. [22]	Wuhan University Hospital, China (16/45)	Pregnant women in the third trimester of pregnancy who were admitted into the hospital during January 30 to February 17, 2020.	Pregnant women with no COVID-19 infection and with cesarean section recommendation were recruited to eliminate the possible impact of different methods of delivery when comparing pregnancy outcomes.	One case had pre-eclampsia and three had gestational diabetes.	The delivery methods of the two groups of pregnant women were all by cesarean section.	One case was classified as severe with oxygen saturation in a resting state of 93%, accompanied by reduced fetal movement.	There were 11 cases of labor, marked uterus, premature rupture of membranes and one case of fetal distress in the group with COVID-19 infection. There were no statistically significant differences in gestation time, parity, gestational weeks, preterm delivery, intraoperative blood loss and neonatal birth weight between the two groups of pregnant women. No events of deaths and vertical transmission occurred in these newborns.

Table 2

Main characteristics of the studies included in the analysis of SARS-CoV-2 in neonates born to mothers with COVID-19.

Study	Country	Period	Type of study	Pregnant woman with COVID-19/ Neonates tested (n/n)	Cesarean (n)	Neonates with SARS-CoV-2 (n)	Neonatal diagnostic method
Chen et al. [9]	China	February 4	Series report	3/3	3	0	RT-PCR: throat swab
Khan et al. [36]	China	January 28 – March 1	Series report	3/3	0	0	RT-PCR: throat swab
Li et al. [21]	China	January 24 – February 29	Case control	34/3	30	0	RT-PCR: throat swab
Lu et al. [22]	China	January 30 – February 17	Case control	16/10	16	0	RT-PCR: throat swab
Liao et al. [23]	China	January 20 – March 2	Case control	10/7	0	0	RT-PCR: throat swab
Yin et al. [24]	China	January 28 – February 28	Cohort	31/27	22	0	RT-PCR: amniotic fluid, placenta, throat swab, anal swab, and breast milk
Nie et al. [25]	China	January 1 – February 20	Cross-sectional	33/26	23	1	RT-PCR: throat, cord blood and placenta
Liu et al. [26]	China	February 2 – February 5	Series report	3/3	2	0	RT-PCR: throat swab
Liu et al. [27]	China	January 31 – February 29	Cross-sectional	19/19	18	1: false positive	RT-PCR: throat swab, blood, urine, feces, amniotic fluid and breast milk
Chen et al. [13]	China	No described	Series report	4/3	3	0	RT-PCR: throat swab
Li et al. [29]	China	February 6	Case report	1/1	1	0	RT-PCR: throat swab
Yang et al. [30]	China	January 20 – January 29	Cross-sectional	7/7	7	0	RT-PCR: throat swab, amniotic fluid, and umbilical cord blood
Peng et al. [31]	China	No described	Case report	1/1	1	0	RT-PCR: throat swab, anal, serum, bronchoalveolar lavage fluid, urine, amniotic fluid, vaginal secretions, cord blood, placenta, and breast milk
Yu et al. [32]	China	January 1 – February 8	Cross-sectional	7/7	7	3	RT-PCR: throat, placenta, and cord blood
Alzamora et al. [33]	Peru	March 29	Case report	1/1	1	1	RT-PCR: throat swab + serology
Xiong et al. [34]	China	January 29	Case report	1/1	0	0	RT-PCR: throat swab, anal swab, breast milk, amniotic fluid and cervical secretion
Chen et al. [35]	China	January 20 – January 31	Cross-sectional	9/9	9	0	RT-PCR: amniotic fluid, cord blood, throat swab and breast milk
Khan et al. [36]	China	January 25 – February 15	Series report	17/18	17	2	RT-PCR: throat swab

(continues)

Table 2 (continued)

Study	Country	Period	Type of study	Pregnant woman with COVID-19/ Neonates tested (n/n)	Cesarean (n)	Neonates with SARS-CoV-2 (n)	Neonatal diagnostic method
Yang et al. [37]	China	January 20 – March 5	Case control	13/14	9	0	RT-PCR: throat swab
Zeng et al. [38]	China	January – February	Cohort	33/33	26	3	RT-PCR: throat and anal swab
Liu et al. [39]	China	January 31 – February 29	Cross-sectional	16/16	10	0	Not described
Dong et al. [40]	China	February 22	Case report	1/1	1	1	RT-PCR: throat swab, vaginal secretions of the mother + serology
Schnettler et al. [41]	USA	March 23	Case report	1/1	1	0	RT-PCR: throat swab and amniotic fluid
Hantoushzadeh et al. [42]	Iran	February – March	Series report	9/4	4	1	RT-PCR: throat swab
Qiancheng et al. [43]	China	January 15 – March 15	Cross-sectional	28/23	17	0	RT-PCR: throat swab
Lyra et al. [44]	Portugal	No described	Case report	1/1	1	0	RT-PCR: throat swab
Kelly et al. [45]	USA	No described	Case report	1/1	1	0	RT-PCR: throat swab
Xu et al. [46]	China	January 21 – February 9	Series report	9/5	4	0	RT-PCR: throat swab
Hu et al. [47]	China	January 20 – February 2	Series report	7/7	6	1	RT-PCR: throat, blood, feces and urine
Lu et al. [48]	China	February 13	Case report	1/1	1	0	RT-PCR: throat swab and blood
Yan et al. [49]	China	January 20 – March 24	Cross-sectional	99/100	85	0	RT-PCR: throat swab, amniotic fluid and umbilical cord blood
Ferrazzi et al. [50]	Italy	March 1 – March 20	Cross-sectional	42/42	18	2	RT-PCR: throat swab
Lee et al. [51]	South Korea	March	Case report	1/1	1	0	RT-PCR: throat swab, placenta, amniotic fluid and cord blood
Breslin et al. [52]	USA	March 13 – March 27	Cross-sectional	43/18	8	0	RT-PCR: throat swab + serology
Sharma et al. [53]	India	No described	Case report	1/1	1	0	Not described
Chen et al. [54]	China	January 20 – February 10	Cross-sectional	3/3	3	0	RT-PCR: throat swab and placenta
Zhu et al. [55]	China	January 20 – February 5	Series report	9/9	7	0	RT-PCR: throat swab
Fan et al. [56]	China	January 31	Series report	2/2	2	0	RT-PCR: throat swab, maternal serum, placenta tissues, umbilical cord blood, amniotic fluid, vaginal swabs, breast milk

RT-PCR: reverse trancription polymerase chain reaction.

Risk of bias assessment

Studies included in this systematic review stated the research question and clearly described information related to the eligibility criteria; studies used representative samples to strengthen the observational evidence on the relationship between COVID-19 infection, preterm delivery, birth weight, and vertical transmission.

Although studies clearly describe the COVID-19 diagnosis and delivery time of the women, there was potential for selection bias, as one of the study did not select a sample for the control group with admission outside the pandemic period, considering the psychological effects may interfere with delivery premature. Other study considered two control groups with differences in admission time. To ensure homogeneity between study samples, this systematic review and meta-analysis extracted data only from pregnant women in the control group admitted in the period similar to the group of women with COVID-19 infection.

Regarding the exposure criterion, studies present a high risk of bias because they did not consider confounding factors for the analysis of outcomes. The criteria for risk of bias assessment is provided in the Supplementary Material (Table S2. http://cadernos.ensp.fiocruz.br/static/arquivo/suppl-csp-0873-20_4342.pdf). From the GRADE tool, the level of evidence of this meta-analysis was considered very low for all outcomes.
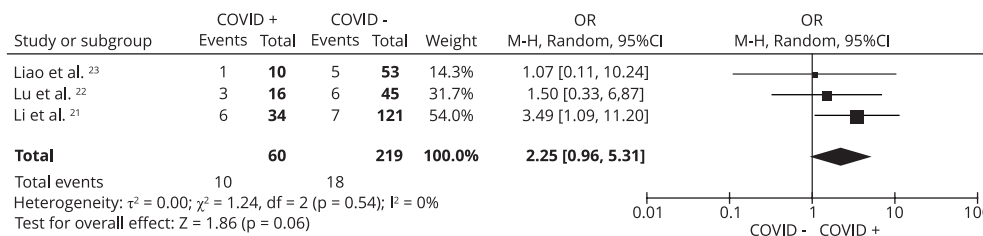
COVID-19 infection and preterm delivery

Studies provided unadjusted data to examine the association between COVID-19 infection and preterm delivery in pregnant women. Preterm delivery was found in 28 cases, and ten of them occurred in pregnant women with COVID-19 infection. Overall results of this meta-analysis showed no significant association between COVID-19 infection and preterm delivery (OR = 2.25; 95%CI: 0.96, 5.31; p = 0.06). There was no between-study heterogeneity ($I^2 = 0\%$) (Figure 1).

COVID-19 infection and birth weight

Studies reported data of birth weight for 281 neonates. Among them, 62 were born to women with COVID-19 infection. No significant relationship was found between the variables (MD = -124.16; 95%CI: -260.54, 12.22; p = 0.07). No between-study heterogeneity was found ($I^2 = 0\%$) (Figure 2).
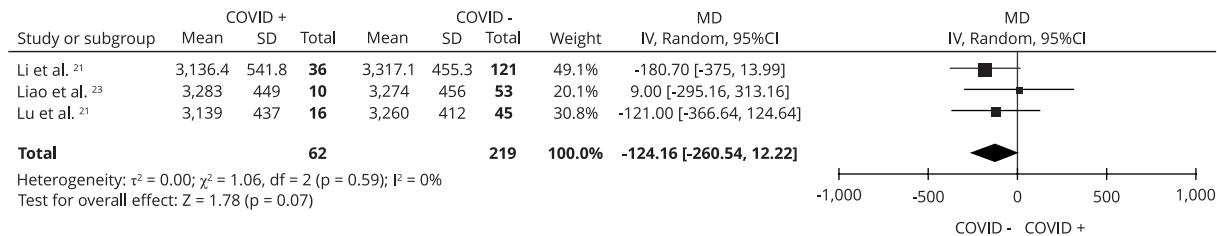
Figure 1

Forest plot showing association between preterm delivery in pregnant women with and without COVID-19 infection.

Study or subgroup	COVID + Events	Total	COVID - Events	Total	Weight	OR M-H, Random, 95%CI
Liao et al. [23]	1	**10**	5	**53**	14.3%	1.07 [0.11, 10.24]
Lu et al. [22]	3	**16**	6	**45**	31.7%	1.50 [0.33, 6,87]
Li et al. [21]	6	**34**	7	**121**	54.0%	3.49 [1.09, 11.20]
Total		**60**		**219**	**100.0%**	**2.25 [0.96, 5.31]**
Total events	10		18			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.24$, df = 2 (p = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 1.86 (p = 0.06)

95%CI: 95% confidence interval; M-H: Mantel-Haenszel test; OR: odds ratio.

Figure 2

Forest plot showing analysis of birth weight in neonates born to women with and without COVID-19 infection.

Study or subgroup	COVID + Mean	SD	Total	COVID - Mean	SD	Total	Weight	MD IV, Random, 95%CI
Li et al. [21]	3,136.4	541.8	**36**	3,317.1	455.3	**121**	49.1%	-180.70 [-375, 13.99]
Liao et al. [23]	3,283	449	**10**	3,274	456	**53**	20.1%	9.00 [-295.16, 313.16]
Lu et al. [21]	3,139	437	**16**	3,260	412	**45**	30.8%	-121.00 [-366.64, 124.64]
Total			**62**			**219**	**100.0%**	**-124.16 [-260.54, 12.22]**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.06$, df = 2 (p = 0.59); $I^2 = 0\%$
Test for overall effect: Z = 1.78 (p = 0.07)

95%CI: 95% confidence interval; IV: inverse variance; MD: mean difference; SD: standard deviation.

COVID-19 infection and possible vertical transmission

Positive results for SARS-CoV-2 were found in 16 neonates. Repeated checks on the same throat swab sample showed the result was false positive for one of these neonates born in China and the virus was undetectable in amniotic fluid and umbilical cord blood for this neonate [27]. In another case in China, three newborns were infected with SARS-CoV-2 36 hours after birth; the authors did not report whether preventive measures were adopted during childbirth and described intrauterine vertical transmission might not have occurred because the viral nucleic acid tests of the placenta and cord blood in this patient were negative for virus [32]. A study carried out in Italy described two cases of neonates with positive test results for SARS-CoV-2, but related to not wearing masks during breast-feeding due to the mother's diagnosis that occurred only in the postpartum period [50].

Thus, a total of ten neonates were reported in the literature [25,33,36,38,40,42,47] with positive test results for SARS-Cov-2 shortly after birth, in situations that may indicate the possibility of vertical transmission intrauterine. The details of the diagnostic results and clinical conditions of these neonates are described in Table 3.

Sensitivity analysis and publication bias

A sensitivity analysis was performed by iteratively adding the different case groups and control groups used in one of the studies [21] at a time to confirm our findings were not driven by any single group considered. The sensitivity analysis showed effect sizes did not change substantially with the exclusion of any group (Supplementary Material – Figures S2 and S3. http://cadernos.ensp.fiocruz.br/static/arquivo/suppl-csp-0873-20_4342.pdf).

Table 3

Main clinical features of the neonates with early SARS-CoV-2 infection in studies included.

Study	Local	Gestational age/Birth weight/ Delivery	Apgar 1'/5'	Diagnostic method	Results and preventive measures
Nie et al. [25]	China n = 1	- Cesarean	8-10/9-10	RT-PCR: throat swab, cord blood and placenta	The mother wore N95 mask during delivery. Newborn was immediately isolated after birth. He tested positive; imaging 53 hours (h) after was consistent with pulmonary infection. Cord blood and placental samples were both negative. He had no clinical symptoms and found negative for SARS-CoV-2 on days 4/8/15. Pulmonary infection had resolved. He did not receive treatment; discharged on day 16.
Alzamora et al. [33]	Peru n = 1	33 weeks 2,970g Cesarean	6/8	RT-PCR: throat swab + serology	Neonate was immediately isolated and intubated due to sedation of the mother. Delayed cord clamping, skin-to-skin contact and breastfeeding was not performed. Baseline and follow-up neonatal serology obtained at birth: negative IgG/IgM. RT-PCR of 16h/48h: positives. Maternal serology on postpartum day 1: negative IgG/IgM levels. IgG/IgM on repeat testing on day 4 (day 9 after symptom onset): positives. The newborn required ventilatory support for 12h, after which he was extubated and placed on continuous positive airway pressure; not requiring antibiotic. On day 6, he presented mild respiratory difficulty and sporadic cough requiring supplemental oxygen. Chest X-ray showed no abnormalities.
Khan et al. [36]	China n = 2	- 3,360g/3,570g Cesarean	9/10 9/10	RT-PCR: throat swab	The testing within 24 hours after the delivery were positive in two neonates. Intrauterine tissue samples such as placenta, cord blood or amniotic fluid were not tested.
Zeng et al. [38]	China n = 3	40/40/31 weeks 3,250g/3,360g /1,580g Cesarean	- - 3/4	RT-PCR: throat and anal swab	Neonates 1/2: On day 2 of life, they experienced lethargy and fever. Imaging showed pneumonia. RT-PCR was positive on days 2/4 of life and negative on day 6. Neonate 3: Resuscitation was required after birth. Neonatal respiratory distress syndrome and pneumonia confirmed by imaging were resolved on day 14 of life after noninvasive ventilation, caffeine, and antibiotics. RT-PCR was positive on days 2/4 of life and negative on day 7. Strict infection control procedures were implemented during the deliveries.
Dong et al. [40]	China n = 1	- 3,120g Cesarean	9/10	RT-PCR: throat swab, vaginal secretions of the mother + serology	Neonate was born in a negative-pressure isolation room; had no symptoms and was immediately quarantined. The mother wore an N95 mask. At 2h of age, IgG (140.32 AU/mL) and IgM (45.83 AU/mL) were positives. Results from five RT-PCR tests on throat swabs taken from 2 h to 16 days were negative. IgM (11.75 AU/mL) and IgG (69.94 AU/mL) levels were still elevated on day 15. The results of test of the mother's vaginal secretions were negative. On day 7 the breastmilk had a negative test result. Laboratory results displaying inflammation and liver injury. Newborn was discharged on day 26.
Hantoushzadeh et al. [42]	Iran n = 1	30 weeks 2,100g Cesarean	9/10	RT-PCR: throat swab	The premature neonate initially tested negative and tested positive on day-of-life seven while intubated.
Hu et al. [47]	China n = 1	40 weeks 3,250g Cesarean	8/9	RT-PCR: throat, blood, feces and urine	The neonate had no clinical symptoms. Chest X-rays performed on the first day of life were also normal.

RT-PCR: reverse trancription polymerase chain reaction.

Discussion

Pregnant women are more susceptible to respiratory pathogens [16,57] due to the anatomical structure and physiological adaptive alterations of the respiratory system that is changed during pregnancy, such as increased oxygen consumption and edema of the respiratory tract [58,59]. There is established evidence that maternal viral infections can cause negative results during pregnancy due to the effect of the pathogen on women. Studies carried out with pregnant women diagnosed with other highly pathogenic coronaviruses causer of severe acute respiratory syndrome (SARS) in 2002 to 2003 have described this infection can increase the risk of maternal death, miscarriage, preterm delivery, and intrauterine growth restriction [60,61,62]. On the other hand, vaccination against influenza has been shown to decrease the risk of preterm birth in pregnant woman exposed to influenza [63].

One possible cause of these complications can be attributed to the induction of the most severe inflammatory state that occurs as a result of viral infection. The normal pregnancy physiological changes in the third semester provide a pro-inflammatory state for the body of woman to prepare for the start of parturition [64] and a recent study indicates infection by COVID-19 is associated with an increase in cytokine production [65], which in serious situations can intensify this immune status in pregnant women [15] resulting in contractions, rupture of membranes, and delivery [66]. A study that compared clinical characteristics between pregnant and non-pregnant women with SARS showed pregnancy appeared to have no effect on clinical symptoms or time to presentation after symptom onset. However, systemic complications and the need for longer hospital stay were associated with pregnancy [67].

Despite the most common adverse obstetrical outcomes associated with maternal pneumonias from all causes had related with premature rupture of membranes and preterm labor [68] and one of the studies included in our systematic review showed significant differences between premature delivery and the group of pregnant women with COVID-19 [21], results of this meta-analysis showed no association between COVID-19 infection in pregnant women and preterm delivery. Similarly, birth weight of the newborns analyzed in this meta-analysis did not differ between groups. This result may be related to the fact that there are no reported cases of COVID-19 in the first trimester until this time. Thus, possible negative neonatal leavcomes related to weight and malformation are unknown.

The reason for early delivery is not well documented in the studies analyzed, despite the fact the groups had compatible ages, similar gestation periods and were treated in the same period in hospitals. Most deliveries in the studies were cesarean, but this was related to local protocols to help improve maternal lung ventilation [20,21]. Experts have reported acute COVID-19 infection should not be an indication for early elective delivery unless maternal or fetal decompensation occurs during treatment [69,70]. For vaginal delivery, pregnant women need to be admitted into the delivery suite for detailed assessment, labor pain management, stratification of infection control precautions, and plans for safe delivery of the fetus and the professional team [70].

In our review, ten newborns with early SARS-CoV-2 infection were found. Although most studies that analyzed neonates born to mothers with COVID-19 found RT-PCR from different samples with negative results, there are reports of neonates with early positive results in situations where strict control and prevention controls have been adopted [71] and, therefore, the possibility of vertical transmission cannot be ruled out. In a study, the laboratory results displaying inflammation and liver injury in a neonate indirectly support this possibility of vertical transmission [40].

Although most studies have used the RT-PCR diagnostic method, there is a possibility that these RT-PCR results are false negative in situations of low viremia or when neonates have already produced their antibodies. An important finding in two studies included in this review were cases with levels of IgM reagents found early in neonates. Whereas IgM antibodies does not usually cross the placental barrier due to its structure, it is possible that IgM was produced in the fetus in response to vertical transmission of SARS-CoV-2. However this is not conclusive evidence, and may also be due to placental alterations allowing the passage of IgM, or false positive testing. Robust studies with evaluation of placental tissue, umbilical cord blood, serology, and essential clinical data are needed to investigate this outcome. Until this outcome is better studied, it is crucial to screen pregnant women and implement strict infection control measures during delivery and puerperium, quarantine of infected mothers, and close monitoring of neonates at risk of COVID-19.

Our findings should be interpreted with caution. The studies included in this systematic review are limited to a few patients because COVID-19 is an emerging disease and the included studies are the only ones published until the time when women with and without COVID-19 infection are compared. Also, the studies present a high risk of bias because they did not consider confounding factors for the analysis of outcomes. There may be variations in the prevalence of premature birth according to other scenarios because the populations differ in terms of socioeconomic characteristics and clinical situations unrelated to COVID-19.

However, these results can provide valid preliminary data to the synthesis of available evidence and indicate the need for further epidemiological and clinical investigation in the obstetric area in the face of the COVID-19 infection pandemic. Due to the low level of evidence of this meta-analysis, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate found here. This systematic review was not recorded in a database of protocols, which represents a limitation.

Conclusion

COVID-19 in pregnant women may not be associated with the occurrence of preterm deliveries or the birth weight of newborn children, however the evidence to date is very uncertain. A few reports suggest that vertical transmission of SARS-CoV-2 to newborn is possible, but the evidence is still uncertain.

Contributors

G. C. Melo and K. C. G. M. Araújo contributed in the conception and design, acquisition of data, and analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval of the version to be published; and are responsible for all aspects of the work in ensuring the accuracy and integrity of any part of the work.

Additional informations

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Resumo

O número de casos confirmados de COVID-19 no mundo ultrapassou 1.684.833 em apenas quatro meses. Ainda não há evidências claras sobre os efeitos da COVID-19 em gestantes. Realizamos uma revisão sistemática e meta-análise em gestantes para esclarecer se a COVID-19 tem relação com a prematuridade e o peso ao nascer, além de resumir os resultados diagnósticos em recém-nascidos de mães com COVID-19 para investigar a possibilidade de transmissão vertical. Foram realizadas buscas em PubMed, Scopus, LILACS, Web of Science, Google Scholar, Preprints, bioRxiv e medRxiv. Como medidas de análise, utilizamos a razão de chances (OR) e a diferença média (DM). Foram calculadas estimativas sintéticas com o uso de modelos de efeitos randômicos. Trinta e oito estudos foram incluídos, com análise de dados de 279 mulheres, 60 das quais diagnosticadas com COVID-19. A meta-análise não mostrou associação significativa entre COVID-19 e parto prematuro (OR = 2,25; IC95%: 0,96, 5,31; p = 0,06; I² = 0%). Não houve relação significativa entre peso ao nascer e COVID-19 (DM = -124,16; IC95%: -260,54, 12,22; p = 0,07; I² = 0%). Entre 432 recém-nascidos, 10 testaram positivos para SARS-CoV-2. Devido às características dos estudos, o nível de evidências do estudo foi considerado muito baixo. A COVID-19 em gestantes pode não estar associada à ocorrência de prematuridade ou peso ao nascer, mas as evidências acumuladas até o momento não são conclusivas. Alguns relatos sugerem que a transmissão vertical do SARS-CoV-2 para o feto seja possível, mas as evidências ainda são incompletas.

COVID-19; Gravidez; Transmissão Vertical de Doenças Infecciosas

Resumen

En menos de cuatro meses, el total de casos confirmados de COVID-19 fue 1.684.833 en todo el mundo. Los resultados entre el colectivo de mujeres embarazadas con COVID-19 son todavía poco claros. Realizamos una revisión sistemática y metaanálisis para analizar si el COVID-19 en mujeres embarazadas está relacionado con el parto prematuro y peso al nacer, así como para resumir los resultados diagnósticos de los neonatos nacidos de madres con COVID-19, con el fin de investigar la posibilidad de una transmisión vertical. Las búsquedas se realizaron en PubMed, Scopus, LILACS, Web of Science, Google Scholar, Preprints, bioRxiv y medRxiv. Usamos odds ratio (OR) y la diferencia media (MD por sus siglas en inglés) como medida de análisis. El resumen estima que se calcularon usando modelos de efectos aleatorios. Se incluyeron 38 estudios; se analizaron datos de 279 mujeres; 60 pacientes fueron diagnosticados con COVID-19. El metaanálisis mostró que no hubo una asociación significativa entre la COVID-19 y el parto pretérmino (OR = 2,25; 95%CI: 0,96, 5,31; p = 0,06; I² = 0%). No se encontró una relación significativa entre el peso al nacer y el COVID-19 (MD = -124,16; IC95%: -260,54, 12,22; p = 0,07; I² = 0%). Entre 432 recién nacidos, 10 fueron diagnosticados como positivos tempranamente en SARS-CoV-2. Debido a las características de los estudios, el nivel de evidencia de este metaanálisis fue considerado como muy bajo. La COVID-19 en mujeres embarazadas, tal vez no está asociada con la ocurrencia de partos prematuros, o el peso al nacer en niños recién nacidos, no obstante, la evidencia hasta la fecha es muy dudosa. Algunos informes sugieren que la transmisión vertical del SARS-CoV-2 al recién nacido es posible, pero la evidencia todavía no está clara.

COVID-19; Embarazo; Transmisión Vertical de Enfermedad Infecciosa