Review PAPER

Intrauterine vertical transmission of COVID-19 during pregnancy: A systematic review

Jasim N. Al Asadi[1*], Sadiq M. Mousa [2]

1. Ph.D. (Community Medicine), Professor of epidemiology of non-communicable diseases, Department of Family & Community Medicine, College of Medicine, /University of Basrah/Basrah-Iraq
2. MB. ChB., M.Sc.(Community Medicine), Thi-Qar Health Directorate, Thi-Qar, Iraq

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Abstract

Background: COVID-19 infection in pregnancy raised concerns about the risk of intrauterine vertical transmission of the SARS-CoV-2 from mother to fetus.

Objectives: To review the current evidence on the possibility of intrauterine vertical transmission potential among COVID-19 infected pregnant mothers.

Methods: Eligible studies published from December 2019 until August 1, 2020, were searched for from PubMed, PubMed Central, Google scholar, medRxiv, and bioRxiv collection databases using MeSH-compliant keywords including COVID-19, pregnancy, intrauterine vertical transmission, Coronavirus 2019, SARS-CoV-2, 2019-nCoV, and maternal-fetal transmission.

Results: The initial search yielded 152 articles. After elimination of duplicates, review, commentaries, and articles from media, 78 articles were deemed relevant and comprised neonatal outcome data for 1231 neonates whose mothers were infected with COVID-19. Of these 78 articles, 24 articles that fulfilled the inclusion criteria were eventually selected for analysis yielding 517 neonates from 514 pregnancies (3 sets of twins). Most of the women (64.4%) were delivered by cesarean section. Vaginal delivery was reported in 31.7%, and in 20 women (3.9%), the mode of delivery was not reported. Of the total 517 neonates reported in the 24 analyzed articles, 51 neonates (9.9%; 95% CI, 7.4-12.8) were tested by positive by at least one of the investigation tools, and 38 neonates (7.3%; 95% CI, 5.3-9.9) were found positive for SARS-CoV-2 by RT-PCR nasopharyngeal swab.

Conclusion: The risk of intrauterine vertical transmission of SARS-CoV-2 in late pregnancy is possible but rare. However, the potential risk of vertical transmission in early pregnancy is not yet assessed.

Key words: COVID-19, intrauterine vertical transmission, neonate, pregnancy, SARS-CoV-2

Correspondence to: Jasim N. Al Asadi**,** Department of community medicine, College of medicine, University of Basrah

✉ jnk5511@yahoo.com
Tel. No. +9647801404284

Introduction

Coronavirus Disease 19 (COVID-19), which is officially named by World Health Organization (WHO) on February 11, 2020 [1] started in Wuhan City, China at the end of December 2019 [2] and spread quickly to involve many countries

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worldwide to be declared as "a public health emergency of international concern". [3] The virus that causes COVID-19 has been named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses. [4]

COVID-19 is a highly contagious disease with multiple possible routes of transmission.[5,6]

There are many studies, which indicate person-to-person transmission of the virus through close contact with infected person or through droplets when the patient coughs or sneezes, [7] or through surfaces touched by an infected person causing a series of respiratory illnesses. [8]

Several studies reported that the virus might be present in feces of some patients, which may be a potential route of transmission; however, such route is not a main feature of the epidemic. [9-11]

Vertical transmission is defined as "mother-to-fetus passage of a disease-causing agent (pathogen) during the period immediately before and after birth. Transmission might occur across the placenta, delivery via ingestion or aspiration of cervico-vaginal secretions, or immediately after birth via breastfeeding". [12]

SARS-COV-2 is a new strain of corona virus, which is recognized to be pathogenic to humans. The homological modeling indicated that SARS-CoV-2 has a similar structure of the receptor-binding domain to the other two famous strains of corona virus; the SARS-CoV-1 and the Middle-East respiratory syndrome (MERS) coronavirus (MERS-CoV). [13]

Previous studies revealed that SARS and MERS infection during pregnancy was associated with adverse maternal and neonatal complications including severe maternal illness and death, spontaneous abortion, preterm delivery, and intrauterine growth restriction. However, the likelihood of vertical transmission occurring with either SARS or MERS was low. [14,15]

It remains essential to see whether the risk of COVID-19 vertical transmission is low as that reported for SARS-CoV-1 and MERS infections.

Some concerns about the vertical transmission potential of Covid-19 and its impact on newborns were reported. [16,17]

Yet, there is existing controversy and non-reliable evidence for vertical transmission of COVID-19 during pregnancy and delivery. Given the importance of the subject and the lack of sufficient knowledge about the vertical transmission potential of COVID-19 in pregnant women, this study designed to review the published articles in this regard and to identify the possibility of intrauterine transmission of COVID-19 infection.

Methods

A retrospective review was done for all articles published in various databases including PubMed, PubMed central, MedRxiv, Scopus, and Google Scholar using MeSH-compliant keywords including COVID-19, Pregnancy, Vertical transmission, Coronavirus 2019, SARS-CoV-2 and 2019-nCoV from December 2019 to August 1, 2020. In addition, references lists of the identified articles were searched manually to recognize any relevant studies. All types of attained articles including clinical studies, primary case reports, case series, review studies, letters and comments about vertical transmission in COVID-19 infected pregnant women were screened.

From each study, various details including the study population, country, age of the mother,

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gestational age, mode of delivery, diagnostic measures, and neonatal outcome were extracted into excel file. The results of the relevant articles were summarized, analyzed, and reported. Studies, which were finally analyzed, should meet the following criteria; clinical studies, studies reporting original data, and studies that assessed the possibility of intrauterine vertical transmission in newborns of COVID-19 infected women who delivered, and found positive results in neonates by at least one method of investigations. Studies, which lack detailed data on neonatal testing and methods of testing, and review articles were excluded from analysis

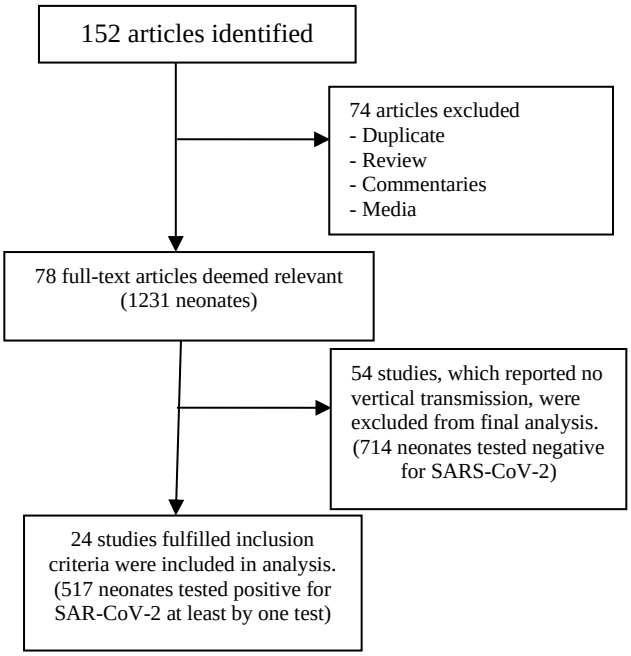

Figure 1 flow diagram of selection process of final included studies

Statistical analysis

The positive rates of the SARS-CoV-2 testing outcomes were estimated. Pooled proportions were calculated with percentages and 95% CI (Confidence interval). Calculations were done using the MedCalc Statistical Software version 19.3.1. [18]

Results

The initial search yielded 152 articles. After elimination of duplicates, review, commentaries, and articles from media, 78 articles were deemed relevant and comprised neonatal outcome data for 1231 neonates whose mothers were infected with COVID-19. Of these, 24 articles that fulfilled the inclusion criteria were eventually selected for analysis [19-42] [Table 1]. Of these 24 selected articles, 11 (45.8% were case reports, 10 (41.7%) were case series, and 3 (12.5%) were cohort studies. A total of 517 neonates from 514 pregnancies (3 sets of twins) were reported. Most of the women (64.4%) were delivered by cesarean section. Vaginal delivery was reported in 31.7%, and in 20 women (3.9%), the mode of delivery was not reported. The age of the women ranged from 20 to 41 years, and the gestational age ranged from 32-41 weeks.

Of the total 517 neonates reported in the 24 analyzed articles, 51 neonates (9.9%; 95% CI, 7.4-12.8) were tested positive by at least one of the investigation tools, and 38 neonates (7.3%; 95% CI, 5.3-9.9) were found positive by RT-PCR nasopharyngeal swab.

Combining all reviewed studies (78 articles) including those, which showed negative testing results and those used for analysis [Table 1] yielded 1231 neonates. Of those, 38 neonates were found to be positive for SARS-CoV-2 by nasopharyngeal swab RT-PCR giving a pooled proportion of 3.1% (95% CI, 2.2-4.2).

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Discussion

After primary infection of the mother, vertical transmission occurs via placenta during intrauterine life, during delivery through aspiration of cervico-vaginal secretions, and postpartum through breastfeeding.[43]

SARS-CoV-2 was found to have a structure with a receptor domain similar to that of SARS-CoV-1. [13] Therefore, it was assumed that the risk of vertical transmission and pathogenecity of COVID-19 may be similar to that of SARS CoV-1. [44]

Previous studies [45,46] showed that in infections caused by similar pathogen of corona virus such as severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), the fetal morbidity is not exclusively caused by vertical transmission.

In this review, most of the analyzed studies tend to conclude that the risk of intrauterine vertical transmission of SARS-CoV-2 is possible but uncommon. However, many other studies confirm no evidence of vertical transmission. [47--50] Such inconsistency and uncertainty about definite intrauterine vertical transmission may be due to first; nasopharyngeal, throat, and anal swabs cannot definitely indicate an intrauterine infection. [17] Many studies showed that most women who tested positive for COVID-19 by nasopharyngeal swabs were found to be negative by amniotic fluid and vaginal specimens. [17,51,52] Second; samples of placental tissues, amniotic fluids, and cord blood either not tested for viral particles or showed negative results[20,21,27,53] Third; in many studies, the investigations delayed 1-7 days after delivery. [20,21,41] In such case, the possibility of postnatal and nosocomial infection cannot be excluded. [54] Carosso et al [55] reported an asymptomatic female infant born by vaginal delivery to a covid-19 infected woman. The neonate was tested positive for SARS-C0V-2 by nasopharyngeal swab at delivery but negative after 36 hours. Placental swab on the fetal side was negative by RT-PCR as well as the vaginal swab, but the maternal rectal swab was positive. They concluded that the second negative result could be explained by the low amount of viral RNA in the second sample or due to fecal contamination through the vaginal canal.

Fourth; SAR-CoV-1, a corona virus with similar genome consequence was not found to be associated with intrauterine vertical transmission. [14,17,56] Fifth; the infrequent occurrence of placental infection with SARS-CoV-2 may be attributed to the minimal placental expression of angiotensin-converting enzyme 2 (ACR2) receptors, which facilitates the cell entry of the virus, particularly during the first trimester of pregnancy. [57,58] Sixth; the presence of maternal fetal interface barrier, even it is not completely effective, could provide fetal protection against infection, [59,60] furthermore, immune cells in the placenta have antiviral ability. [61] Seventh; some studies, [19,22,62] postulate the probability of intrauterine vertical CVID-19 transmission on the basis of IgM detection in fetal blood. However, due to its structure, IgM antibody cannot usually cross the placental barrier. It was suggested that this could be a possible fetal immune response to the infection. [63] Such evidence is not crucial since placental alterations may allow passage of IgM, or the serological test might be false positive. Eighth, the detection rate by existing methods depends on viral load; therefore, the negative results in

placenta or umbilical cord nucleic acid might be false negatives. [44] Ninth, since all the infected women were in their late pregnancies (second or third trimester), it is difficult to have an idea about the dynamics of transmission of infection and the impact on the fetus when mother's infection occurs early in gestation, as there is no explicit data available yet. [32,64]

Few emerging studies assume the confirmation of intrauterine vertical transmission of SARS-CoV-2. Vivanti et al, [32] reported a proven case of transplacental transmission delivered for a COVID-19 infected woman in her late pregnancy delivered by a cesarean section. Histological examination and immunohistochemistry of the placenta showed chronic intervillous inflammation and very high viral load.

In addition to the nasopharyngeal and rectal swabs, amniotic fluid collected during cesarean section showed positive results by RT-PCR for both the E and S genes of SARS-CoV-2 in nonbronchoscopic bronchoalveolar lavage fluid collected at 1 hour of life and then repeated at 3 and 18 days of postnatal age.

Patane et al [41] reported the presence of SARS-CoV-2 RNA by RT-PCR on the fetal side of the placenta of two COVID-19 infected mothers whose neonates were also positive for SARS-CoV-2 at birth raising the possibility of intrauterine vertical transmission of SARS-CoV-2 from mother to the fetus.

These results are supported by that of Facchetti et al [65] who analyzed by immunohistchemistry 101 placenta including 15 from COVID-19 infected women. In one case, expression of the S protein as well as the N (nucleocapsid) protein in the syncytiotrophoblast was shown. They provided evidence that SARS-CoV-2 can pass across the maternal-fetal interface to infect fetus prior to delivery. However, Hecht et al [58] reported that the best way to prove the infection of placenta is by identifying cellular evidence of viral infection rather than PCR detection of the virus in placental swab. They also indicated that the placenta could be infected by SARS-CoV-2 but this event is rare. Similarly, Penfield et al [66] reported that the existence of viral RNA in placental and membranes samples at time of delivery detected by RT-PCR was not found to be associated with infection of the neonates and not necessarily indicates vertical transmission.

In regards to nasopharyngeal swab RT-PCR, which is commonly used for testing for SARS-CoV-2 infection, the pooled proportion of possible vertical transmission was 3.1% (95% CI, 2.2-4.2). This result is in agreement with that reported by Kotlyar et al [67] systematic review and meta-analysis study.

Conclusion

Based on the results of this review, the risk of intrauterine vertical transmission of SARS-CoV-2 is controversial. It can occur but is rare. It was found that the virus could be detected in the placenta; however, the placenta can act as a barrier even if it is not completely effective. Extensive investigations and further studies are needed to examine the mechanisms and the placenta barrier particularly during early pregnancy.

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Table 1 Summary of the main studies' findings

Author, country	Type of study	Population	Maternal age (Years)	Gestational age (Weeks)	Mode of delivery	Investigations	NP RT-PCR + ve	Key findings
Dong et al., China[19]	Case report	1	29	34w+2days	CS	-IGM-IGG - INPS - Milk swab - Vaginal swab	0/1	- 1/1 5 minute Apgar (>7) - 1/1 IgM+IgG+ - Elevate IL6 - Negative INP swab - Negative Milk swab - Negative vaginal swab - Possible vertical transmission
Wang et al., China[20]	Case report	1	34	40	CS	- Cord Blood - Infant oropharngeal swab (IOPS) - Milk sample - Placenta tissue	1/1	- 1/1 5-minute Apgar (>7) - Infant nasopharyngeal swab +ve 36 hours after birth - Cord blood -ve - Placenta tissue -ve - Milk sample -ve - Possible vert. transmission
Yu et al., China[21]	Retrospective clinical series	7	29–34 Mean 32	37–41 Mean 39	CS	- Viral nucleic acid test (NAT) of throat swab, cord blood & placenta	1/3	- 7/7 5-minute Apgar (>7) - 4 infants not tested - 2/3 NAT -ve - 1/3 NAT +ve 36 hours after birth - NAT -ve for cord blood & placenta - suspected vert. transmission
Zeng et al., China[22]	Retrospective clinical series	6	NR	NR	CS	-IB -IgM-IgG, -ITS	0/6	- 6/6 5-minute Apgar (>7) - 6/6 -ve RT-PCR Throat swab - 2/6 +ve IgM+ IgG -3/6 +ve IgG but normal IgM - 6/6 increased IL6 - Suspected vert. transmission
Zhang et al., China[23]	Retrospective clinical series	4	NR	NR	CS	- INPS (2/4) - IS (anal swabs (2/4) -RT-PCR - CT	4/4	-1/4 no symptom -4/4 SARS-CoV-2(+) -vertical transmission is possible
Zamaniyan et al, Iran[24]	Case report	1	22	32	CS	- Amniotic fluid (AF) - Cord blood (CB) - vaginal swab (VS) - INPS - RT-PCR	0/1	- LBW infant - 5-minute Apgar (>7) - AF SARS-CoV-2 (+ - SARS-CoV-2 (+) after 24 h -vertical transmission is possible
Hu et al., China[25]	Retrospective clinical series	7	30-40	37-41	6/7 CS 1/7 VD	- Amniotic fluid (AF) - ITS+, - IB, IS, IU - RT-PCR	1/7	- 7/7 5-minute Apgar (>7) -1/7 Throat swab SARS-CoV-2 (+) 36 h

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								after delivery - Possible vertical transmission
Alzamora et al., Peru[26]	Case report	1	41	33	CS	- IgG-IgM - INPS, RT-PCR	1/1	- 5-minute Apgar (>7) - SARS-CoV-2 (+) 16 h & 48 h after delivery - IgG & IgM -Ve - Possible vertical transmission
Kirtsman et al., Canada[27]	Case report	1	40	35 +5 days	CS	-INPS -PT -IB - IS - RT-PCR	1/1	- 5-minute Apgar (>7) - 1/1INPS SARS-CoV-2 (+) at day1,2 & 7 after delivery -Probable case of vertical transmission
Ferrazzi et al., italy[28]	Retrospective case series	42	21-44 Mean 32.9	<34->37	24/42 VD 18/42 CS	- INPS, RT-PCR	3/42	- 40/42 5-minute Apgar (>7) - 3/42 SARS-CoV-2 (+) 2 at day 1 and 1 at day 3 after delivery] - Vertical transmission cannot be excluded
Nie et al., china[29]	Retrospective clinical series	28 (born to 27 pregnant women)	24-36	17- >37	22/27 CS 5/27 VD	- ITS (Done for 26 infants) -CB - PT - RT-PCR	1/28	- 5/28 LBW - 28/28 5-minute Apgar (>7) - 1/28SARS-CoV-2 (+) - CB & PT -ve - The infant tested -ve at days 4,8, and 15 afterbirth - cannot prove vertical transmission
Khan et al, China [30]	Case series	17	24-34	35-41	CS	- ITS - RT-PCR	2/17	- 3/17 LBW - 16/17 5-minute Apgar (>7) - 2/17 SARS-CoV-2 (+) 24 hours after delivery - The placenta, cord blood or amniotic fluid were not tested - No convincing evidence of vert. transmission
Yang et al, China[31]	Retrospective clinical series	24 (born to 23 women)	21-40	30-40	18/23 CS 5/23 VD	- IgG-IgM - INFS, RT-PCR	0/24	- 1/24 LBW - 1/24 10-minute Apgar (>7) - 1/24 IgG & IgM + - 23/24 TS -ve for SARS-CoV-2 - Suspected vert. transmission
Vivanti et al, France [32]	Case report	1	23	35	CS	- Amniotic fluid -Blood & bronchoalveolar lavage RT-PCR - INP swabs - Rectal swabs - Placenta tissue histology	1/1	- Bronchoalveolar lavage fluid +ve for SARS-CoV-2 - INP & rectal swabs +ve for SAR-CoV-2 - RT-PCR on the placenta +ve for SAR-CoV-2 - Proven case of transplacental transmission
Hinojosa-Velasco, Mexico [33]	Case report	1	21	38	CS	- INPS for RT-PCR during and after delivery - Mother milk - Infant stool	1/1	- 1/1 5-minute Apgar (>7) - INP S +ve for SAR-CoV-2 - Mother milk RT-PCR +ve for SAR-CoV-2 4 days after delivery - Infant stool RT-PCR +ve 4 days after delivery - intrauterine vertical transmission

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Wu et al, China [34]	Retrospective case series	30	29.6±3.6	NR	CS	- Throat swab - anal swabs qRT-PCR - IgM & IgG - chest X-ray - Chest CT scan	2/30	- 2 neonates tested + by throat swab RT-PCR - 2 neonates tested positive by IgM & IgG but negative by throat swab RT-PCR
Baud et al, Switzerland [35]	Case report	1	28	19	VD	- Amniotic fluid - Vaginal swab	0/1	- Still birth baby - Fetal lung, liver, mouth, cord blood, armpit, and thymus biopsies tested -ve by RT-PCR - Fetal surface of the placenta was +ve for SARS-CoV-2 at time of placenta expulsion and 24 h later - No evidence of vertical transmission
Hoseir et al, USA [36]	Case report	1	35	22	Dilatation & evacuation	Placenta RT-PCR Cord blood	NR	- Fetal heart and lung tissues were also tested and were found negative for viral RNA - Placenta + ve for SARS-CoV-2 - Cord blood +ve for SARS-CoV-2
Zeng L et al, China [37]	Cohort study	33	NR	31-41	CS 26 VD 7	- Nasopharyngeal and anal swabs - Amniotic fluid, cord blood, and breast milk	3/33	- 3/33 Nasopharyngeal and anal swabs were +ve for RASR-Cov-2 at days 2&4 - Amniotic fluid, cord blood, and breast milk, were negative for SARS-CoV-2
Pierce-Williams et al, United states [38]	Cohort study	33 (1 set twins)	NR	16-39	8/32 CS 24/32 VD	Nasopharyngeal swab	1/33	- 1/33 nasopharyngeal swab tested -ve at 24 hours of life was negative, but a repeat test at 48 hours was +ve
Bounsenso et al (Italy) [39]	observational study	2	42 years 38 years	- 37 weeks - 35 weeks	2/2 CS	Nasopharyngeal swabs RT-PCR - Breast milk	O/2 at birth But 1/2 On day 15	- 1/2 LBW - 2/2 Apgar's scores > 7 - 2/2 at birth and 3 days of life were negative to SARS-CoV-2 - At 2-week follow-up 1/2 tested positive - RT-PCR test on the placenta and cord blood was positive - IgG slightly positive
Knight et al, United Kingdom [40]	Cohort study	253	29-38	Median 34	- 156 CS - 106 V- - 4 Lost pregnancies	-Nasopharyngeal swab or aspirate RT-PCR	12/253	- 6/253 neonate tested +ve for SARS-CoV-2 < 12 hours - 6/253 tested + ve after > 12 hours
Patane et al, Italy [41]	Case report	22	NR	37 weeks 35 weeks	- 1 VD - 1CS - 20 NR	Nasopharnygeal RT-PCR swab - Placenta	2/22	- 1/2 NP RT-PCR +ve at birth, 2h hr, and 7 days later - 1/2 NP swab was -ve at birth , but + ve after 7 days - 2/2 placenta showed chronic intervillositis but placenta swabs were -ve by RT-PCR - Vertical transmission cannot be excluded
Govind et al, UK [42]	Case series	9	18-39	27-39	8 CS 1 VD	RT-PCR for SARS-Cov-2 nucleic acid nasal pharyngeal swabs performed.	1/9	Only one of the nine babies was subsequently confirmed as COVID-19 positive based on nasopharyngeal RT-PC

Abbreviations: AF, amniotic fluid; CB, cord blood; ITS, infant throat swab; M, milk; INPS, infant nasopharyngeal; swab; PT, placenta tissues; VS, vaginal swab; IOPS, infant oropharyngeal swab; IB, infant blood; IS, infant stool; IU, infant urine; IGJ, infant gastric juice; Nr, not reported; LBW, low birth weight; RT-PCR, reverse-transcription polymerase chain reaction

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الانتقال العمودي داخل الرحم لمرض فايروس كورونا المستجد (كوفيد- 19) أثناء الحمل: مراجعة منهجية

الملخص

خلفية البحث: أثارت عدوى فايروس كورونا المستجد (كوفيد- 19) أثناء الحمل مخاوف بشأن خطر الانتقال العمودي داخل الرحم لـ SARS-CoV-2 من الأم إلى الجنين.

الأهداف: مراجعة البَيِّنَة الحالية حول إمكانية انتقال العدوى داخل الرحم بين الأمهات الحوامل المصابات بمرض فايروس كورونا المستجد (كوفيد- 19).

الطرق: تم البحث عن الدراسات المؤهلة المنشورة من ديسمبر 2019 حتى 1 أغسطس 2020 من قواعد بيانات PubMed و PubMed Central و Google Scholar و medRxiv و bioRxiv باستخدام كلمات رئيسية متوافقة مع MeSH بما في ذلك COVID-19 والحمل والانتقال العمودي داخل الرحم وفيروس كورونا 2019 ، SARS-CoV-2، 2019-nCoV ، والانتقال من الأم الى الجنين.

النتائج: أسفر البحث الأولي عن 152 مقالاً. بعد إزالة التكرارات والمراجعة والتعليقات والمقالات من وسائل الإعلام ، تم اعتبار 78 مقالة ذات صلة وتضمنت بيانات نتائج لـ 1231 من حديثي الولادة الذين أصيبت أمهاتهم بـ COVID-19. من بين هذه المقالات الـ 78 ، تم أخيرًا اختيار 24 مقالة حققت معايير الاشتمال للتحليل وأسفرت عن 517 وليدا من 514 حالة حمل (3 مجموعات من التوائم). وُلدت معظم النساء (64.4٪) بعملية قيصرية.و 31.7٪ بالولادة المهبلية، وفي 20 امرأة (3.9٪) ، لم يتم ذكر طريقة الولادة. من اجمالي 517 وليدا الذي تم تحليل بيانتهم, 51 طفلا حديثي الولادة (9.9٪؛ 95٪ CI، 7.4- 12.8) اظهروا نتيجة ايجابية على الاقل بواحد من الفحوصات المجراة, و 38 حديثي الولادة (7.3٪ ، 95٪ CI، 5.3-9.9) كانت النتيجة ايجابية لفايروس SARS-CoV-2 بواسطة مسحة البلعوم الأنفي RT-PCR.

الاستنتاجات: إن خطر الانتقال العمودي داخل الرحم لـ SARS-CoV-2 في أواخر الحمل ممكن ولكنه نادر. ومع ذلك ، فإن الخطر المحتمل للانتقال العمودي في الحمل المبكر لم يتم تقييمه بعد

الكلمات المفتاحية: مرض فايروس كورونا المستجد (كوفيد- 19)، انتقال عمودي داخل الرحم ، حديثي الولادة ، الحمل

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