

Coronavirus disease 2019 and preterm birth: A systematic review and meta analysis

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Received: 2021-05-24.

Accepted: 2021-08-18



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J Clin Med Kaz 2021; 18(5):54-58

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Abstract

Background: The Coronavirus disease 2019 (COVID-19) has been a challenge for the healthcare system in most countries and its association with adverse pregnancy outcomes, especially preterm birth is controversial. The present study aims to understand the relation between severe acute respiratory syndrome coronavirus 2 infection of pregnancy and outcome of preterm birth.

Material and methods: A search was performed in Cochrane Library, PubMed, Scopus, E library and local databases up to 30 April, 2021. Searching strategy was used PICOS (Population, Intervention, Comparison and Outcomes, Study design) framework. Study group included COVID-19 pregnant patients compared with healthy pregnant women. Main outcome was perform birth (< 37 gestational week). The data were extracted from two authors and statistical analyses carried out using Review Manager (RevMan). Random-effects meta-analysis was conducted to calculate odds ratios (ORs) and weighted mean differences with 95% confidence intervals (CI).

Results: Twenty six cohort studies involving 436695 pregnant participants were included in this study. COVID-19 was associated with significantly increased risk of preterm birth [OR =1.30, CI = 1.20 to 1.39; p = 0.02; I² = 41%].

Conclusion: COVID-19 may be associated with increased risks of preterm birth, it is important to further understand the mechanism that explain the association and identify effective prevention methods to avoid COVID-19 caused adverse pregnancy outcome.

Key words: COVID-19, Premature Birth, SARS-CoV-2

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic is a challenge for the healthcare system in most countries with more than 160 million COVID-19 cases and 3.4 million deaths worldwide. The current outbreak of coronavirus disease 2019 (COVID-19) was first emerging in Kazakhstan on 13th March 2020 and quickly spread over all territories of the country [1]. The obstetric health care has always been an area of increased responsibility for the life and health of the mother and her child. Clinical protocols, standards and guidelines for managing pregnancy and childbirth are urgent in such a pandemic. In the Republic of Kazakhstan, up to 1st September, 2020, the registered number of pregnant COVID-19 cases reached to 4851, 3473 of which were pregnant, 1378 of which were postpartum, COVID-19 was confirmed in

8.75% of the newborns, 35.7% of infected newborns were born prematurely [2] and data from Russia, suggested that preterm birth rate of COVID-19 patient was 18.3% [3]. Findings from a multi-center study in Washington reported a higher infection rates in pregnant women coupled with an elevated risk of morbidity and maternal mortality [4]. High rate of adverse pregnancy outcomes including preterm birth among pregnant women with COVID-19 were reported in our country and worldwide [2, 4].

Pregnant women and their fetuses are more predisposed to infectious disease outbreaks and infection-associated morbidity and mortality, especially in the absence of established therapies [5]. In addition, disruption of health-care services and lack of attendance in health-care facilities may have indirect negative

impact on pregnancy outcomes. It's reasonable to believe that respiratory pathogens pose a threat to pregnant women, due to more cardiopulmonary burden than non-pregnant women. Although current observational data have described respiratory symptoms similar to the general population and large majority of cases are asymptomatic [3, 4], the hospital and intensive care unit (ICU) admission rates of pregnant women with the disease are higher than unaffected pregnant women [6]. Demographic factors, such as age, race, socioeconomic status, increased body mass index and preexisting comorbidity increase the risk of severe or critical COVID-19 symptoms and special clinical management, such as ICU, invasive ventilation, and extra corporeal membrane oxygenation [7]. In addition to the impact of COVID-19 infection on a pregnant woman, there are also concerns about possible effects on the fetus and newborn; for these reasons, mother to fetus vertical transmission of the SARS-CoV-2 has been required special attention. However, Available evidence warrants the mother to fetus vertical transmission of the SARS-CoV-2 is negligible [8].

Preterm births are the most common adverse pregnancy outcomes which can lead to neonatal complications and it is considered as the leading cause neonatal mortality and morbidity [9]. In Kazakhstan, the rate is as high as 15.2% in 2017 compare to 8.8% reported in 2010 [9]. Infectious diseases concomitant with inflammation play a key role in preterm parturition among current researched multifactorial etiology [9]. As a special population, SARS-CoV-2 infected pregnant women may be at higher risk for worse pregnancy outcomes when compared to the healthy matches [10, 11]. The possible effect on pregnancy and birth outcomes were reported inconsistently [12, 13]. An increased frequency of preterm births and caesarean deliveries in pregnant patients with COVID-19 was reported [14, 15]. However, SARS-CoV-2 related risk of preterm birth is conflicting. Limitation of population representativeness, sample size, lack of appropriate comparison may affect the variety of the results. To better understand the potential effect of the SARS-CoV-2 on pregnancy outcomes, the well-designed studies are essential which include pregnant women with and without COVID-19 in matches.

A systematic review and meta-analysis was conducted to review the impact of the COVID-19 on pregnancy outcomes to further understand the association between COVID-19 and adverse pregnancy outcomes.

Materials and methods

Searching and screening methods
PRISMA statement guidelines was used to instruct the present study [16]. The following data bases were used for access the available evidence: Cochrane Library, PubMed, Scopus, Google Scholar E library and local databases. "COVID-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS-CoV-2 OR 2019 novel coronavirus" AND "pregnancy outcomes OR preterm birth OR preterm delivery OR preterm labor " were used as search terms. All available observational studies published before 30th of April were included in this study. PECOS framework, including Population, Exposure, Comparison, Outcomes, and Study design, was used as a search strategy tool. Literature and systematic reviews, meta analyses, case reports, and case series were excluded from the study.

Methodological quality of the screened studies was independently assessed by two reviewers. The third reviewer was involved to get consensus. The following information was extracted from the included studies: the first author's last name, and countries of origin. Newcastle-Ottawa Scale (NOS) was

used to assess the quality of included cohort and case control studies. Sample representativeness, study subjects recruitment methods, case and control comparability, confounding variables were evaluated and enrolled respectively high and moderate-quality studies. Newcastle-Ottawa Scale contains 8 items within 3 domains and the total maximum score is 9. A study with score from 7 to 9 has high quality, with score from 4 to 6 has high risk, and with score from 0 to 3 has very high risk of bias.

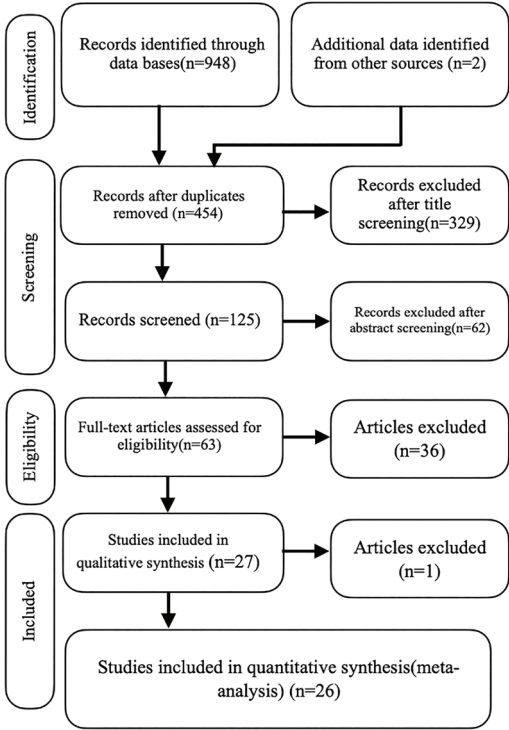
Data analysis

The data were extracted and statistical analyses carried out using Review Manager (RevMan) 5.4. We used unadjusted estimates for meta-analysis and Mantel– Haenszel method to combine data on dichotomous outcomes, and measures of effect are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity with the I2 statistic was used for the data evaluation and consideration for whether apply random effects model or a fixed effect model. When the value of $p < 0.05$, we considered statistically significant.

Results

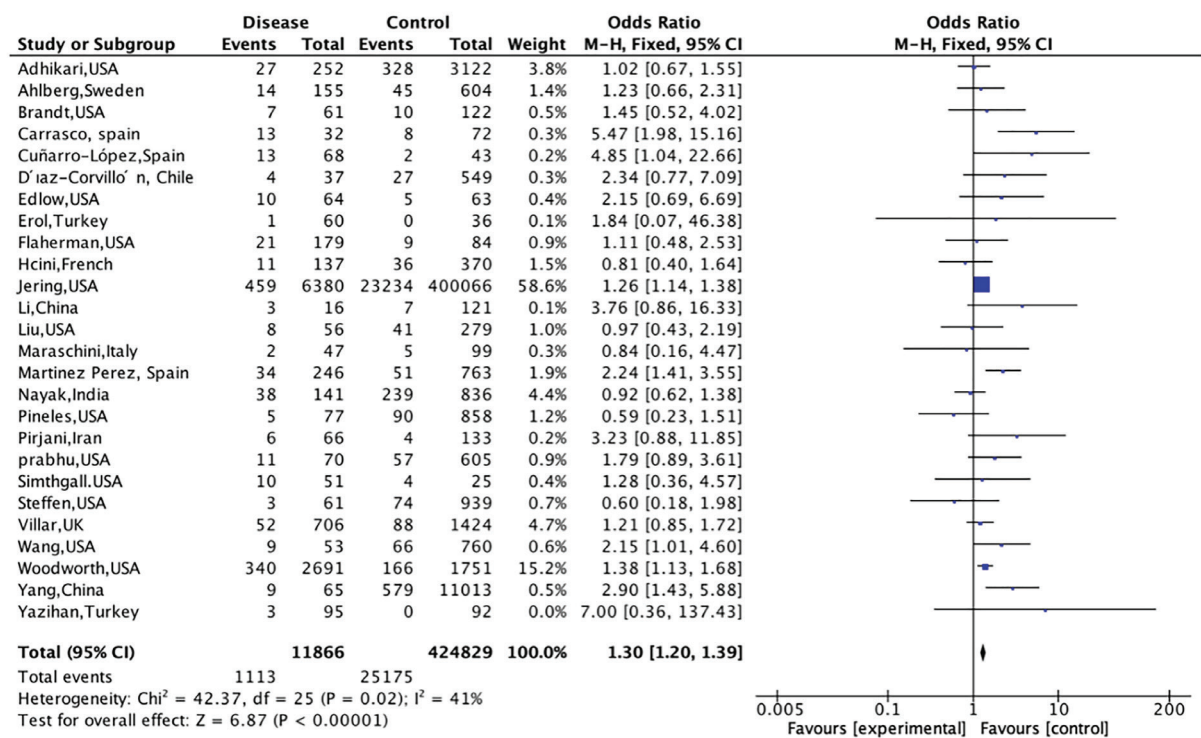
The search strategy resulted in 454 potentially relevant citations. We 391 excluded citations by screening the title and abstract. The PRISMA Flow Diagram (Figure 1) summarizes the process of literature search and selection of studies. After screening the titles and abstracts, we read 63 full-text papers and enrolled 26 studies with comparable outcomes [11-15, 17-36] and 10 of them were prospective cohorts, 13 were retrospective cohorts, 4 were case control studies.

Figure 1 - Flow diagram of the study search and identification



Of the 436695 pregnant participants, 11866 SARS-CoV-2 infected pregnant women and 424829 unaffected pregnant controls assessed for the SARS-CoV-2 on preterm birth in this systematic review and meta-analysis, compared with pregnant women without SARS-CoV-2 infection , the affected pregnant women were at higher risk of experience preterm birth (OR 1.30, 95% CI 1.20 to 1.39; $I^2 = 41\%$; 26 studies) (Figure 2).

Figure 2 - Forest plots of summary crude odds ratios (ORs) and 95% confidence intervals (CIs) for the association between coronavirus disease 2019 (COVID-19) and preterm birth. (patients with COVID-19 versus patients without COVID-19)



Discussion

At present, to understand the potential adverse effects of the disease on the course of pregnancy, perinatal outcomes, fetal health are critical to provide evidence-based recommendations to antenatal and obstetrical health care for pregnancy-specific administration and monitoring. This systematic review focuses on analysis the available global and local data on the effects of the COVID-19 pandemic on most prevalent pregnancy outcome, preterm birth. Our present study involved 436695 pregnant participants from different countries. Our result found COVID-19 in pregnancy is associated with preterm birth compared with no COVID-19 pregnancies. This finding suggests that health care system should be aware of the adverse outcome to manage, administer and monitor pregnancies in patients with COVID-19 and adopt effective strategies to prevent or reduce risks of adverse pregnancy outcomes.

The number of publications on COVID-19 in pregnant people continues to increase, along with the further understanding the nature of the virus. Case reports and case series were reviewed in the early stage of the pandemic, followed by systematic reviews included good-quality data, were well summarized the antenatal care and fetal surveillance clinical futures, maternal-fetal complications, vertical transmission status, treatment options and the possible negative effects on maternal and fetal outcomes [37, 38]. However, the data with regards to preterm birth is conflicting. A meta-analysis of recent good-quality cohort and case control studies suggested that COVID-19 is associated with a considerable risk of adverse pregnancy outcomes such as preterm birth, low birth weight and preeclampsia, and the risk was increased with the disease severity [38]. Another systematic review only involved the cohort studies which was consisted of positive cases with contemporaneous controls with negative test results to reduce the selection bias suggested a contrary conclusion regarding with preterm birth [37]. The original studies which were reported the relation of COVID-19

to adverse pregnancy outcomes had a different research design. Some studies used inappropriate control groups which included non-pregnant general population or without a comparison group, some of them didn't considered baseline of the selected population or confounding factors. This may confuse the effects of the virus.

The strengths of our study include the comprehensive search on the last global and local data which included appropriate comparisons, and included and synthesized a broad range of literature. Our findings suggest that local or neighbor studies are needed for contributing the international database after we screened the methodological part and design of the original studies.

Our meta-analysis also suggests that SARS-CoV-2 infection was associated with preterm birth compared with the absence of SARS-CoV-2 infection. The mechanisms underlying the association between COVID-19 and preterm birth are unclear, but the studies have shown that the pathogen may cause exaggerated systemic inflammatory responses which may disturb the optimal status of placenta for fetal growth and development [39]. Vascular malperfusion of the placenta-fetal unit may be the another contribution factor for developing the adverse pregnancy outcomes [40]. A recent study in the Netherlands found that COVID-19 mitigation measures were associated with a reduced incidence of preterm birth may suggested the adverse pregnancy outcomes may be influenced by changes of obstetric management during the pandemic condition. However, the reason for preterm birth was not clear, including if preterm birth was medically indicated or spontaneous.

Our study is limited by the inconsistency research design and heterogeneous quality of included studies. Preterm birth and COVID-19 infection have some major confounding factors like race/ethnicity, socioeconomic status, comorbidity like hypertension and diabetes which may bias the estimates. We enrolled studies regardless of the prospective and retrospective

design and baseline of the sample, this may increase the bias which caused by variety of adjusted and unadjusted estimates. The nature of observational studies contributes to the possibility of residual confounding. Secondly, the inconsistency of research population among the enrolled studies. In addition, our literature search was restricted to publications in Russian, Kazakh and English. Future studies are needed to collect more robust data to further validate or substantiate these findings, better understand the pathophysiologic pathways that explain these associations

and identify effective strategies to prevent adverse outcomes in pregnant people with COVID-19.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

References

1. Semenova Y, Glushkova N, Pivina L, Khismetova Z, Zhunussov Y, Sandybaev M, Ivankov A. Epidemiological Characteristics and Forecast of COVID-19 Outbreak in the Republic of Kazakhstan. *J Korean Med Sci.* 2020; 35(24):e227. doi: 10.3346/jkms.2020.35.e227.
2. Lokshin V.N., Sharman A.T., Mirzakhmetova D.D., Terlikbaeva A.T., Aimbetova A.R., Karibaeva Sh.K., Urazymbetova K.A. The modern organizational principles of specialized medical care for pregnant and puerperant women during the coronavirus pandemic in the Republic of Kazakhstan [in Russian]. *Akusherstvo i Ginekologiya/Obstetrics and Gynecology.* 2020; 12:34-43. doi:10.18565/aig.2020.12.34-43
3. Belokrinitskaya T.E., Artymuk N.V., Filippov O.S., Frolova N.I. Clinical course, maternal and perinatal outcomes of 2019 novel coronavirus infectious disease (COVID-19) in pregnant women in Siberia and Far East [in Russian]. *Akusherstvo i Ginekologiya/Obstetrics and gynecology.* 2021; 2:48-54. doi:10.18565/aig.2021.2.48-54
4. Lokken EM, Taylor GG, Huebner EM, Vanderhoeven J, Hendrickson S, Coler B, et al. Higher severe acute respiratory syndrome coronavirus 2 infection rate in pregnant patients. *Am J Obstet Gynecol.* 2021; S0002-9378(21)00098-3. doi: 10.1016/j.ajog.2021.02.011.
5. World Health Organization. Summary of probable SARS cases with onset of illness from November 2002 to 31 July 2003 [EB/OL]. (2004-04)[2020-01-19]. https://www.who.int/csr/sars/country/table2004_04_21/en/.
6. Narang K, Enninga EAL, Gunaratne MDSK, Ibiroga ER, Trad ATA, Elrefaie A, Theiler RN, Ruano R, Szymanski LM, Chakraborty R, Garovic VD. SARS-CoV-2 Infection and COVID-19 During Pregnancy: *A Multidisciplinary Review.* *Mayo Clin Proc.* 2020; 95(8):1750-1765. doi: 10.1016/j.mayocp.2020.05.011.
7. Hudak ML. Consequences of the SARS-CoV-2 pandemic in the perinatal period. *Curr Opin Pediatr.* 2021; 33(2):181-187. doi: 10.1097/MOP.0000000000001004.
8. Edlow AG, Li JZ, Collier AY, Atyeo C, James KE, Boatman AA, et al. Assessment of Maternal and Neonatal SARS-CoV-2 Viral Load, Transplacental Antibody Transfer, and Placental Pathology in Pregnancies During the COVID-19 Pandemic. *JAMA Netw Open.* 2020; 3(12):e2030455. doi: 10.1001/jamanetworkopen.2020.30455.
9. Vogel JP, Chawanpaiboon S, Moller AB, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. *Best Pract Res Clin Obstet Gynaecol.* 2018; 52:3-12. doi: 10.1016/j.bpobgyn.2018.04.003.
10. Martinez-Perez O, Prats Rodriguez P, Muner Hernandez M, The association between SARS-CoV-2 infection and preterm delivery: a prospective study with a multivariable analysis. *BMC Pregnancy Childbirth.* 2021; 21(1):273. doi: 10.1186/s12884-021-03742-4.
11. Villar J, Ariff S, Gunier RB, Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study. *JAMA Pediatr.* 2021; e211050. doi: 10.1001/jamapediatrics.2021.1050.
12. Carrasco I, Muñoz-Chapuli M, Vigil-Vázquez S, SARS-COV-2 infection in pregnant women and newborns in a Spanish cohort (GESNEO-COVID) during the first wave. *BMC Pregnancy Childbirth.* 2021; 21(1):326. doi: 10.1186/s12884-021-03784-8.
13. Jering KS, Claggett BL, Cunningham JW, Rosenthal N, Vardeny O, Greene MF, Solomon SD. Clinical Characteristics and Outcomes of Hospitalized Women Giving Birth With and Without COVID-19. *JAMA Intern Med.* 2021; 181(5):714-717. doi: 10.1001/jamainternmed.2020.9241.
14. Steffen HA, Swartz SR, Jackson JB, Kenne KA, Ten Eyck PP, Merryman AS, Castaneda CN, Marsden K, Maxwell T, Merrill AE, Krasowski MD, Rysavy MB. SARS-CoV-2 Infection during Pregnancy in a Rural Midwest All-delivery Cohort and Associated Maternal and Neonatal Outcomes. *Am J Perinatol.* 2021; 38(6):614-621. doi: 10.1055/s-0041-1723938.
15. Pineles BL, Alamo IC, Farooq N, Green J, Blackwell SC, Sibai BM, Parchem JG. Racial-ethnic disparities and pregnancy outcomes in SARS-CoV-2 infection in a universally-tested cohort in Houston, Texas. *Eur J Obstet Gynecol Reprod Biol.* 2020; 254:329-330. doi: 10.1016/j.ejogrb.2020.09.012.
16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009; 151(4):W65-94. doi: 10.7326/0003-4819-151-4-200908180-00136.
17. Hcini N, Maamri F, Picone O, Carod JF, Lambert V, Mathieu M, Carles G, Pomar L. Maternal, fetal and neonatal outcomes of large series of SARS-CoV-2 positive pregnancies in peripartum period: A single-center prospective comparative study. *Eur J Obstet Gynecol Reprod Biol.* 2021; 257:11-18. doi: 10.1016/j.ejogrb.2020.11.068.
18. Prabhu M, Cagino K, Matthews KC. Pregnancy and postpartum outcomes in a universally tested population for SARS-CoV-2 in New York City: a prospective cohort study. *BJOG.* 2020; 127(12):1548-1556. doi: 10.1111/1471-0528.16403. Epub 2020 Aug 13.
19. Smithgall MC, Liu-Jarin X, Hamele-Bena D, Cimic A, Mourad M, Debelenko L, Chen X. Third-trimester placentas of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive women: histomorphology, including viral immunohistochemistry and in-situ hybridization. *Histopathology.* 2020; 77(6):994-999. doi: 10.1111/his.14215. Epub 2020 Sep 26.
20. Díaz-Corvillón P, Mönckeberg M, Barros A, Illanes SE, Soldati A, Nien JK, Schepeler M, Caradeux J. Routine screening for SARS CoV-2 in unselected pregnant women at delivery. *PLoS One.* 2020; 15(9):e0239887. doi: 10.1371/journal.pone.0239887.

21. Brandt JS, Hill J, Reddy A, Schuster M, Patrick HS, Rosen T, Sauer MV, Boyle C, Ananth CV. Epidemiology of coronavirus disease 2019 in pregnancy: risk factors and associations with adverse maternal and neonatal outcomes. *Am J Obstet Gynecol*. 2021; 224(4):389.e1-389.e9. doi: 10.1016/j.ajog.2020.09.043. Epub 2020 Sep 25.
22. Flaherman VJ, Afshar Y, Boscardin J, Keller RL, Mardy A, Prah MK, Phillips C, Asiodu IV, Berghella WV, Chambers BD, Crear-Perry J, Jamieson DJ, Jacoby VL, Gaw SL. Infant Outcomes Following Maternal Infection with SARS-CoV-2: First Report from the PRIORITY Study. *Clin Infect Dis*. 2020; ciaa1411. doi: 10.1093/cid/ciaa1411.
23. Li N, Han L, Peng M, Lv Y, Ouyang Y, Liu K, Yue L, Li Q, Sun G, Chen L, Yang L. Maternal and Neonatal Outcomes of Pregnant Women With Coronavirus Disease 2019 (COVID-19) Pneumonia: A Case-Control Study. *Clin Infect Dis*. 2020; 71(16):2035-2041. doi: 10.1093/cid/ciaa352.
24. Maraschini A, Corsi E, Salvatore MA, Donati S; ItOSS COVID-19 Working Group. Coronavirus and birth in Italy: results of a national population-based cohort study. *Ann Ist Super Sanita*. 2020; 56(3):378-389. doi: 10.4415/ANN_20_03_17.
25. Nayak AH, Kapote DS, Fonseca M, Chavan N, Mayekar R, Sarmalkar M, Bawa A. Impact of the Coronavirus Infection in Pregnancy: A Preliminary Study of 141 Patients. *J Obstet Gynaecol India*. 2020; 70(4):256-261. doi: 10.1007/s13224-020-01335-3.
26. Pirjani R, Hosseini R, Soori T, Rabiei M, Hosseini L, Abiri A, Moini A, Shizarpour A, Razani G, Sepidarkish M. Maternal and neonatal outcomes in COVID-19 infected pregnancies: a prospective cohort study. *J Travel Med*. 2020 ; 27(7):taaa158. doi: 10.1093/jtm/taaa158.
27. Wang MJ, Schapero M, Iverson R, Yarrington CD. Obstetric Hemorrhage Risk Associated with Novel COVID-19 Diagnosis from a Single-Institution Cohort in the United States. *Am J Perinatol*. 2020; 37(14):1411-1416. doi: 10.1055/s-0040-1718403.
28. Patberg ET, Adams T, Rekawek P, Vahanian SA, Akerman M, Hernandez A, Rapkiewicz AV, Ragolia L, Sicuranza G, Chavez MR, Vintzileos AM, Khullar P. Coronavirus disease 2019 infection and placental histopathology in women delivering at term. *Am J Obstet Gynecol*. 2021; 224(4):382.e1-382.e18. doi: 10.1016/j.ajog.2020.10.020.
29. Yang R, Mei H, Zheng T, Fu Q, Zhang Y, Buka S, Yao X, Tang Z, Zhang X, Qiu L, Zhang Y, Zhou J, Cao J, Wang Y, Zhou A. Pregnant women with COVID-19 and risk of adverse birth outcomes and maternal-fetal vertical transmission: a population-based cohort study in Wuhan, China. *BMC Med*. 2020; 18(1):330. doi: 10.1186/s12916-020-01798-1.
30. Ahlberg M, Neovius M, Saltvedt S, Söderling J, Pettersson K, Brandkvist C, Stephansson O. Association of SARS-CoV-2 Test Status and Pregnancy Outcomes. *JAMA*. 2020; 324(17):1782-1785. doi: 10.1001/jama.2020.19124.
31. Cuñarro-López Y, Cano-Valderrama Ó, Pintado-Recarte P, Cueto-Hernández I, González-Garzón B, García-Tizón S, Bujan J, Asúnsolo Á, Ortega MA, De León-Luis JA. Maternal and Perinatal Outcomes in Patients with Suspected COVID-19 and Their Relationship with a Negative RT-PCR Result. *J Clin Med*. 2020; 9(11):3552. doi: 10.3390/jcm9113552.
32. Woodworth KR, Olsen EO, Neelam V, Lewis EL, Galang RR, Oduyebo T, Aveni K, Yazdy MM, Harvey E, Longcore ND, Barton J, Fussman C, Siebman S, Lush M, Patrick PH, Halai UA, Valencia-Prado M, Orkis L, Sowunmi S, Schlosser L, Khuwaja S, Read JS, Hall AJ, Meaney-Delman D, Ellington SR, Gilboa SM, Tong VT; CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team; COVID-19 Pregnancy and Infant Linked Outcomes Team (PILOT). Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy - SET-NET, 16 Jurisdictions, March 29-October 14, 2020. *MMWR Morb Mortal Wkly Rep*. 2020; 69(44):1635-1640. doi: 10.15585/mmwr.mm6944e2.
33. Yazihan N, Tanacan A, Erol SA, Anuk AT, Sinaci S, Biriken D, Keskin HL, Moraloglu OT, Sahin D. Comparison of VEGF-A values between pregnant women with COVID-19 and healthy pregnancies and its association with composite adverse outcomes. *J Med Virol*. 2021; 93(4):2204-2209. doi: 10.1002/jmv.26631.
34. Adhikari EH, Moreno W, Zofkie AC, MacDonald L, McIntire DD, Collins RRJ, Spong CY. Pregnancy Outcomes Among Women With and Without Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *JAMA Netw Open*. 2020; 3(11):e2029256. doi: 10.1001/jamanetworkopen.2020.29256.
35. Edlow AG, Li JZ, Collier AY. Assessment of Maternal and Neonatal SARS-CoV-2 Viral Load, Transplacental Antibody Transfer, and Placental Pathology in Pregnancies During the COVID-19 Pandemic. *JAMA Netw Open*. 2020; 3(12):e2030455. doi: 10.1001/jamanetworkopen.2020.30455.
36. Erol SA, Tanacan A, Anuk AT, Evaluation of maternal serum afamin and vitamin E levels in pregnant women with COVID-19 and its association with composite adverse perinatal outcomes. *J Med Virol*. 2021; 93(4):2350-2358. doi: 10.1002/jmv.26725.
37. Huntley BJB, Mulder IA, Di Mascio D, Vintzileos WS, Vintzileos AM, Berghella V, Chauhan SP. Adverse Pregnancy Outcomes Among Individuals With and Without Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Systematic Review and Meta-analysis. *Obstet Gynecol*. 2021; 137(4):585-596. doi: 10.1097/AOG.0000000000004320.
38. Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. *CMAJ*. 2021; 193(16):E540-E548. doi: 10.1503/cmaj.202604.
39. Patberg ET, Adams T, Rekawek P, et al. COVID-19 infection and placental histopathology in women delivering at term. *Am J Obstet Gynecol*. 2020; [Epub ahead of print];S0002-9378(20)31194-7. doi: 10.1016/j.ajog.2020.10.020.
40. Tasca C, Rossi RS, Corti S, et al. Placental Pathology in COVID-19 Affected Pregnant Women: a Prospective Case-Control Study [published online ahead of print, 2021 May 5]. *Placenta*. 2021; doi:10.1016/j.placenta.2021.04.002