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Original Article

Nasopharyngeal SARS-CoV-2 load and perinatal outcomes after maternal infection diagnosed close to delivery

Alexandre J. Vivanti[a,*], Christelle Vauloup-Fellous[b], Asma Khalil[c], Dominique A. Badr[d], Francesco Raimondi[e], Serena Salome[e], Smriti Prasad[c], Giuseppe Portella[f], Mariano Fiorenza[f], Jacques C. Jani[d], Luce Landraud[g], Olivier Picone[h], Lucilla Pezza[i], Nadege Bourgeois-Nicolaos[j], Anne-Gael Cordier[a], Luca Vedovelli[k], Daniele De Luca[i]

[a] Division of Obstetrics and Gynecology, "Antoine Béclère" Hospital, Paris Saclay University Hospitals, APHP, Paris, France
[b] Division of Virology, "Paul Brousse" Hospital, Paris Saclay University Hospitals, APHP, Paris, France
[c] Fetal Medicine Unit, Department of Obstetrics and Gynaecology, St. George's University Hospitals NHS Foundation Trust, London, United Kingdom
[d] Department of Obstetrics and Gynecology, University Hospital Brugmann, Université Libre de Bruxelles, Belgium
[e] Division of Neonatology, Department of Translational Medical Sciences, "Federico II" University, Naples, Italy
[f] Division of Virology, Department of Translational Medical Sciences, "Federico II" University, Naples, Italy
[g] Division of Microbiology, "Louis Mourier" Hospital, Paris Saclay University Hospitals, APHP, Paris, France
[h] Division of Obstetrics and Gynecology, "Louis Mourier" Hospital, Paris Saclay University Hospitals, APHP, Paris, France
[i] Division of Pediatrics and Neonatal Critical Care, "A.Béclère" Medical Centre, Paris Saclay University Hospitals, APHP, Paris, France
[j] Division of Microbiology, "Antoine Béclère" Hospital, Paris Saclay University Hospitals, APHP, Paris, France
[k] Unit of Biostatistics, Epidemiology, and Public Health, Department of Cardiac, Thoracic, Vascular Sciences, and Public Health, University of Padova, Padova, Italy

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ABSTRACT

Background: The occurrence of COVID-19 during the pregnancy can cause several negative maternal and neonatal outcomes. Nasopharyngeal viral load is associated with inflammatory markers and might influence the disease severity in non-pregnant patients, but there are no data about the relationship between viral load and perinatal outcomes in pregnant patients.
Objective: To investigate the hypothesis that nasopharyngeal SARS-CoV-2 load (estimated with real-time polymerase chain reaction delta cycle (ΔCt), measured in hospital clinical laboratories) is associated with perinatal outcomes, when COVID-19 is diagnosed in the third trimester of pregnancy.
Study design: International, retrospective, observational, multi-center, cohort study enrolling 390 women (393 neonates, three pairs of twins), analyzed with multivariate generalized linear models with skewed distributions (gamma) and identity link. The analyses were conducted for the whole population and then followed by a subgroup analysis according to the clinical severity of maternal COVID-19.
Results: The estimated viral load in maternal nasopharynx is not significantly associated with gestational age at birth (adjusted B: -0.008 (95%CI: -0.04; 0.02); p = 0.889), birth weight (adjusted B: 4.29 (95%CI: -25; 35); p = 0.889), weight Z-score (adjusted B: -0.01 (95%CI: -0.03; 1); p = 0.336), 5′ Apgar scores (adjusted B: -0. -9.8e^{-4} (95%CI: -0.01; 0.01); p = 0.889), prematurity (adjusted OR: -0.97 (95%CI: 0.93; 1.03); p = 0.766) and the small for gestational age status (adjusted OR: 1.03 (95%CI: 0.99; 1.07); p = 0.351). Similar results were obtained in subgroup analyses according to COVID-19 clinical severity.
Conclusions: The estimated maternal nasopharyngeal viral load in pregnant women affected by COVID-19 during the third trimester is not associated with main perinatal outcomes.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has affected several pregnant women worldwide with possibly relevant consequences both on maternal and newborn health. In fact, COVID-19 is more severe in pregnant women than in age-matched, non-pregnant patients leading to higher rates of mortality, need for intensive care, stillbirth and post-partum depression [1–4]. On the neonatal side, babies born to mothers affected by COVID-19 have a higher chance to be preterm [5], to suffer from several typical neonatal disorders, such as respiratory distress and perinatal asphyxia [6], and to be admitted to neonatal intensive care

* Corresponding author at: Service de Obstetrique et Gynecologie, Hôpital A. Béclère, GHU Paris Saclay, APHP, 157 rue de la Porte de Trivaux, 92140 Clamart, France.
E-mail address: alexandre.vivanti@aphp.fr (A.J. Vivanti).

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units (NICU) [2]. Moreover, the World Health Organization recognized SARS-CoV-2 as a vertically transmittable virus and issued a definition for SARS-CoV-2 mother-to-child transmission [7], although this is considered a relatively uncommon event [8,9]. The mother-to-child transmission can rarely cause neonatal COVID-19, whose clinical features have been described in detail [10].

Nasopharyngeal viral load is known to be associated with inflammatory markers in non-pregnant COVID-19 patients [11], and may influence the clinical severity although its association with clinical outcomes is still debated as conflicting data are available [12]. Moreover, the relationship between SARS-CoV-2 viral load and perinatal outcomes in pregnant women affected by COVID-19 in late pregnancy is unknown. We hypothesized that nasopharyngeal viral load is associated with perinatal outcomes when COVID-19 is diagnosed in the third trimester of pregnancy, and, therefore, we sought to verify this.

Material and methods

Design

This was an international, retrospective, observational, multi-center, cohort study performed in tertiary referral academic centers in Belgium, France, Italy and United Kingdom. Centers have been chosen through contacts between peers, based on their research interest and availability of electronic patients' file databases. The study was registered in the ISRCTN registry (ISRCTN11681816) and the full protocol is available there. The study is pragmatic as it focused on the estimated viral load measured from the "real world" clinical activity, using techniques available in clinical laboratories rather than more refined methods performed in dedicated research structures. Moreover, the participation did not change the clinical management, which was provided according to local protocols, essentially based on optimal prenatal care and international guidelines. Study protocol was approved by institutional ethical board of the coordinating center (n.2020-A00924−35, on Nov 3, 2020 with approval for retrospectively collected data). Other participating centers attained local ethical approval, if needed and informed consent was also obtained from women, if needed, according to local regulations. European and local privacy policies were always respected. STROBE guidelines were followed for the manuscript preparation [13].

Patients

Pregnant women who gave birth between the onset of the first pandemic wave (spring 2020) and the end of summer 2021 were considered eligible if they presented COVID-19 related symptoms and the diagnosis was confirmed by real-time polymerase chain reaction according to World Health Organization criteria [14]. Additionally, to be enrolled in the study, their viral load should have been estimated by real-time polymerase chain reaction delta cycle (ΔCt) value for any viral gene. Exclusion criteria were the following: 1) any congenital malformations; 2) major genetic or chromosomal abnormalities; 3) missing outcome data (see below).

Data

Patients' data were extracted from the institutional electronic database of each center, where they were real-time collected during clinical care. Data were merged in a dedicated, secured and anonymized database, managed at the coordinating center. Only local investigators in each center maintained an identification log, separate from the spreadsheet used for data collection and analysis. Collected data were demographics, as well as basic clinical maternal and obstetrical data. Maternal COVID-19 severity was classified according to World Health Organization criteria [14]. The following were chosen as perinatal outcomes: gestational age at the birth (calculated on last menstrual period and early gestation ultrasonographic measurements), birth weight (measured in the delivery room with a dedicated scale after having stabilized and dried the neonate), birth weight Z-score (calculated according to AUDIPOG curves [15]), 5′ Apgar score, and cord arterial pH (available only in centers routinely measuring it). Additionally, prematurity (defined as gestational age $<37^{+0}$ weeks) and small for gestational age (SGA) weight (defined as birthweight < 10th percentile on the AUDIPOG curve [15]) were considered. The occurrence of any mother-to-child transmission was also defined and classified in three levels of likelihood according to the specific World Health Organization definition [7].

Viral load estimation

Nasopharyngeal swabs were obtained as soon as women reported COVID-19 related symptoms and were performed following US Center for Disease Control and Prevention guidelines [16]. Extraction and amplification were performed with commercial assay kits validated for SARS-CoV-2 diagnosis by national healthcare authorities and following manufacturer's recommendations. The assays included heterologous amplification systems (internal positive controls) to identify any possible inhibition and reagent validity [17]. The SARS-CoV-2 load was estimated for any viral gene, according to each laboratory protocol, by expert virologists blinded to any perinatal data. All ΔCt values were normalized for the number of analyzed cells. ΔCt values obtained on different viral genes were averaged for each patient and finally used to estimate the viral load. Results were interpreted following European centre for Disease Control guidelines and a ΔCt cut-off value of 35 was used as positive threshold [18].

Statistics

Being the first study on the topic, a formal sample size calculation was unfeasible. We originally thought to enroll a convenience sample size of at least 100 patients as it has been done in earlier studies on SARS-CoV-2 load in non-pregnant patients [11]. As the data collection was easy, we enlarged the population size collecting data from all available cases during the study period.

Descriptive statistics was used. To investigate the effect of the ΔCt value on the perinatal outcomes (gestational age, birth weight, birth weight z-score, 5′ Apgar score, prematurity, and SGA weight) we used multivariate generalized linear models with a skewed distribution (gamma) and identity link. Maternal age, time between COVID-19 diagnosis and delivery and the recruiting center were used as covariates in all models. Recruiting center was added as covariate as we anticipated differences in basic population details between the participating centers; the other covariates were added as they are known to potentially modify the perinatal outcomes. The analysis was first conducted for the whole population and then followed by a subgroup analysis according to the clinical severity of maternal COVID-19. *p*-values for ΔCt were also adjusted (Adj-*p*) considering the false discovery rate. Analyses were done with R software v.4.1.1 and *p*-values<0.05 was considered significant.

Results

Study flowchart is shown in the **online supplement:** 390 women were enrolled, and they gave birth to 393 neonates (three pairs of twins). The distribution of their basic data between recruiting centers is described in Table 1. The studied population consisted of 339 (86.9%) and 51 (13.1%) women affected by mild and moderate-to-severe COVID-19, respectively; their ΔCt was significantly different (mild: 27 [19−30], moderate-to-severe: 22 [18−27,31,32], $p = 0.006$). No maternal death occurred, and no patient needed extracorporeal life support. According to the WHO classification [7], three cases of

Table 1
Maternal and neonatal basic data. Data are expressed as median [25th; 75th percentile] or number (%), as appropriate. Abbreviations: COVID-19: Coronavirus Disease-2019; ICU: intensive care unit.

Maternal data (n = 390 pregnancies)	
Maternal age *(years)*	30.7 (5.5)
Cesarean section	152 (38.7%)
Cesarean section for COVID-19	17 (4.3%)
Gestational diabetes	134 (34.1%)
Systemic hypertension	12 (3%)
Asthma	20 (5%)
Gestational age at diagnosis *(weeks)*	35.7 (5.4)
Time between diagnosis and delivery (days)	3 [1–14]
Hospitalized for COVID-19	65 (16.5%)
Need for supplemental O_2	42 (10.7%)
ICU admission for COVID-19	18 (4.6%)
Nasopharyngeal ΔCt	26 [19–30,32]
Newborn data (n = 393 neonates)	
Gestational age at the birth *(weeks)*	39 [38; 40]
Birth weight *(grams)*	3145 [2790; 3530]
Birth weight Z-score	−0.22 [−0.93; 0.49]
Male sex	178 (45.3%)
Cord arterial pH	7.28 [7.23;7.34]
5′ Apgar score	9 [9;10]

Table 2
Effect of estimated SARS-CoV-2 load in the maternal nasopharynx on perinatal outcomes: analysis of the whole population. Adjusted *B* coefficient (with 95% confidence interval) are shown, together with crude and adjusted *p*-values. Abbreviations: Adj-*p*: p-values adjusted for the false discovery rate; CI: confidence interval; OR: odds ratio; SGA: small for gestational age.

	Adjusted *B* (95%CI)	*p*	Adj-*p*
Gestational age at the delivery	−0.008 (−0.04; 0.02)	0.597	0.889
Birth weight	4.29 (−25; 35)	0.775	0.889
Birth weight Z-score	−0.01 (−0.03; 1)	0.056	0.336
5′ Apgar score	$-9.8e^{-4}$ (−0.01;0.01)	0.889	0.889
	Adjusted OR (95%CI)	*p*	Adj-*p*
Prematurity	0.97 (0.93; 1.03)	0.383	0.766
SGA	1.03 (0.99;1.07)	0.117	0.351

confirmed and one case of possible *in utero* SARS-CoV-2 mother-to-child transmission were reported: one of these neonates experienced neonatal COVID-19 with cerebral vasculitis [5], the others experienced typical prematurity-related complications. They were all admitted to NICUs and then recovered successfully.

Table 2 shows the main results: ΔCt was not significantly associated with gestational age at birth, birth weight, weight Z-score and 5′ Apgar score. There was also no significant effect of ΔCt on prematurity and SGA status. Table 3 shows the subgroup analysis for COVID-19 severity: there was no association of ΔCt with any perinatal outcome, except for gestational age at the delivery and birth weight in mothers with mild COVID-19. These latter had, however, tiny effect sizes and results were not confirmed by the adjusted *p*-values. Although cord pH had been originally considered, this was not analyzed for lack of sufficient data.

Discussion

Principal findings

Our findings show that the estimated viral load of SARS-CoV-2 in the upper airways of women affected by COVID-19 in the third trimester is not associated with relevant perinatal outcomes. Plasmatic viral load is linked to disease severity and mortality risk, while inflammatory and host response markers correlate with viral loads both in upper airways and plasma [11]. Despite these data, the association of nasopharyngeal SARS-CoV-2 with main clinical outcomes is still debated [12], supporting the concept that COVID-19 has a complex pathophysiology and its clinical consequences are also related to the host response and not only directly to viral invasion.

In this context, no data were available regarding the maternal viral load and possible perinatal consequences, and these were important to expand our knowledge. Our data come only now because the perinatal consequences of COVID-19 have been discovered relatively late due to the higher proportion of older patients affected by COVID-19 and the effect of lockdowns during 2020. These factors made initially difficult to understand the effect of COVID-19 on pregnant women and offspring.

Since COVID-19 during the pregnancy increases the risk for relevant negative outcomes, particularly if the disease occurs after 26 weeks' gestation [6], we might hypothesize that these consequences are unlikely to be significantly caused by SARS-CoV-2 load only. Excessive or dysregulated host inflammatory reaction might play a main role, as it is already known for severe consequences observed in

Table 3
Effect of estimated SARS-CoV-2 load in the maternal nasopharynx on perinatal outcomes: sub-group analysis according to maternal COVID-19 severity. Adjusted *B* coefficient (with 95% confidence interval) are shown, together with crude and adjusted *p*-values. Abbreviations: Adj-*p*: p-values adjusted for the false discovery rate; CI: confidence interval; SGA: small for gestational age.

	Mild			Moderate-to-severe		
	Adjusted *B* (95%CI)	*p*	Adj-*p*	Adjusted *B* (95%CI)	*p*	Adj-*p*
Gestation al age at the delivery	−0.03 (−0.07; −0.002)	0.037	0.111	0.02 (−0.1; 0.14)	0.751	0.999
Birth weight	−10.9 (−20; −1.8)	0.019	0.111	4.29 (−25.1; 35.2)	0.775	0.999
Birth weight Z-score	−0.009 (−0.03; 0.007)	0.274	0.368	−0.015 (−0.05; 0.02)	0.503	0.999
5′ Apgar score	−0.007 (−0.02; 0.006)	0.287	0.368	$1.75e^{-4}$ (−0.06; 0.06)	0.996	0.999
	Adjusted OR (95%CI)	*p*	Adj-*p*	Adjusted OR (95%CI)	*p*	Adj-*p*
Prematurity	1.03 (0.97; 1.11)	0.331	0.368	0.99 (0.88–1.12)	0.999	0.999
SGA	1.02 (0.98; 1.06)	0.368	0.368	1.02 (0.87; 1.19)	0.763	0.999

non-pregnant COVID-19 patients [31]. The peculiar immunological and hormonal features of pregnant women might facilitate this mechanism and increase the risk in this particular population [32]. The host reaction might also be a main responsible for the clinical features observed in cases of neonatal COVID-19 due to vertical transmission [5,10,19].

Despite these data, we cannot exclude that a combination of the two mechanisms, that is the viral cytopatic effect and the host response, might play a relevant role, at least in some patients. In fact, in more severe cases, SARS-CoV-2 has been detected in the bloodstream and thus it may directly reach the placenta and the fetus [20]. The occurrence of viremia does not seem a rare event [21], but its actual incidence in pregnant patients is unknown and no data about maternal viremia or placental viral load were available in our population. A specific study would be needed to clarify if maternal viremia is associated with perinatal outcomes, but such a study would present several logistic problems. Furthermore, SARS-CoV-2 has been only rarely detected in cord blood and in the placenta and, while this can be associated with neonatal COVID-19 [5,10] or miscarriage [22], it seems unlikely to be the main responsible for the observed increase in prematurity and perinatal morbidity [2,6].

Since, for all participating centers, the recruited cases were observed from the first pandemic wave to the end of summer of 2021, infections were represented by a mix of SARS-CoV-2 wild type and its $\alpha-$ and $\delta-$ variants. Certain variants are associated with higher viral loads [23] and might potentially entail a higher risk for placental infection: however due to the retrospective study design and the inconstant unavailability of viral sequencing during pandemic waves, it is impossible to evaluate the effect of any variant.

These data are useful to indicate possible strategies for the management of COVID-19 in pregnancy. If the excessive host inflammatory reaction is actually responsible for prematurity and other negative perinatal outcomes, through the so-called “cytokine storm” [24], the use of steroids could theoretically have a dual benefit since they might boost fetal lung maturation and, simultaneously, reduce the host response. Following this theory, steroids have been preliminarily recommended with both aims [25]. We consider our findings important to better understand the effect of SARS-CoV-2 infection during the pregnancy, but also for the organization of perinatal care. In fact, the aforementioned perinatal consequences of COVID-19 are strongly linked with the need of neonatal critical care. Furthermore, it is important to avoid NICU beds shortage since the number of neonates and infants needing critical care for reasons unrelated to COVID-19 is not decreasing [26,27].

Preterm labor and delivery are triggered by bio-active lipids, such as prostaglandins, whose release depends on secretory phospholipase A2 (sPLA2), the enzyme regulating the first step of the inflammatory cascade: thus, sPLA2 activity is increased in women giving birth prematurely [28,29], and inflammatory cytokines regulating sPLA2 expression are raised in pregnancy complicated by chorioamnionitis, which is often associated with preterm labor and delivery [30,33]. Unsurprisingly, sPLA2 activity is also increased in COVID-19 patients and associated with clinical severity, multi-organ failure and mortality [34]. Therefore, sPLA2 inhibition is currently under advanced clinical investigation in non-pregnant COVID-19 patients [35]. We need however to clarify the relationship between SARS-CoV-2 load, sPLA2 activity and perinatal outcomes to understand if targeting this pathway might be interesting in pregnant women. If so, clinically tested sPLA2 inhibitors with a good safety profile [36] could represent a dual weapon to reduce hyper-inflammation and block the cascade leading to preterm labor and parturition.

Limitations of this study include the retrospective design and the lack of multiple adjustments for other possible covariates, as well as the lack of other newborn anthropometric indexes and placental function measurements. Similarly inflammatory mediators and plasmatic viral load were not measured and are not available to explore the role of host response. Our data do not include patients with earlier (that is, first and second trimester) SARS-CoV-2 infections because they were not hospitalized, and therefore our population is skewed toward less severe or incidentally diagnosed infections. Interestingly, a recent study demonstrated that earlier infections in pregnancy were associated with increased risk for preterm birth and stillbirth [37], raising the question about the exposure time (that is, the time from infection to delivery). It is important to notice that most of SARS-CoV-2 infections occurred during late third trimester. Therefore, we cannot expect to correctly assess the risk of SARS-CoV-2 infections on growth restriction. Nonetheless, due to our study design, we cannot investigate the effect of exposure time. Further studies are warranted to clarify if there is a critical time window for SARS-CoV-2 load to influence COVID-19-related negative perinatal consequences. Conversely, we have analyzed a large cohort coming from tertiary referral centers in different countries pragmatically representing an optimal perinatal care level, thus these should be considered as “real world” data. More and above this, as vaccination of young women progress across the world, a study investigating this matter on a larger population and with a more refined design is unlikely to be conducted. Finally, 427 women were excluded due to a lack of availability of the Ct value for RT-PCR. Some women were able to be screened for SARS-CoV-2 internally within the referring departments. However, many women were tested in external laboratories and for these women, retrieval of the Ct value was not always possible. Our strengths are the novelty and timeliness of our data, their possible clinical and research implication and the quite large population analyzed with the best possible design.

In conclusion, the estimated maternal nasopharyngeal viral load in pregnant women affected by COVID-19 during the late third trimester is not associated with main perinatal outcomes, such as gestational age at the delivery or prematurity, birth weight, fetal growth or SGA status and Apgar score at 5 min.

Key points

#1 Nasopharyngeal viral load might influence the clinical severity in non-pregnant COVID-19 patients.

#2 The viral load in pregnant women is not associated with gestational age at the delivery or prematurity

#3 The viral load in pregnant women is not associated with birth weight and 5′ Apgar score

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jogoh.2023.102569.

References

[1] Chmielewska B, Barratt I, Townsend R, Kalafat E, van der Meulen J, Gurol-Urganci I, et al. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. Lancet Global Health 2021;9:e759–72. doi: 10.1016/S2214-109X(21)00079-6.

[2] Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 2020;370 m3320. doi: 10.1136/bmj.m3320.

[3] Khalil A, von Dadelszen P, Draycott T, Ugwumadu A, O'Brien P, Magee L. Change in the incidence of stillbirth and preterm delivery during the COVID-19 Pandemic. JAMA 2020;324:705. doi: 10.1001/jama.2020.12746.

[4] Badr DA, Mattern J, Carlin A, Cordier A-G, Maillart E, El Hachem L, et al. Are clinical outcomes worse for pregnant women at ≥20 weeks' gestation infected with

coronavirus disease 2019? A multicenter case-control study with propensity score matching. Am J Obstet Gynecol 2020;223:764–8. doi: 10.1016/j.ajog.2020.07.045.
[5] Vivanti A., Vauloup-Fellous C., Prevot S., Zupan V., Suffee C., Cao J.D., et al. Transplacental transmission of SARS-CoV-2 infection. In Review; 2020. https://doi.org/10.21203/rs.3.rs-28884/v1.
[6] Badr DA, Picone O, Bevilacqua E, Carlin A, Meli F, Sibiude J, et al. Severe acute respiratory syndrome coronavirus 2 and pregnancy outcomes according to gestational age at time of infection. Emerg Infect Dis 2021;27:2535–43. doi: 10.3201/eid2710.211394.
[7] 2020, https://www.who.int/publications/i/item/WHO-2019-nCoV-mother-to-child-transmission-2021., 1 n.d.
[8] Kotlyar AM, Grechukhina O, Chen A, Popkhadze S, Grimshaw A, Tal O, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. Am J Obstet Gynecol 2020. doi: 10.1016/j.ajog.2020.07.049.
[9] Marchand G, Patil AS, Masoud AT, Ware K, King A, Ruther S, et al. Systematic review and meta-analysis of COVID-19 maternal and neonatal clinical features and pregnancy outcomes up to June 3, 2021. AJOG Global Reports 2022;2:100049. doi: 10.1016/j.xagr.2021.100049.
[10] Raschetti R, Vivanti AJ, Vauloup-Fellous C, Loi B, Benachi A, De Luca D. Synthesis and systematic review of reported neonatal SARS-CoV-2 infections. Nat Commun 2020;11. doi: 10.1038/s41467-020-18982-9.
[11] The Massachusetts Consortium for Pathogen Readiness, Fajnzylber J, Regan J, Coxen K, Corry H, Wong C, et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. Nat Commun 2020;11:5493. doi: 10.1038/s41467-020-19057-5.
[12] Dadras O, Afsahi AM, Pashaei Z, Mojdeganlou H, Karimi A, Habibi P, et al. The relationship between COVID-19 viral load and disease severity: a systematic review. Immunity Inflam & Disease 2022;10. doi: 10.1002/iid3.580.
[13] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9. doi: 10.1016/j.jclinepi.2007.11.008.
[14] 2020, https://apps.who.int/iris/rest/bitstreams/1466546/retrieve
[15] 2020, https://www.audipog.net/Estimation-croissance#formu, n.d.
[16] 2020, https://www.cdc.gov/coronavirus/2019-ncov/hcp/inpatient-obstetric-healthcare-guidance.html. n.d.
[17] Uhteg K, Jarrett J, Richards M, Howard C, Morehead E, Geahr M, et al. Comparing the analytical performance of three SARS-CoV-2 molecular diagnostic assays. J Clin Virol 2020;127:104384. doi: 10.1016/j.jcv.2020.104384.
[18] 2020, https://www.ecdc.europa.eu/en/all-topics-z/coronavirus/threats-and-outbreaks/covid-19/laboratory-support/questions. n.d.
[19] Joma M, Fovet C-M, Seddiki N, Gressens P, Laforge M. COVID-19 and pregnancy: vertical transmission and inflammation impact on newborns. Vaccines (Basel) 2021;9:391. doi: 10.3390/vaccines9040391.
[20] Li Y, Schneider AM, Mehta A, Sade-Feldman M, Kays KR, Gentili M, et al. SARS-CoV-2 viremia is associated with distinct proteomic pathways and predicts COVID-19 outcomes. J Clin Invest 2021;131:e148635. doi: 10.1172/JCI148635.
[21] Järhult JD, Hultström M, Bergqvist A, Frithiof R, Lipcsey M. The impact of viremia on organ failure, biomarkers and mortality in a Swedish cohort of critically ill COVID-19 patients. Sci Rep 2021;11:7163. doi: 10.1038/s41598-021-86500-y.
[22] Baud D, Greub G, Favre G, Gengler C, Jaton K, Dubruc E, et al. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. JAMA 2020;323:2198. doi: 10.1001/jama.2020.7233.
[23] Huai Luo C, Paul Morris C, Sachithanandham J, Amadi A, Gaston DC, Li M, et al. Infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) delta variant is associated with higher recovery of infectious virus compared to the alpha variant in both unvaccinated and vaccinated individuals. Clin Infect Dis 2021:ciab986. doi: 10.1093/cid/ciab986.
[24] Yang L, Xie X, Tu Z, Fu J, Xu D, Zhou Y. The signal pathways and treatment of cytokine storm in COVID-19. Sig Transduct Target Ther 2021;6:255. doi: 10.1038/s41392-021-00679-0.
[25] 2020, https://www.rcog.org.uk/globalassets/documents/guidelines/2021-08-25-coronavirus-covid-19-infection-in-pregnancy-v14.pdf, n.d.
[26] De Luca D. Managing neonates with respiratory failure due to SARS-CoV-2. Lancet Child Adolescent Health 2020;4:e8. doi: 10.1016/S2352-4642(20)30073-0.
[27] Pozzi N, Cogo P, Moretti C, Biban P, Fedeli T, Orfeo L, et al. The care of critically ill infants and toddlers in neonatal intensive care units across Italy and Europe: our proposal for healthcare organization. Eur J Pediatr 2022. doi: 10.1007/s00431-021-04349-9.
[28] Lappas M, Rice GE. Phospholipase A2 isozymes in pregnancy and parturition. Prostaglandins, Leukotrienes Essent Fatty Acids 2004;70:87–100. doi: 10.1016/j.plefa.2003.04.001.
[29] Koyama M, Ito S, Nakajima A, Shimoya K, Azuma C, Suehara N, et al. Elevations of group II phospholipase A2 concentrations in serum and amniotic fluid in association with preterm labor. Am J Obstet Gynecol 2000;183:1537–43. doi: 10.1067/mob.2000.107789.
[30] Gomez-Lopez N, Romero R, Panaitescu B, Leng Y, Xu Y, Tarca AL, et al. Inflammasome activation during spontaneous preterm labor with intra-amniotic infection or sterile intra-amniotic inflammation. Am J Reprod Immunol 2018;80:e13049. doi: 10.1111/aji.13049.
[31] Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355–62. doi: 10.1038/s41577-020-0331-4.
[32] Kumar R, Yeni CM, Utami NA, Masand R, Asrani RK, Patel SK, et al. SARS-CoV-2 infection during pregnancy and pregnancy-related conditions: concerns, challenges, management and mitigation strategies—a narrative review. J Infect Public Health 2021;14:863–75. doi: 10.1016/j.jiph.2021.04.005.
[33] Gomez-Lopez N, Garcia-Flores V, Chin PY, Groome HM, Bijland MT, Diener KR, et al. Macrophages exert homeostatic actions in pregnancy to protect against preterm birth and fetal inflammatory injury. JCI Insight 2021;6:e146089. doi: 10.1172/jci.insight.146089.
[34] Snider JM, You JK, Wang X, Snider AJ, Hallmark B, Zec MM, et al. Group IIA secreted phospholipase A2 is associated with the pathobiology leading to COVID-19 mortality. J Clin Invest 2021;131:e149236. doi: 10.1172/JCI149236.
[35] 2020, https://clinicaltrials.gov/ct2/show/NCT04969991, n.d.
[36] De Luca D, Minucci A, Trias J, Tripodi D, Conti G, Zuppi C, et al. Varespladib inhibits secretory phospholipase a2 in bronchoalveolar lavage of different types of neonatal lung injury. J. Clin. Pharmacol. 2012;52:729–37. doi: 10.1177/0091270011405498.
[37] Piekos SN, Roper RT, Hwang YM, Sorensen T, Price ND, Hood L, et al. The effect of maternal SARS-CoV-2 infection timing on birth outcomes: a retrospective multicentre cohort study. Lancet Digital Health 2022;4:e95–104. doi: 10.1016/S2589-7500(21)00250-8.