J Gynecol Obstet Hum Reprod 52 (2023) 102579

Contents lists available at ScienceDirect

Journal of Gynecology Obstetrics and Human Reproduction

journal homepage: www.elsevier.com

CONTENTS

Indexed in: Embase, Pubmed/Medline, Science Citation Index Expanded, Scopus

Editorial

Original articles

Case report

Letter to the editor

Journal of Gynecology Obstetrics and Human Reproduction

Official journal of the French College of Obstetricians and Gynecologists
Collège National des Gynécologues et Obstétriciens Français (CNGOF)
http://www.cngof.fr/

Journal of Gynecology Obstetrics and Human Reproduction **Editorial Office**
Professeur Hervé Fernandez: JOGOH-GJP@elsevier.com

Submit a manuscript: https://www.editorialmanager.com/jogoh/

Guide for Authors available on the website: http://www.em-consulte.com/revue/jogoh

Indexed in: Embase, Pubmed/Medline, Science Citation Index Expanded, Scopus®

Journal of Gynecology Obstetrics and Human Reproduction (eISSN 2468-7847) 2023 (volume 52) monthly 10 issues. **E-only journal**. See complete rates on https://www.elsevier-masson.fr/journal-of-gynecology-obstetrics-and-human-reproduction.html. Address order and payment to Elsevier Masson SAS, Service Abonnements, 65, rue Camille-Desmoulins, 92442 Issy-les-Moulineaux Cedex, France: payment by check or credit card (CB, EuroCard, MasterCard or Visa: indicate no, and expiration date); CIC, n° RIB 30066 10947 00010034501 43.

Members of the French College of Obstetricians and Gynecologists (Collège National des Gynécologues et Obstétriciens Français/CNGOF) have special prices for their subscription. For further information, please contact the College.

Journal manager - Fabienne Loÿe. E-mail: JOGOH-GJP@elsevier.com
Head of Content Solutions - Monika Giergielewicz. E-mail: m.giergielewicz@elsevier.com
Supplements and Partnerships - Claire Ebersold. Tel.: +33 (0)6 61 94 44 14.
E-mail: c.ebersold@elsevier.com.
Advertising sales - Nathalie Gérard. Tel.: +33 (0)6 14 42 26 32. E-mail: n.gerard@elsevier.com
Subscriptions - Tel.: +33 (0)1 71 16 55 99. Fax: +33 (0)1 71 16 55 77. https://www.elsevier-masson.fr/journal-of-gynecology-obstetrics-and-human-reproduction.html
Publisher - Pascal Léger. Tel.: +33 (0)1 71 16 54 12. E-mail: p.leger@elsevier.com
General manager and publishing Director - Daniel Rodriguez

Subscription conditions, Guide for Authors, the contents of each issue as well as the abstracts of the articles published in *Journal of Gynecology Obstetrics and Human Reproduction* are available on the website of the Journal: http://www.em-consulte.com/revue/jogoh

---

E-only journal. eISSN : 2468-7847

J Gynecol Obstet Hum Reprod 52 (2023) 102566

Contents lists available at ScienceDirect

Journal of Gynecology Obstetrics and Human Reproduction

journal homepage: www.elsevier.com

Original Article

Impact of variants of SARS-CoV-2 on obstetrical and neonatal outcomes

M. Poisson[a,§], J. Sibiude[a,b,c,d,§], E. Mosnino[e], M. Koual[d,f], L. Landraud[b,d,g], N. Fidouh[h], L. Mandelbrot[a,b,c,d], C. Vauloup-Fellous[i,j], D. Luton[j,k], A. Benachi[e,j], A.J. Vivanti[d,j,#], O. Picone[a,b,c,d,#,*]

[a] AP-HP, Hôpital Louis Mourier, Department of Gynecology and Obstetrics, Colombes, France
[b] Université Paris Cité, IAME, INSERM, Paris, France
[c] Groupe de Recherche sur les Infections pendant la Grossesse, Colombes, France
[d] Fédération Hospitalo-Universitaire PREMA (FHU), Paris, France
[e] Division of Obstetrics and Gynecology, Antoine Béclère Hospital, Paris Saclay University Hospitals, APHP 157 rue de la Porte de Trivaux, 92140, Clamart, France
[f] AP-HP, Hôpital Bichat, Department of Gynecology and Obstetrics, Paris, France
[g] AP-HP, Hôpital Louis Mourier, Department of Hygiene and Microbiology, Colombes, France
[h] AP-HP, Hôpital Bichat, Department of Virology, Paris, France
[i] Saclay University, Gif-sur-Yvette, France
[j] AP-HP, Division of Virology, Paul Brousse Hospital, Paris Saclay University Hospitals, INSERM U1193, Villejuif, France
[k] APHP, Hôpital Bicêtre, Department of Gynecology and Obstetrics, Le Kremlin-Bicêtre, France

ARTICLE INFO

Article History:
Received 8 December 2022
Revised 7 February 2023
Accepted 27 February 2023
Available online 2 March 2023

Keywords:
COVID-19
SARS-CoV-2
Pregnancy
Outcome
Variant

ABSTRACT

Background: SARS-CoV-2 can lead to several types of complications during pregnancy. Variant surges are associated with different severities of disease. Few studies have compared the clinical consequences of specific variants on obstetrical and neonatal outcomes. Our goal was to evaluate and compare disease severity in pregnant women and obstetrical or neonatal complications between variants of SARS-CoV-2 that have circulated in France over a two-year period (2020–2022).

Method: This retrospective cohort study included all pregnant women with a confirmed SARS-CoV-2 infection (positive naso-pharyngeal RT-PCR test) from March 12, 2020 to January 31, 2022, in three tertiary maternal referral obstetric units in the Paris metropolitan area, France. We collected clinical and laboratory data for mothers and newborns from patients' medical records. Variant identification was either available following sequencing or extrapolated from epidemiological data.

Results: There were 234/501 (47%) Wild Type (WT), 127/501 (25%) Alpha, 98/501 (20%) Delta, and 42/501 (8%) Omicron. No significative difference was found regarding two composite adverse outcomes. There were significantly more hospitalizations for severe pneumopathy in Delta variant than WT, Alpha and Omicron respectively (63% vs 26%, 35% and 6%, $p<0.001$), more frequent oxygen administration (23% vs 12%, 10% and 5%, $p = 0{,}001$) and more symptomatic patients at the time of testing with Delta and WT (75% and 71%) versus Alpha and Omicron variants (55% and 66% respectively, $p<0.01$). Stillbirth tended to be associated with variants ($p = 0.06$): WT 1/231 (<1%) vs 4/126 (3%), 3/94 (3%), and 1/35 (3%) in Alpha, Delta and Omicron cases respectively. No other difference was found.

Conclusion: Although the Delta variant was associated with more severe disease in pregnant women, we found no difference regarding neonatal and obstetrical outcomes. Neonatal and obstetrical specific severity may be due to mechanisms other than maternal ventilatory and general infection.

Introduction

The Coronavirus Disease pandemic, due to the SARS-Coronavirus-2 has been affecting our world since 2020, causing pneumonia, acute respiratory distress syndrome (ARDS), and multiorgan failure [1]. Thrombotic events have also been described [2–4]. Up to autumn of 2022, it has led to over 6 500 000 deaths in the world [5].

This RNA-messenger virus has been affected by several mutations that had an impact on virus transmissibility, disease severity, immune, therapeutic or diagnostic performances [6,7].

Since the emergence of these genetic modifications there has been questioning about their clinical implications. For example, the Alpha variant was characterized by increased virulence and transmissibility. [8] From the early July 2021, the Delta variant became the world's

* Corresponding author.
E-mail address: olivier.picone@aphp.fr (O. Picone).
§ MP and JS contributed equally and should be considered as first co authors
# AJV and OP contributed equally and should be considered as co-last authors

https://doi.org/10.1016/j.jogoh.2023.102566
2468-7847/

predominant form of SARS-CoV-2 variant and was associated with more transmission(8) and a higher risk of hospitalization or death [9,10]. Finally, the latest variant, Omicron, has been found to be associated with lesser severity [11].

Being pregnant is a risk factor for poor outcome, with greater need for oxygen administration, intensive care unit hospitalization or mechanical ventilation when compared to non-pregnant population [12,13]. There are also specific obstetrical complications of Covid-19, principally an increased rate of preterm birth, which can be spontaneous or medically induced if required by maternal illness severity. An increased risk of stillbirth directly related to SARS CoV-2 infection, but also potentially driven by placental lesions, has also been reported [14–16].

Few studies have compared clinical consequences of specific variants on obstetric and neonatal outcome. Our goal was to evaluate and compare disease severity in pregnant women and obstetrical or neonatal complications between variants of SARS-CoV-2 that have circulated in France over a two-year period (2020–2022).

Material and methods

Study design

This retrospective cohort study included all pregnant women with a confirmed SARS-CoV-2 infection (positive naso-pharyngeal RT-PCR test) from March 12, 2020 to January 31, 2022, in three tertiary maternal referral obstetric units in the Paris metropolitan area, France. The reasons for sampling were either maternal symptoms or contact case or systematic screening applied for every hospital admission in all centers regardless of the indication for admission, whether for inpatient care, labor or surgery, as recommended in France since May 2020r. Our study population comprised thus women who were or were not hospitalized.

Sample collection

Nasopharyngeal swabs were collected in Virocult viral transport media (Sigma, https://www.sigmaaldrich.com) and processed following US Center for Disease Control and prevention Guidelines [17]. All specimens were kept at +4 °C and tested within 24 h.

RT-PCR

Viral RNA was extracted from clinical samples and RealStar® SARS-CoV-2 RT-PCR Kit 1.0 (Altona Diagnostics GmbH, https://www.altona-diagnostics) targeting the E gene (specific for lineage B-beta-coronavirus) and the S gene (specific for SARS-CoV-2) was used according to manufacturer's recommendations. Alternatively, Thermofisher assay (Thermo Fisher Scientific, https://www.thermofisher.com) targeting the S-gene and ORF1AB gene was used. Both assays include a heterologous amplification system as internal positive control to identify possible RT-PCR inhibition and to confirm the integrity of the reagents of the kit. A 45 thermal cycling was performed. A cycle threshold <40 was interpreted as positive for SARS-CoV-2 RNA.

Variant identification

Variant identification was either available following sequencing, and if not available, it was extrapolated from epidemiological data as already done in some studies. *Seasely* et al., *Birol* et al., *and Adhikari* et al., for example, used local or official resources outlining periods of variants dominance to divide variants periods and thus patients groups. [18–21]

In our study, we used data regionally collected and weekly edited by *Santé Publique France*. Extrapolation was made if the predominant variant over the considered week accounted for more than 75% of the overall positive tests [22]. If the variant was not identified by sequencing AND the patient reported a positive test in a period with no variant exceeding 75% of tests positivity, this patient was excluded from our analysis (no extrapolation possible).

Variant screening with TaqPath assay (ThermoFisher, Waltham, Massachusetts, USA) and VirSNiP SARS-CoV-2 Spike 484K-501Y assay (TIB Molbiol, Berlin, Germany) allowed detecting common variants circulating during the period in France. Variants were further confirmed by Sanger sequencing of the S gene, and sequences analyzed on SeqScape 4 software.

Data

We collected retrospectively clinical and laboratory data for mothers and newborns that was prospectively entered in medical records.

Socio-demographic data included age, geographic origin, parity, body mass index (BMI), pre-existing medical condition and smoking status. Data collected concerning SARS-CoV-2 infection were gestational age at testing, reason for testing (symptoms or screening), symptoms at testing, hospitalization, oxygen administration, and management of severe disease if relevant.

We assessed the presence of suggestive lesions of viral pneumopathy in computed tomography chest scans when available as *proven pneumopathy*. Of note, not all women had a CT scan performed, even in case of severe disease.

Severity evaluation was performed using clinical criteria defined by *Wu and MacGoogan* and used by *World Health Organization (WHO):* mild disease (non-pneumonia, mild pneumonia), severe (dyspnea, polypnea, blood oxygen saturation < 93%) or critical disease (respiratory failure, septic shock, multiple organ dysfunction) [23].

Hospitalization was systematic in case of severe or critical disease or in case of concomitant obstetrical motive (i.e. non-reassuring fetal heart rate tracing). In mild pneumopathy, pregnant women would be admitted to maternity in case of relevant comorbidities or if occuring at an advanced gestational age.

Pregnancy data collected were presence of preeclampsia or not, delivery mode, and post-partum hemorrhage or not. Neonatal data collected were gestational age at birth, birth weight Z-score, arterial cord pH and Apgar scores, and neonatal intensive care unit (ICU) hospitalization and neonatal death.

Fetal macrosomia was suspected if estimated fetal weight was above the 95th centile of the national curves recommended by the French Fetal Ultrasound College. Small for gestational age was defined by a birthweight Z score less than −1.28 according to the reference curves of Salomon et al. [24].

The two primary outcomes were composite outcomes and were similar to those previously published. [25]

- The composite adverse obstetric outcome (CAOO) included preterm delivery (<37 WG), preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, unscheduled cesarean delivery, deep venous thrombosis (DVT), pregnancy loss at <24 WG, intrauterine fetal demise (fetal loss occurring after 15 WG), or maternal death.
- The composite adverse neonatal outcome (CANO) included low birthweight (<2500 g), neonatal intensive care unit (NICU) admission, or APGAR score of <7 at 5 min.

Secondary outcomes were disease severity (hospitalization for severe respiratory distress, oxygen administration, intubation, proven COVID pneumonia with characteristic CT-scan lesions), Intensive care unit (ICU) hospitalization, ARDS), neonatal acidosis, induction of labor due to maternal covid, cesarean delivery, neonatal complications, maternal complications (infection, postpartum hemorrhage), hospitalization rate, preterm labor, premature preterm rupture of membrane, and all compounds of both composite adverse obstetrical and neonatal outcomes.

Statistics

For descriptive statistics, we calculated means and standard deviations for continuous variables and percentages for categorical variables.

Comparisons between variants were conducted using Pearson's and Fisher's exact tests.

Sensitivity analysis

A sensitivity analysis was conducted by restricting the study population to women with symptoms at time of testing. Concerning delivery outcomes, because of higher missing data in this group, we conducted a sensitivity analysis with exclusion of the Omicron group.

Statistics were performed with Stata 14.2.

Ethics

The research protocol was approved by the institutional review board of *the French College of Obstetricians and Gynecologists (approval no. CEROG 2021 – OBST – 0602).* All data were de-identified. Written consent was not needed for this non interventional research.

Results

Descriptive data

Overall, 594 patients met the inclusion criteria during the study period. By comparison, there were nearly 11,500 deliveries in these three hospitals during this two-year period (respectively 3500, 3000 and 2500 deliveries per year).

Among them, 340/594 (57%) variants were identified by sequencing and 161/594 (27%) were extrapolated from epidemiological data. We excluded 84 patients for whom variant was unavailable nor extrapolated. We further excluded nine patients with rare variants (ie 2 "Belgian", 4 Beta, 1 Gamma, 2 others unknown). Centers 1, 2 and 3 respectively included 197, 159, and 145 patients. Fifteen (15/501, 3%) patients were lost to follow up. SARS-CoV-2 variants identified during the period were 234/501 (47%) wild type, 127/501 (25%) Alpha, 98/501 (20%) Delta, and 42/501 (8%) Omicron.

Regarding variants, three periods can be differentiated according to the regional Ile-de France descriptive data. Alpha variant was predominant from the second week of February 2021 through the first week of June 2021. Delta variant became prevalent in the first week of July 2021, until the Omicron variant outbreak, in December 2021, which has been largely dominating until the end of the study period (March 2022).

Population description at diagnosis

Mean maternal age was 32.4 years (26.9 – 37.8 years). Most patients were multiparas (65%, *N* = 326/501). Comorbidities were 9/501 (2%), pre-existing diabetes, 10/501 (2%) hypertension and 35/501 (7%) asthma. Active smoking was reported in 35/501 (7%) of women and 109/501 (22%) patients were obese (BMI ≥ 30 kg/m2).

Reasons for testing for SARS-CoV-2 were missing in 4% (22/501). Patients were symptomatic in 64% (322/501) and asymptomatic diagnosed by screening in 31% (157/501) .

Cough was the most common clinical symptom of SARS-CoV-2 infection, reported in 180/501 (36%) cases, followed by 158/501 (31%) sinusitis, 113/501 (22%) fever, and 85/501 (17%) dyspnea.

Less frequently reported symptoms were low back pain, asthenia, dysphagia, chest pain, hemoptysis, pyrosis, pruritus, vertigo and heart palpitations. In 3 cases, women consulted for decreased fetal movements and were diagnosed by systematic screening.

Parity, maternal age, and BMI did not differ significantly between groups with each variant, nor did the presence of preexisting medical conditions hence there was no difference regarding risk factors for severe infection. Gestational age at testing was significantly higher for the Omicron variant (93% being over 37 WG vs only 63% in WT, $p<0.001$) (table 1).

Primary outcomes

Regarding the two composite obstetrical and neonatal adverse outcomes, we found no significant difference according to the variant. Composite adverse obstetrical outcome was reported in 24% in the Delta cohort vs respectively 27%, 31% and 20% with WT, Alpha and Omicron variants respectively ($p = 0.51$). Likewise, the composite adverse neonatal outcome was reported with 11% vs 19%, 19% and 15% respectively ($p = 0.32$) (*table 2*).

*COVID severity and symptoms according to variant (*table 3*)*

There were significantly more hospitalizations for severe Covid with the Delta variant than WT, Alpha and Omicron respectively (63% vs 26%, 35% and 6%, $p<0.001$) and more frequent oxygen administration (23% vs 12%, 10% and 5%, $p = 0.01$). Specific comparisons between the Delta variants and other variants grouped as one were made and were highly significant ($p<0.001$, data not shown) concerning those two variables.

There were no significant differences for intubation, proven pneumonia, Intensive care unit (ICU) hospitalization, ARDS or COVID-induced delivery. Chest imaging was indicated according to local protocols, as mentioned above. No difference between variants was identified regarding findings when CT-scans were performed.

There were significantly more symptomatic patients at the time of testing with Delta and WT (75% and 71%) versus Alpha and Omicron variants (55% and 66% respectively, $p<0.01$).

Concerning initial symptoms, the Delta variant was associated with a higher frequency of symptoms for fever (27% vs 20%, 24% and 19% for WT, Alpha and Omicron, $p<0.001$), cough (57% vs 40%, 38% and 29%, $p = 0.01$), dyspnea (33% vs 15%, 21% and 7%, $p = 0.001$) and sinusitis (47% vs 30%, 42% and 32%, $p = 0.02$).

*Pregnancy outcomes according to the variant (*table 2*)*

There were 470/501 livebirths (94%). Pregnancy outcome was significantly associated with variant, (Table 2; $p<0.001$), with a trend toward a lower incidence of stillbirths with the WT variant ($p = 0.06$).

Medical termination of pregnancy was performed in 3/501 cases (1%). Two were for antenatal diagnoses of fetal anomalies unrelated to COVID-19, a case of cystic fibrosis and a case of Dandy-Walker malformation. Both were Alpha variants, asymptomatic and detected by systematic screening.

In the last case (Delta variant) the parturient was unconscious, remained in a critical state for one month, requiring extracorporeal oxygenation, and the aggravation of her condition required prompt delivery. Furthermore, fetal ultrasound at that moment showed major fetal cerebral ventricular dilatation with a high suspicion of cerebral damage due to low cardiac output syndrome from hemodynamic distress. Termination of pregnancy was decided and followed by immediate induction of labor that allowed a prompt improvement of maternal respiratory function.

Fetal loss by late miscarriage or extreme preterm birth (< 23WG) occurred in 1/234 (<1%) WT cases vs 1/127 (1%), 1/98 (1%) and 1/42 (2%) for Alpha, Delta and Omicron cases respectively. However, only one case complicated a severe Delta infection at 22.2 WG, two days after the introduction of extra corporeal oxygenation because the mother was in critical state. The other cases occurred following mild or asymptomatic SARS-CoV-2 infection.

Stillbirth occurred in 9/501 (2%) cases: only 1/234 (<1%) 1 case in the WT group vs 4/127 (3%), 3/98 (3%), and 1/42 (2%) in Alpha, Delta and Omicron cases respectively. The etiology was extensively investigated for all except for one case where autopsy was declined by parents. There was only one case in the WT cohort, concomitant with

Table 1
Maternal characteristics at diagnosis.

	Wild type (*N* = 234) N (%)	Alpha (*N* = 127) N (%)	Delta (*N* = 98) N (%)	Omicron (*N* = 42) N (%)	p
Maternal characteristics					
Maternal age (years)					
< 25	14 (6)	12 (9)	6 (6)	5 (12)	0.77
25–34	135 (58)	72 (57)	59 (60)	22 (52)	
≥ 35	85 (36)	43 (34)	33 (34)	15 (36)	
Body Mass Index (Kg/m2)					
< 25	103 (44)	60 (50)	40 (43)	12 (32)	0.23
25–29	84 (36)	30 (25)	30 (32)	13 (35)	
≥ 30	45 (19)	29 (24)	23 (25)	12 (32)	
Missing	*2*	*8*	*5*	*5*	
Geographic origin					
Europe	64 (32)	27 (22)	23 (24)	8 (19)	0.01
Sub Saharan Africa	56 (28)	25 (20)	20 (21)	13 (32)	
North Africa	53 (26)	57 (47)	43 (45)	14 (34)	
Asia	10 (5)	10 (8)	4 (4)	4 (10)	
America/Caribbean	18 (9)	3 (2)	5 (5)	2 (5)	
Missing	33	5	3	1	
Parity					
Nulliparous	78 (34)	50 (39)	26 (27)	16 (38)	0.28
Missing	2	0	2	0	
Previous medical condition					
Pre existing diabetes	4 (2)	3 (2)	2 (2)	0 (0)	0.92
Missing	1	3	0	0	
Hypertension	4 (2)	2 (2)	3 (3)	1 (2)	0.75
Missing	2	3	0	0	
Smoking	19 (8)	6 (5)	6 (6)	4 (9)	0.62
Missing	1	5	1	0	
Asthma	17 (7)	4 (3)	11 (11)	3 (7)	0.14
Missing	0	3	0	0	
Gestational age					
T1	20 (8)	2 (2)	0 (0)	0 (0)	< 0.001
T2	66 (28)	29 (23)	22 (22)	3 (7)	
T3	148 (63)	95 (75)	76 (78)	39 (93)	
Missing	0	1	0	0	

Pearson test or Fisher exact test as appropriate.
BMI: Body mass index.
Gestational age: first trimester up to 13 WG and 6 days (T1), 14 to 27 WG and 6 days for the second trimester (T2) and from 28 WG onfor the third trimester.

asymptomatic infection at 18.1 WG. This case was a recurrence of stillbirth, in the context of maternal preexisting diabetes mellitus. During the Alpha period, one case occurred at 37.1 WG during mildly symptomatic infection and placental pathology showed a 90% functional volume decrease, severe acute intervillous inflammation and positive SARS-CoV-2 RT-PCR. Only one case complicated a severe Alpha variant infection requiring ICU hospitalization at 22.4 WG. One case occurred at 26.1 WG in context of multiple pregnancy and a previously diagnosed fetal malformation. Other cases occurred during mild disease between 17.5 WG and 24 WG. In the Delta variant period, 3 cases of stillbirth were diagnosed between 18 WG and 23.3 WG and occurred within 7 days of mild disease evolution. The last case was diagnosed during a non-severe Delta variant infection at 23.2 WG. The patient presented to the emergency room the previous night with mild pneumopathy and fetal ultrasound at that time showed normal fetal heartbeats and movements. The patient was discharged after routine blood sampling. She was reconvened the next day due to severe biological abnormalities with disseminated intravascular coagulation (DIC) and fetal demise was then diagnosed by sonography, 5 days after symptoms began. One case was in the Omicron cohort, occurring 7 weeks following mild disease at 41.5 WG during routine post-dates screening.

The significant association between pregnancy outcome and variants persisted in sensitivity analysis restricted to symptomatic patients or after exclusion of Omicron variants (table 5).

When conducting specific comparisons between stillbirths versus all non-stillbirths with known pregnancy outcomes, we found a non-significant difference (1/231 in WT vs 4/126, 3/94 and 1/35 for Alpha, Delta and Omicron variants, $p = 0.06$) (table 2). This trend reached significance when restricting to symptomatic patients ($p = 0.04$) but further analysis was not pursued to avoid over-interpretation (data not shown).

Concerning deliveries, 165/501(34%) were induced by mechanical or hormonal methods, and 134/501 (27%) were cesarean sections of which 52 emergency C-sections. No significant association was found between variants and induced labor, cesarean birth, emergency C-section nor COVID-related delivery induction. Regarding medical reasons for induction of labor, fetal monitoring abnormalities were reported as the cause in 25 cases. In one case, emergency C-section was performed at 35 WG after diagnosis of DIC complicating COVID-19 infection. Resolution was quick in postpartum.

Post-partum hemorrhage occurred in *N* = 54/501 (11%) cases and appeared to be more frequent in the WT group (15%) when compared with Alpha, Delta and Omicron (9%, 5%, and 11%, $p = 0.05$).

No maternal death nor thrombotic event was registered in our cohort.

Neonatal outcomes (table 2)

Median birthweight was 3200 g. Median Z-score was −0.183 with 33/501 (5%) neonates being small for gestational age (SGA). Neonatal complications were essentially respiratory distress and neonatal icterus. No statistics have been made upon different complications. Neonatal intensive care hospitalization occurred in 55/501 (11%) cases and 2/501 neonates died (<1%). One of the deceased newborns was born 8 days earlier by emergency C-section at 27.6WG, his mother was infected with WT strain at time of delivery and C-section

Table 2
Delivery maternal and neonatal outcomes according to SARS-CoV-2 variants.

	WILD TYPE *N* = 234 N (%)	ALPHA *N* = 127 N (%)	DELTA *N* = 98 N (%)	OMICRON *N* = 42 N (%)	P
Pregnancy outcome					<0.001
Medical termination of pregnancy	0 (0)	2 (2)	1 (1)	0 (0)	
Stillbirth	1 (0)	4 (3)	3 (3)	1 (2)	
Late miscarriage	1 (0)	1 (1)	1 (1)	1 (2)	
Livebirth	229 (98)	119 (94)	89 (91)	33 (82)	
Unknown	3	1	4	7	
Obstetrical outcomes					
Induced labor	80 (35)	36 (29)	35 (37)	14 (40)	0.44
Trial of labor	184 (79)	108 (86)	80 (85)	33 (94)	0.09
Cesarean section	73 (31)	32 (26)	24 (25)	5 (14)	0.16
Emergency C-section	25 (11)	14 (11)	10 (11)	3 (9)	1
Post partum hemorrhage	34 (15)	11 (9)	5 (5)	4 (11)	0.05
Severe post partum hemorrhage	7 (3)	2 (2)	0 (0)	2 (6)	
Maternal death	0 (0)	0 (0)	0 (0)	0 (0)	
Composite Adverse Obstetrical Outcome (CAOO)	63 (27)	39 (31)	23 (24)	7 (20)	0.51
Neonatal outcomes					
Preterm birth < 37 WG	35 (15)	20 (16)	11 (12)	3 (9)	0.60
Severe preterm < 32 WG	14 (6)	4 (3)	5 (5)	0 (0)	0.36
Small for gestational age	16 (7)	9 (7)	6 (6)	2 (5)	0.99
NICU hospitalization	31 (13)	15 (13)	6 (7)	3 (9)	0.40
Neonatal acidosis	16 (7)	10 (9)	5 (6)	3 (10)	0.85
Neonatal Apgar score < 7 at 5 min	4 (2)	2 (2)	3 (3)	0 (0)	0.76
Neonatal death	2 (1)	0 (0)	0 (0)	0 (0)	0.76
Composite Adverse Neonatal Outcome (CANO)	44 (19)	23 (19)	10 (11)	5 (15)	0.32

Pearson test or Fisher exact test as appropriate.
Missing data was < 5 or 10% except for the following variable: delivery outcome.
Unknown outcome at delivery: lost to follow up (information missing over delivery even after due-date achievement).
Severe postpartum hemorrhage: total blood loss > 1000 ml.
Stillbirth*: over all non-stillbirth known pregnancy outcomes pooled together.
CAOO (composite adverse obstetric outcome): preterm delivery (<37 WG), preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, unscheduled cesarean delivery, deep venous thrombosis (DVT), preeclampsia, pregnancy loss at <24 WG, intrauterine fetal demise (fetal loss occurring after 15 WG), or maternal death.
CANO (composite adverse neonatal outcome): low birthweight (<2500 g), neonatal intensive care unit (NICU) admission, or APGAR score of <7 at 5 min.
NICU: Neonatal intensive care unit.
Small for gestational age: Z score <−1,28.
Neonatal acidosis: umbilical arterial pH < 7.15.
Premature birth: < 37 WG.
Severe premature birth: <32WG.

Table 3
Disease severity depending on SARS-CoV-2 variants.

	Wild type *N* = 234 N (%)	Alpha *N* = 127 N (%)	Delta *N* = 98 N (%)	OMICRON *N* = 42 N (%)	P
Reason for testing					
Reason for testing					
Screening	64 (29)	55 (45)	24 (25)	14 (34)	0.01
Symptoms	156 (71)	67 (55)	72 (75)	27 (66)	
Initial symptomatology					
Fever	48 (20)	30 (24)	27 (27)	8 (19)	<0.001
Cough	72 (40)	44 (38)	52 (57)	12 (29)	0.01
Dyspnea	27 (15)	25 (21)	30 (33)	3 (7)	0.001
Anosmia	39 (21)	18 (15)	17 (19)	3 (7)	0.16
Myalgia	41 (22)	27 (23)	22 (25)	9 (22)	0.97
Sinusitis	54 (30)	49 (42)	42 (47)	13 (32)	0.02
GI symptoms	13 (7)	11 (9)	14 (16)	5 (12)	0.15
Maternal severity					
COVID-related hospitalization	57 (24)	29 (23)	33 (34)	9 (22)	0.19
Hospitalization for severe COVID (among hospitalizations)	26 (26)	17 (35)	26 (63)	1 (6)	< 0.001
Oxygen administration	29 (12)	13 (10)	22 (23)	2 (5)	0.01
ICU hospitalization	16 (7)	9 (7)	9 (9)	0 (0)	0.25
Intubation	10 (4)	2 (2)	6 (6)	0 (0)	0.18
COVID pneumonia	27 (12)	19 (15)	18 (19)	2 (5)	0.12
ARDS	10 (4)	4 (3)	4 (4)	0 (0)	0.68
Induced delivery because of COVID-infection	21 (9)	10 (8)	8 (8)	1 (3)	0.75

Pearson test or Fisher exact test as appropriate.
Missing data was < 5 or 10% except for the following variables: Cough (14.2%), Fever (13.7%), dyspnea (13.8%), anosmy (14.6%), myalgy (14.8%), sinusitis (14.6%), gastro-intestinal symptoms (14.8%).
GI: gastro-intestinal.
ICU: Intensive care unit.
ARDS: Acute respiratory distress syndrome.
Hospitalization for severe COVID*: overall hospitalization causes happening during pregnancy.

Table 4
Pregnancy course according to SARS-CoV-2 variants.

	Wild type *N* = 234 N (%)	Alpha *N* = 127 N (%)	Delta *N* = 98 N (%)	OMICRON *N* = 42 N (%)	P
Hospitalization during pregnancy	97 (42)	47 (37)	42 (44)	17 (42)	0.75
Missing	1	1	3	2	
Hospitalization for premature labor	14 (14)	3 (6)	2 (5)	2 (12)	0.30
Hospitalization for PPROM	6 (6)	5 (10)	1 (2)	1 (6)	0.51
Prenatal ultrasound diagnosis of FGR	22 (9)	9 (7)	1 (1)	2 (6)	0.06
Pre eclampsia	7 (3)	1 (1)	2 (2)	2 (6)	0.28
Other pregnancy complications					
Gestational diabetes mellitus	41 (18)	27 (23)	22 (24)	3 (9)	0.14
Prenatal ultrasound diagnosis of macrosomia	16 (7)	14 (11)	9 (9)	7 (20)	0.08
Antenatal steroids	44 (19)	12 (10)	19 (20)	3 (8)	0.04

Pearson test or Fisher exact test as appropriate.
PPROM: Preterm premature rupture of membranes.
FGR: Fetal growth restriction, suspected if estimated fetal weight inferior to 10% of the CFEF national curves.
Macrosomia: estimated fetal weight over rating 95% of the national curves recommended by the French Fetal Ultrasound College - CFEF),.

had been performed for maternal severe COVID pneumonia requiring mechanical ventilation. He had received antenatal steroids and neuronal protection by Magnesium Sulfate administration.

The second child was slightly premature (36.2WG), delivered one month after the maternal COVID by cesarean section for vaginal bleeding in the context of placenta praevia and had neonatal respiratory distress preceding his death.

No differences were found between variants concerning prematurity, severe prematurity, neonatal acidosis (umbilical arterial pH <7.15), low Apgar score at birth (<7 at 5 min,) intensive care hospitalization or death or small for gestational age.

Pregnancy course according to variant (table 4)

No difference was found between variants for overall hospitalization rates (44% for Delta, vs 42%, 37% and 42% for WT, Alpha and Omicron, p = 0.75), nor for obstetrical complications such as preterm labor (equally, 5% vs 14%, 6% and 12%, p = 0.3) or premature preterm rupture of membrane (2% vs 6%, 10% and 6%, p = 0.51).

Fetal maturation with corticosteroids for any indication was administered more frequently in Wild Type and Delta variant than Alpha and Omicron (19% and 20% vs 10% and 8%, p<0.05).

SARS-CoV-2 variant was not associated with incidence of pre-eclampsia, gestational diabetes mellitus, or fetal macrosomia. There was a non-significant trend toward higher suspected fetal growth restriction risk in WT than Alpha, Delta and Omicron (9% vs 7%, 1% and 6%, p = 0.06).

Subgroup analysis (Table 5)

Results were similar in sensitivity analysis restricted to symptomatic patients.

Moreover, differences in postpartum hemorrhage were not significantly different in the sensitivity analysis (15% in WT vs 11%, 7% and 10% in Alpha, Delta and Omicron variant, p = 0.32).

Discussion

Main findings

Infection with the Delta variant was associated with a greater severity of COVID-19, but which did not lead to a significant difference regarding obstetrical and neonatal outcomes. Maternal severity was lowest with the Omicron variant, while there was a higher incidence of post-partum hemorrhage with the WT variant.

Results in the context of what is known

The greater severity of respiratory disease in case of the Delta variant in a pregnant population is consistent with existing literature on non-pregnant persons [8–10]. Adhikari et al. performed a multicenter cohort study including 1515 pregnant women in the USA, from May 2020 to September 2021, comparing maternal severity of the disease between the Delta variant surge from July to September with all other variants before this date. They found an increased severity for Delta variant and reported that over a quarter of pregnant patients diagnosed over one week were admitted for severe or critical illness. [18] In comparison, our hospitalization rate for the Delta variant was 63%.

Similarly, Seasely et al., in a retrospective monocenter cohort study comparing admission rates, neonatal and maternal outcomes between the pre-Delta period (March 2020 to May 2021) and the Delta period (July to August 2021), reported a higher proportion of severe or critical disease in the Delta period (36% vs 13%, aRR 2.76, 95% CI 1.73–4.40). They also found increased rates of cesarean delivery for maternal severity (71% vs 14%, aRR 4.94 95% CI 1.90–12.88), preterm birth (73% vs 32%, aRR 2.36 95% CI 1.68–3.32), and neonatal ICU admission (74% vs 44%, aRR 1.77 95% CI 1.25–2.51) [26]. More recently in France, a retrospective single-center study by *Zayet* et al. comparing 3 times periods (WT, Alpha and Delta) in 77 hospitalized pregnant women observed an increased risk of admission in ICU and need for oxygen support in the Alpha and mostly in the Delta variant period when compared to the WT period. [20]

To date, few studies have reported data on the Omicron period: a bicentric, binational retrospective study conducted in Turkey and United Kingdom, explored three time periods (pre-Delta, Delta and Omicron periods), and showed as previously that Delta was associated with more maternal severity. In this study, the Omicron wave was not associated with milder disease compared to the WT period [21]. A Japanese survey drawn from the national COVID-19 registry comparing respectively 111 and 119 hospitalized pregnant patients during the Delta and Omicron periods found different symptomatology and greater severity in the Delta cohort [27]. *Adhikari* et al. conducted a second cohort with similar design including the Omicron period and found greater severity in the Delta period and decreased severity of illness in the Omicron period, after adjustment for prior vaccination [19].

Concerning the trend toward a higher risk of stillbirth that we reported, this has been previously described for the Delta variant in a retrospective cohort study exploring the risk of stillbirth in women with COVID-19 compared to women without COVID-19. [28] The increased incidence of stillbirth had been primarily highlighted in few retrospective cohort studies without regards to variant identification, yet this study reported a higher magnitude of association

Table 5
Severity, pregnancy course and delivery issue in symptomatic patients according to SARS-CoV-2 variants.

	WILD TYPE *N* = 158 N (%)	ALPHA *N* = 84 N (%)	DELTA *N* = 74 N (%)	OMICRON *N* = 25 N (%)	p
Pregnancy outcomes					<0.001
Medical termination of pregnancy	0 (0)	0 (0)	1 (1)	0 (0)	
Stillbirth	0 (0)	3 (4)	3 (4)	1 (4)	
Late miscarriage	1 (1)	0 (0)	1 (1)	0 (0)	
Live birth	155 (98)	80 (95)	65 (88)	19 (76)	
Unknown	2	1	4	5	
Obstetrical outcomes					
Induced labor	51 (33)	27 (32)	27 (39)	9 (45)	0.6
Trial of labor	120 (76)	70 (84)	58 (83)	18 (90)	0.28
Cesarean birth	52 (33)	23 (28)	20 (29)	5 (25)	0.83
Emergency C-section	15 (9)	10 (12)	8 (11)	3 (15)	0.76
Post-partum hemorrhage	24 (15)	9 (11)	5 (7)	2 (10)	0.32
Severe post partum hemorrhage	24 (15)	9 (11)	5 (7)	2 (10)	
Maternal death	0 (0)	0 (0)	0 (0)	0 (0)	
Composite adverse obstetrical outcome (CAOO)	44 (28)	26 (32)	19 (27)	4 (20)	0.75
Neonatal outcomes					
Preterm birth < 37 WG	28 (18)	13 (16)	9 (13)	1 (5)	0.46
Preterm < 32 WG	12 (8)	2 (2)	5 (7)	0 (0)	0.25
Small for gestational age	10 (6)	7 (8)	4 (5)	0 (0)	0.55
NICU hospitalization	25 (16)	10 (12)	6 (9)	0 (0)	0.19
Neonatal acidosis	8 (5)	8 (11)	4 (7)	0 (0)	0.35
Neonatal Apgar < 7 at 5 min	3 (12)	2 (2)	3 (4)	0 (0)	0.74
Composite adverse neonatal outcome	33 (21)	15 (19)	9 (13)	1 (5)	0.28

Pearson test or Fisher exact test as appropriate.
Missing data was < 5 or 10% except for the following variable: delivery outcome.
Unknown outcome at delivery: lost to follow up (information missing over delivery even after due-date achievement).
Severe postpartum hemorrhage: total blood loss > 1000 ml.
CAOO (composite adverse obstetric outcome): preterm delivery (<37 WG), preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, unscheduled cesarean delivery, deep venous thrombosis (DVT), preeclampsia, pregnancy loss at <24 WG, intrauterine fetal demise (fetal loss occurring after 15 WG), or maternal death.
CANO (composite adverse neonatal outcome): low birthweight (<2500 g), neonatal intensive care unit (NICU) admission, or APGAR score of <7 at 5 min.
NICU: Neonatal intensive care unit.
Small for gestational age: Z score <−1,28.
Neonatal acidosis: umbilical arterial pH < 7.15.
Premature birth: < 37 WG.
Severe premature birth: <32WG.

during the Delta period when compared to the pre-Delta period (aRR 4.04, 95% CI 3.28−4.97 vs aRR 1.47, 95% CI 1.27−1.71). Stillbirth was also associated with maternal morbidity (ie, ICU admission aRR 2.74 95% CI 1.93−3.89) [29,30].

Fetal demise might be due to fetal hypoxia associated with maternal decreased oxygenation, although only 1/9 cases occurred during severe COVID pneumonia. Feto-placental infection is another possibility, as pathology analysis has shown placental positivity during mild maternal disease. Coagulopathy and microvascular inflammation are involved even in non-severe or mild cases of maternal Sars CoV-2 infection. In light of similar findings of stillbirths occurring during asymptomatic infection, a prospective study in French Guyana hypothesized an implication of vascular damage in the feto-placental unit [31].

Excessive local immune response and resulting placental inflammation may promote transplacental transmission or placental insufficiency possibly leading to stillbirth [32,33].

Interpretation

The lack of differences in obstetrical and neonatal outcomes despite a greater respiratory severity of the Delta variant may have several causes. Acquired immunity (past infections, vaccination) can modulate and lower virulence of emerging variants, most certainly with Delta wave. For example, according to *Santé Publique France*, seropositivity rate of SARS-CoV-2 infection grew from 60.8% in May 2021 to 83.3% in October 2021, during Delta wave, when it was measured at a level of 20.6% in the beginning of Alpha wave (2021, February) [34]. As evidence accumulated regarding safety and efficacy of vaccination of pregnant women [35], COVID mRNA vaccines were approval in France in December 2020, pregnant women were declared high-priority for vaccination in April 2021, and the recommendation was extended to pregnancy first trimester in July 2021. Our study covers the whole epidemic from January 2020 to March 2022. While pregnant women are still excluded from therapeutic and vaccine trials, safety data are now reassuring regarding SARS-CoV-2 vaccination during pregnancy, regarding adverse events [36], perinatal complications [37,38] or fetal malformations [39,40]. In addition to reducing the risk of severe disease, vaccination against SARS-CoV-2 can also reduce the risk of prematurity and stillbirths in the general population [41]. Although vaccination rate is unknown in our study population, it is most certainly greater in the Delta period rather than Alpha period and may have weakened variant impact in our study.

We can also hypothesize that growing progress in the management of SARS-CoV-2-infected pregnant women during this crisis allowed the health care providers to both maintain maternal health, without any maternal death in our series, and prolong their pregnancy thus minimizing cases of induced prematurity and its own neonatal complications. The introduction of corticosteroids in hospitalized patients has led to improvements in maternal and fetal outcomes. [42−44] Although at the beginning of the pandemic C-section was often performed at diagnosis, we are now able to treat maternal hypoxemia thus avoiding fetal hypoxic lesions, which may have contributed to avoiding adverse obstetrical outcomes with the Delta variant. [45] Another hypothesis is that obstetrical and neonatal outcomes may be independent from the severity of maternal lung

disease, except for induced preterm birth and rare cases of fetal demise during extra corporeal oxygenation. COVID-19 has been shown to induce complex inflammatory phenomenon, with endothelial inflammation leading to microvascular complications [33,46]. COVID-19 might thus be considered as vascularitis, with specific complications when involving the placenta.

When compared to the outcomes in the French general pregnant population of the National Perinatal Study (*Enquête Nationale Périnatale*, ENP, 2016), our study highlights the obstetrical and neonatal impact of COVID regardless of the variant. Even with a study population slightly more comorbid than national benchmarks (diabetes, hypertension and overweight prevalence 2%, 2% and 50% in our study vs < 1%, <1% and 20% in the general population), there was a higher rate of prenatal hospitalization (40% vs 18%), need for fetal lung maturation (16% vs 5.9%), C-section (27% vs 20%, labor induction (27% vs 20% of deliveries), and preterm birth (14% vs 7.5%) [47].

Strengths and limitations

The main strength of our study is that it is the largest cohort to date comparing obstetrical and neonatal outcomes between variants among pregnant women to our knowledge. It is also one of the largest in literature regarding maternal severity between variants after Adhikari's and Zayet's studies [19,20]. Secondly, its multicenter design provides a better external validity than monocentric studies. Moreover, our study covers the pandemic until its main last surge. All SARS CoV-2 infections were diagnosed by biological testing. Although viral typing required recurrent sampling and was not systematically performed, variant identification by sequencing was available for more than 50% of the subjects in our study, and epidemiological extrapolation based on local data was conducted for the remainder, giving more accuracy to the identification than previous studies based only on the date of diagnosis. [18–21]. Inclusion of all patients with a positive RT-PCR test, and not restricting the study to the hospitalized people, also gave us a less biased vision of this disease than studies conducted only in hospitalized populations. This also contributes to give our study a better external validity.

There are also limitations to this study. RT-PCR tests have imperfect sensitivity as well as the possibility of prolonged positivity. Thus, we cannot eliminate the possibility that we over-diagnosed this disease during pregnancy (in the few cases diagnosed during the first trimester) and cannot assure that we were accurate regarding the trimester of infection. However, false positives concern only weakly positive PCR with CT>33 in asymptomatic patients and rarely exceeds 4 weeks. Variant distribution differed between centers, with smaller proportions of Delta variants in center 3 and no Omicron in center 2. The retrospective design of this study may be responsible for some bias, with a significant number of missing outcomes in the Omicron cohort restricting our interpretation. Furthermore, COVID testing practices changed over time, leading to a likely selection bias. During the first pandemic wave (Wild Type variant), because RT-PCR reagents were rare, only symptomatic patients were tested. Systematic screening at admission, in particular for delivery, was adopted homogeneously thereafter. Thus, the higher incidence of symptoms in the Delta cohort occurred despite a higher rate of screening, which reinforces our findings.

Omicron variant surge being apparently less severe, it can explain that patients were more likely to have been lost to follow-up, but these results must still be interpreted with caution. Especially for this variant, lack of power may have prevented us from finding significant associations.

Lack of data concerning vaccination in our pregnant population is also a limit of this study. This data was not available in medical files during this retrospective analysis. Further stratification upon vaccine status would be required.

Implication for practice

The higher severity that we report for the Delta variant concerning respiratory disease may guide clinical teams toward specific surveillance and follow-up in these cases. The fact that it is not related to obstetrical and neonatal complications can help us deliver reassuring information to the patients and insist on the importance of vaccination in this high-risk population.

Implication for research

In the event of the emergence of new variants, which is to be expected, their potential association with adverse outcomes will be crucial to evaluate. Further characterization of endothelial and placental phenomena associated to COVID-19 should be performed by biological and pathological investigations. Pre-clinical research may be interesting to explore how neonatal and obstetrical specific severity may be independent from maternal ventilatory and general infection.

Conclusion

During pregnancy, although maternal respiratory morbidity was greater with the Delta variant as in the general population, SARS-CoV-2 variants did not appear to be associated with significant differences in obstetrical and neonatal outcomes, except for a possible association with the risk of stillbirth in non-wild-type variants. Further studies investigating the endothelial pathology should be conducted in order to understand the fetal and placental effects of COVID-19.

Declaration of Competing Interest

There are no conflicts of interest.

Acknowledgements

none

References

[1] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the chinese center for disease control and prevention. JAMA 2020;323 (13):1239. Apr 7.
[2] Connors J.M., Levy J.H. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020 4;135(23):2033-2040.
[3] Schulman S. Coronavirus disease 2019, prothrombotic factors, and venous thromboembolism. Semin Thromb Hemost 2020;46(07):772–6 Oct.
[4] Miesbach W, Makris M. COVID-19: coagulopathy, risk of thrombosis, and the rationale for anticoagulation. Clin Appl Thromb 2020;26:107602962093814 Jan 1.
[5] WHO Coronavirus (COVID-19) Dashboard [Internet]. [cited 2022 Sep 22]. Available from: https://covid19.who.int
[6] Perez-Gomez R. The development of SARS-CoV-2 variants: the gene makes the disease. J Dev Biol 2021;9(4):58. Dec 15.
[7] Choi JY, Smith DM. SARS-CoV-2 variants of concern. Yonsei Med J 2021;62 (11):961.
[8] Lin L, Liu Y, Tang X, He D. The disease severity and clinical outcomes of the SARS-CoV-2 variants of concern. Front Public Health 2021;9:775224 Nov 30.
[9] Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. The Lancet 2021;397(10293):2461–2 Jun.
[10] Ong SWX, Chiew CJ, Ang LW, Mak TM, Cui L, Toh MPHS, et al. Clinical and virological features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern: a retrospective cohort study comparing B.1.1.7 (Alpha), B.1.351 (Beta), and B.1.617.2 (Delta). Clin Infect Dis 2021:ciab721. Aug 23.
[11] Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and outcomes of hospitalized patients in south africa during the COVID-19 omicron wave compared with previous waves. JAMA 2022;327(6):583–4 Feb 8.
[12] Badr DA, Mattern J, Carlin A, Cordier AG, 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(5):764–8 Nov.

[13] Allotey J, Fernandez S, Bonet M, Stallings E, Yap M, 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: m3320. Sep 1.
[14] Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun 2020;11(1):3572. Dec.
[15] Khalil A, Kalafat E, Benlioglu C, O'Brien P, Morris E, Draycott T, et al. SARS-CoV-2 infection in pregnancy: a systematic review and meta-analysis of clinical features and pregnancy outcomes. EClin Med 2020;25:100446 Aug.
[16] Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM 2020;2(2):100107 May.
[17] Interim guidelines for clinical specimens for COVID-19 | CDC [Internet]. [cited 2021 Jan 4]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html
[18] Adhikari EH, SoRelle JA, McIntire DD, Spong CY. Increasing severity of COVID-19 in pregnancy with Delta (B.1.617.2) variant surge. Am J Obstet Gynecol 2022;226 (1):149–51 Jan.
[19] Adhikari EH, MacDonald L, SoRelle JA, Morse J, Pruszynski J, Spong CY. COVID-19 cases and disease severity in pregnancy and neonatal positivity associated with delta (b.1.617.2) and omicron (b.1.1.529) variant predominance. JAMA 2022;327 (15):1500–2 Apr 19.
[20] Zayet S, Gendrin V, Gay C, Selles P, Klopfenstein T. Increased COVID-19 severity among pregnant patients infected with SARS-CoV-2 delta variant, France. Emerg Infect Dis 2022;28(5):1048–50 May.
[21] Birol Ilter P, Prasad S, Mutlu MA, Tekin AB, O'Brien P, von Dadelszen P, et al. Maternal and perinatal outcomes of SARS-CoV-2 infection in unvaccinated pregnancies during Delta and Omicron waves. Ultrasound Obstet Gynecol 2022 Apr 20. doi: 10.1002/uog.24916.
[22] Coronavirus : chiffres clés et évolution de la COVID-19 en France et dans le Monde [Internet]. [cited 2022 Aug 27]. Available from: https://www.santepublique-france.fr/dossiers/coronavirus-covid-19/coronavirus-chiffres-cles-et-evolution-de-la-covid-19-en-france-et-dans-le-monde
[23] Clinical management of COVID-19 patients: living guideline [Internet]. [cited 2022 Sep 22]. Available from: https://app.magicapp.org/#/guideline/j1WBYn
[24] Estimation of fetal weight: reference range at 20–36 weeks' gestation and comparison with actual birth-weight reference range - Salomon - 2007 - Ultrasound in Obstetrics & Gynecology - Wiley Online Library [Internet]. [cited 2022 Aug 27]. Available from: https://obgyn.onlinelibrary.wiley.com/doi/10.1002/uog.4019
[25] 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(10):2535–43 Oct.
[26] Seasely AR, Blanchard CT, Arora N, Battarbee AN, Casey BM, Dionne-Odom J, et al. Maternal and perinatal outcomes associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta (B.1.617.2) variant. Obstet Gynecol 2021;138(6):842–4 Dec.
[27] Shoji K, Tsuzuki S, Akiyama T, Matsunaga N, Asai Y, Suzuki S, et al. Comparison of clinical characteristics of COVID-19 in pregnant women between the Delta and Omicron variants of concern predominant periods. J Infect Chemother Off J Jpn Soc Chemother 2022 Sep 11S1341-321X(22)00264-1.
[28] DeSisto CL, Wallace B, Simeone RM, Polen K, Ko JY, Meaney-Delman D, et al. Risk for stillbirth among women with and without COVID-19 at delivery hospitalization — United States, March 2020–September 2021. Morb Mortal Wkly Rep 2021;70(47):1640–5 Nov 26.
[29] 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 Jul 10.
[30] KC A, Gurung R, Kinney MV, Sunny AK, Moinuddin M, Basnet O, et al. Effect of the COVID-19 pandemic response on intrapartum care, stillbirth, and neonatal mortality outcomes in Nepal: a prospective observational study. Lancet Glob Health 2020;8(10):e1273–81 Oct.
[31] Hcini N, Maamri F, Picone O, Carod JF, Lambert V, Mathieu M, et al. 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;257:11–8 Feb.
[32] Vivanti AJ, Vauloup-Fellous C, Escourrou G, Rosenblatt J, Jouannic JM, Laurent-Bellue A, et al. Factors associated with SARS-CoV-2 transplacental transmission. Am J Obstet Gynecol 2022;227(3):541–3 Sepe11.
[33] Lu-Culligan A, Chavan AR, Vijayakumar P, Irshaid L, Courchaine EM, Milano KM, et al. Maternal respiratory SARS-CoV-2 infection in pregnancy is associated with a robust inflammatory response at the maternal-fetal interface. Med 2021;2 (5):591–610 Maye10.
[34] Géodes - Santé publique France - Indicateurs : cartes, données et graphiques [Internet]. [cited 2022 Sep 12]. Available from: https://geodes.santepublique-france.fr/#bbox=112134,6339468,333003,236195&c=indicator&i=seroprev_sarscov_reg.seroprevalence_sarscov2&s=2021-42&selcodgeo=11&t=a01&view=map1
[35] Harder T, Külper-Schiek W, Reda S, Treskova-Schwarzbach M, Koch J, Vygen-Bonnet S, et al. Effectiveness of COVID-19 vaccines against SARS-CoV-2 infection with the Delta (B.1.617.2) variant: second interim results of a living systematic review and meta-analysis, 1 January to 25 August 2021. Eurosurveillance [Internet] 2021;26(41) Oct 14 [cited 2022 Mar 19]Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.41.2100920.
[36] Fu W, Sivajohan B, McClymont E, Albert A, Elwood C, Ogilvie G, et al. Systematic review of the safety, immunogenicity, and effectiveness of COVID-19 vaccines in pregnant and lactating individuals and their infants. Int J Gynaecol Obstet 2022;156:406–17.
[37] Fell DB, Dhinsa T, Alton GD, Török E, Dimanlig-Cruz S, Regan AK, et al. Association of COVID-19 vaccination in pregnancy with adverse peripartum outcomes. JAMA 2022;327:1478–87.
[38] Magnus MC, Örtqvist AK, Dahlqwist E, Ljung R, Skår F, Oakley L, et al. Association of SARS-CoV-2 vaccination during pregnancy with pregnancy outcomes. JAMA 2022;327:1469–77.
[39] Goldshtein I, Steinberg DM, Kuint J, Chodick G, Segal Y, Shapiro Ben David S, et al. Association of BNT162b2 COVID-19 vaccination during pregnancy with neonatal and early infant outcomes. JAMA Pediatr 2022;176:470–7.
[40] Ruderman RS, Mormol J, Trawick E, Perry MF, Allen EC, Millan D, et al. Association of COVID-19 vaccination during early pregnancy with risk of congenital fetal anomalies. JAMA Pediatr 2022;176:717–9.
[41] Hui L, Marzan MB, Rolnik DL, Potenza S, Pritchard N, Said JM, Palmer KR, Whitehead CL, Sheehan PM, Ford J, Mol BW, Walker SP. Reductions in stillbirths and preterm birth inCOVID-19 vaccinated women: a multi-center cohort study of vaccination uptake and perinatal outcomes. Am J Obstet Gynecol 2022.
[42] RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021;384(8):693–704 Feb 25.
[43] Saad AF, Chappell L, Saade GR, Pacheco LD. Corticosteroids in the management of pregnant patients with coronavirus disease (COVID-19). Obstet Gynecol 2020;136(4):823–6 Oct.
[44] Magala Ssekandi A, Sserwanja Q, Olal E, Kawuki J, Bashir Adam M. Corticosteroids use in pregnant women with COVID-19: recommendations from available evidence. J Multidiscip Healthc 2021;14:659–63 Mar 16.
[45] Huntley BJF, Huntley ES, Di Mascio D, Chen T, Berghella V, Chauhan SP. Rates of maternal and perinatal mortality and vertical transmission in pregnancies complicated by severe acute respiratory syndrome coronavirus 2 (SARS-Co-V-2) infection: a systematic review. Obstet Gynecol 2020;136(2):303–12 Aug.
[46] Fajgenbaum D.C., June C.H. Cytokine Storm. N Engl J Med . 2020 Dec 3;383 (23):2255-2273.
[47] [:*fr*]Les enquêtes nationales périnatales[:*en*]french national perinatal surveys[:] [Internet]. EPOPé; 2022. [citedMay 28]. Available from: http://www.xn--epop-inserm-ebb.fr/grandes-enquetes/enquetes-nationales-perinatales.

J Gynecol Obstet Hum Reprod 52 (2023) 102547

Contents lists available at ScienceDirect

Journal of Gynecology Obstetrics and Human Reproduction

journal homepage: www.elsevier.com

Letter to the Editor

SARS-COV-2 excretion and maternal-fetal transmission: Virological data of French prospective multi-center cohort study COVIPREG during the first wave

Keywords:
SARS-CoV-2
Pregnancy
Transmission rate
RT-PCR

Objective

Our objective was to evaluate SARS-CoV-2 excretion in different maternal sites at delivery and during the postpartum period. We also aimed to evaluate the materno-fetal transmission rate according to the WHO classification.

Study design

COVIPREG study is a prospective study conducted in France (The study was approved by the national ethics comity, the CPP SUD MEDITERRANEE (2020-A00924−35) on April 23, 2020, and recorded in the clinical trial registry (NCT04355234) during the first two waves of COVID-19 pandemic (inclusion between 04/28/2020 and 01/13/2021) and before vaccines availability. A written consent was obtained from both parents. In women with positive SARS-CoV-2 nasopharyngeal RT-PCR at any time during pregnancy, several samples were collected at delivery or in the 48H later, for RT-PCR analysis (vagina (VS), rectum (RS), Maternal blood (MB), nasopharynx (NP), Placenta (P), Amniotic fluid (AF) and milk (M)). In the neonate, Umbilical Cord Blood (UCB), NP, gastric fluid (GF), urine (U), and RS were collected to investigate transmission rate. A total of 12 samples could be collected from either the mother or the child. (Methods in Supplemental Data).

Results

310 women/child pairs were included in the study but unfortunately not all 12 samples were collected for each pair: in 297 pairs at least one maternal and one neonatal sample (excluding blood samples) was available (Fig. 1).

In our series, we identified a total of 31 women with at least one positive SARS-CoV-2 RT-PCR in one sample at delivery or in the post-partum period. Among those 7/31 (22.5%) were infected more than 5 weeks before delivery between 11.4 WG and 31.4 WG. The main maternal excretion sites were RS (20/272, 7.4%), followed by VS (5/255, 2.0%) and P (7/262, 2.7%). AF and M were found positive only once in two different mothers (1/176, 0.6%; 1/197, 0.5%). NP RT-PCR at delivery were negative for all mothers. There was no correlation between the different excretion sites.

At birth or during the first 48 h of life, 8/289 (2.8%) neonates had at least one SARS-CoV-2 positive RT-PCR in one sample site, and according to WHO classification, 5/289 (1.7%) cases of proven materno-fetal infection were diagnosed.

Among the 31 women with at least one positive SARS-CoV-2 RT-PCR and the 8 neonates with at least one positive SARS-CoV-2 RT-PCR, 5 women/child pairs both had at least one positive RT-PCR, 26 women had at least one positive RT-PCR without positive RT-PCR in their children and 3 children had at least one positive RT-PCR with an unknown mother's status at delivery. Among the 34 positive pairs (31 mother with a positive sample + 3 neonates with a positive sample with a mother without positive sample). 25positive mothers had symptoms.23/25 symptomatic mothers had a positive sample. 7 neonates had a positive sample (5/7 congenital infections, for 5 positive women/child pairs and 2 positive neonates with an unknown mother status). Ten mothers were hospitalized, 9 had a positive sample and 4 neonates had a positive sample (one positive neonate with an unknown woman status). Therefore, for the five identified neonates with congenital infections all mothers were symptomatic and 2/5 were hospitalized.

Discussion

Excretion in these different sites has been reported in small series in the literature (5 to 56 patients) [1–4]. Therefore, our series is the larger to date. Furthermore, in these series the delay between maternal SARS-CoV-2 infection and delivery was not stated.

Interestingly, none of the mothers whose neonate had a congenital infection, had positive RT-PCR in blood. However, all had either VS or RS positive RT-PCR. This observation suggests transmission mainly occurs during delivery. One neonate was positive at 48 h of life but was negative at birth, suggesting an immediate postnatal infection. Three neonates were positive at birth but negative in a RT-PCR later, suggesting a superficial exposure to SARS-CoV-2 (one mother had three positive samples (VS, RS and P), and two did not have any RT-PCR positive among samples collected). The rate of transmission we observe (1.7%) is similar to that was reported in the review of Poblete et al. [5].

https://doi.org/10.1016/j.jogoh.2023.102547

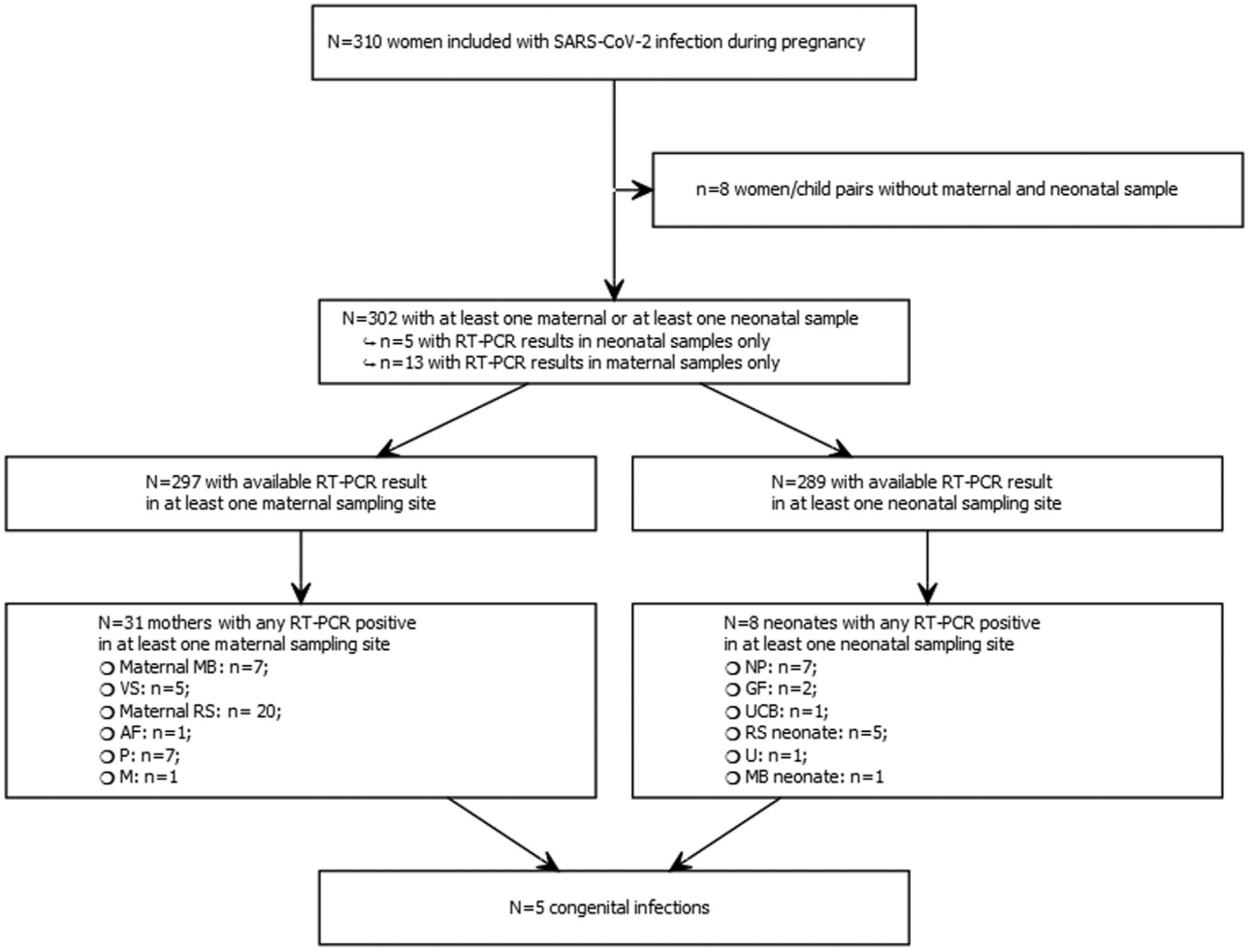

Fig. 1. flowchart of positive RT-PCR for each compartment for the mother and the newborn. vagina (VS), rectum (RS), Maternal blood (MB), nasopharynx (NP), Placenta (P), Amniotic fluid (AF), milk (M), Umbilical Cord Blood (UCB), NP, gastric fluid (GF), urine (U).

Conclusion

Our cohort is the largest one before the anti-SARS-CoV-2 vaccination era, and it aimed to evaluate maternal viral excretion at delivery and in the post-partum period. Routes of transmission remain to be confirmed but materno-fetal transmission is a rare event.

The COVIPREG study group:

H. Abdoul, V. Alessandrini, PY Ancel, E. Azria, A.Benachi, C. Borie, V. Buth, C. Cabanne, AG Cordier, C. Couffignal, M. Dommergues, V Alessandrini, S. Dreux, E. Dufour, M. Eloit, J. Guibourdenche, O. Launay, L. Lecomte, F. Goffinet, G. Kayem, M Leruez-Ville, D. Luton, E. Marcault, AA Mariaggi, JF Meritet, B. Parfait, P. Peretout, O. Picone, S. Prieur, J. Rousseau, F. Rozenberg, V. Tsatsaris, Ch Vauloup Fellous, A. Vivanti, Y. Ville.

Funding

Different sources of funding were obtained for the COVIPREG study: a grant from the AP-HP Foundation, a grant from the foundation of the GHU AP-HP centre, a Ferring pharmaceutics grant, a grant from the Université de Paris, a grant from the Groupe de Recherche sur les Infections pendant la Grossesse.

Declaration of Competing Interest

C.V.F. has obtained a grand from Ferring pharmaceutics for the COVIPREG study.

Acknowledgments

The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et a l'Innovation)

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jogoh.2023.102547.

References

[1] Schwartz A, Yogev Y, Zilberman A, Alpern S, Many A, Yousovich R, Gamzu R. Detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vaginal swabs of women with acute SARS-CoV-2 infection: a prospective study. BJOG 2021;128(1):97–100.
[2] Fenizia C, Saulle I, Di Giminiani M, Vanetti C, Trabattoni D, Parisi F, Biasin M, Savasi V. Unlikely SARS-CoV-2 transmission during vaginal delivery. Reprod Sci 2021;28 (10):2939–41.
[3] Sinaci S, Ocal DF, Seven B, Anuk AT, Besimoglu B, Keven MC, Goncu Ayhan S, Akin MS, Tayman C, Keskin HL, Yapar Eyi EG, Dinc B, Moraloglu Tekin O, Sahin D. Vertical transmission of SARS-CoV-2: a prospective cross-sectional study from a tertiary center. J Med Virol 2021;93(10):5864–72.
[4] Wu Y, Liu C, Dong L, Zhang C, Chen Y, Liu J, Zhang C, Duan C, Zhang H, Mol BW, Dennis C-L, Yin T, Yang J, Huang H. Coronavirus disease 2019 among pregnant Chinese women: case series data on the safety of vaginal birth and breastfeeding. BJOG 2020;127(9):1109–15.
[5] Poblete CA, Bancalari AM. Vertical transmission of Covid - 19. What does the evidence say? Andes Pediatr. 2021;92(5):790–8.

Olivier Picone*
IAME U1137, Inserm, Université Paris Cité
AP-HP.Nord Université Paris Cité, Site Hôpital Louis Mourier, Service de Gynécologie Obstétrique, Colombes, France
Groupe de Recherche sur les Infections pendant la Grossesse (GRIG), France

Alexandre J. Vivanti
Groupe de Recherche sur les Infections pendant la Grossesse (GRIG), France
Division of Obstetrics and Gynecology, Antoine Béclère Hospital, Paris Saclay University Hospitals, APHP, Clamart, France

Jeanne Sibiude
IAME U1137, Inserm, Université Paris Cité
AP-HP.Nord Université Paris Cité, Site Hôpital Louis Mourier, Service de Gynécologie Obstétrique, Colombes, France
Groupe de Recherche sur les Infections pendant la Grossesse (GRIG), France

Anne-Gael Cordier
Groupe de Recherche sur les Infections pendant la Grossesse (GRIG), France
Bicêtre Hospital, Department of Gynecology and Obstetrics, Paris Saclay University, Le Kremlin Bicêtre, France

Vivien Alessandrini
Université Paris Cité, Division of Obstetrics and Gynecology, Hôpital Cochin-Port-Royal, Paris

Gilles Kayem
Université de Paris, CRESS, Obstetrical, Perinatal and Pediatric Epidemiology Research Team, EPOPé, Inserm, INRA, DHU Risks in Pregnancy, Paris, France
Department of Obstetrics and Gynecology, Trousseau Hospital, Assistance publique-Hôpitaux de Paris, Paris, France

Constance Borie
Division of Obstetrics and Gynecology, Antoine Béclère Hospital, Paris Saclay University Hospitals, APHP, Clamart, France
Université de Paris, F-75006 Paris, France
Maternité, AP-HP, Hôpital Robert Debré, F-75019 Paris, France

Dominique Luton
Division of Obstetrics and Gynecology, Antoine Béclère Hospital, Paris Saclay University Hospitals, APHP, Clamart, France
Maternité, AP-HP, Hôpital Robert Debré, F-75019 Paris, France
Maternité, AP-HP, Hôpital Bichat, F-75018 Paris, France

Pauline Manchon
AP-HP.Nord Université Paris Cité Site Hôpital Bichat, Département d'Epidémiologie, Biostatistiques et Recherche Clinique, Paris, France

Camille Couffignal
AP-HP.Nord Université Paris Cité Site Hôpital Bichat, Département d'Epidémiologie, Biostatistiques et Recherche Clinique, Paris, France
IAME U1137, Inserm, Université Paris Cité

Christelle Vauloup Fellous
for the COVIPREG study group
Virology Department, Paul Brousse Hospital, AP-HP, Inserm U 1193, Université Paris Saclay, Villejuif, France
Groupe de Recherche sur les Infections pendant la Grossesse (GRIG), France

*Corresponding author.
E-mail address: olivier.picone@aphp.fr (O. Picone).

Received 29 December 2022
Revised 5 February 2023
Accepted 6 February 2023

Available online 15 February 2023