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ORIGINAL ARTICLE

COVID-19-related medicine utilization study in pregnancy: The COVI-PREG cohort

Guillaume Favre[1] | Eva Gerbier[1,2] | Emeline Maisonneuve[1,2] | Léo Pomar[1,3] | Ursula Winterfeld[4] | Karine Lepigeon[1] | Kitty W. M. Bloemenkamp[5] | Odette de Bruin[5,6] | Hurley Eimir[7] | Hedvig Nordeng[7] | Satu J. Siiskonen[8] | Miriam C. J. M. Sturkenboom[6] | David Baud[1] | Alice Panchaud[2,9] | the COVI-PREG and CONSIGN group

[1]Materno-fetal and Obstetrics Research Unit, Department "Femme-Mère-Enfant", University Hospital, Lausanne, Switzerland

[2]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

[3]School of Health Sciences (HESAV), University of Applied Sciences and Arts Western Switzerland, Lausanne, Switzerland

[4]Swiss Teratogen Information Service, Clinical pharmacology service, Lausanne University Hospital and University of Lausanne, Switzerland

[5]Department of Obstetrics, WKZ Birth Centre, Division Woman and Baby, UMC Utrecht, Utrecht, the Netherlands

[6]Julius Global Health, University Medical Center Utrecht, Utrecht, Netherlands

[7]PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, and PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway

[8]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands

[9]Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Correspondence
Alice Panchaud, Institute of Primary Health Care (BIHAM), University of Bern, Bern 3012, Switzerland.
Email: alice.panchaudmonnat@biham.unibe.ch

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Aim: The objective of this study was to describe the use of COVID-19-related medicines during pregnancy and their evolution between the early/late periods of the pandemic.

Methods: Pregnant women who tested positive for SARS-CoV-2 from March 2020 to July 2021 were included using the COVI-PREG registry. Exposure to the following COVID-19-related medicines was recorded: antibiotics, antivirals, hydroxychloroquine, corticosteroids, anti-interleukin-6 and immunoglobulins. We described the prevalence of medicines used, by trimester of pregnancy, maternal COVID-19 severity level and early/late period of the pandemic (before and after 1 July 2020).

Findings: We included 1964 pregnant patients who tested positive for SARS-CoV-2. Overall, 10.4% (205/1964) received at least one COVID-19-related medicine including antibiotics (8.6%; 169/1694), corticosteroids (3.2%; 62/1964), antivirals (2.0%; 39/1964), hydroxychloroquine (1.4%; 27/1964) and anti-interleukin-6 (0.3%; 5/1964). The use of at least one COVID-19-related medicine was 3.1% (12/381) in asymptomatic individuals, 4.2% (52/1233) in outpatients, 19.7% (46/233) in inpatients without oxygen, 72.1% (44/61) in those requiring standard oxygen, 95.7% (22/23) in those requiring high flow oxygen, 96.2% (25/26) in patients who required intubation and 57.1% (4/7) among patients who died. The proportion who received medicines to treat COVID-19 was higher before than after July 2020 (16.7% *vs.*

7.7%). Antibiotics, antivirals and hydroxychloroquine had lower rates of use during the late period.

Conclusion: Medicine use in pregnancy increased with disease severity. The trend towards increased use of corticosteroids seems to be aligned with changing guidelines. Evidence is still needed regarding the effectiveness and safety of COVID-19-related medicines in pregnancy.

KEYWORDS

COVID-19, COVID-19-related medicine, drug use, medicine use, pharmaco-epidemiology, pregnancy, SARS-CoV-2

1 | INTRODUCTION

During this unprecedented COVID-19 crisis, pregnant women were particularly at risk of severe disease compared to non-pregnant women of the same age, with up to 9% requiring intensive care unit admission.[1–3] Pregnant women were also at higher risk of preterm birth, mostly induced.[2,4] Newborn transmission ranged from 1 to 4% among SARS-CoV-2 positive pregnant women close to delivery, mainly after birth, with exceptional severe adverse neonatal outcome directly caused by the virus.[5–7]

Repurposed medicines have been proposed to treat COVID-19. Corticosteroids, remdesivir, anakinra, tocilizumab and other anti-SARS-CoV2 monoclonal antibodies are currently authorized to treat COVID-19 in the European Union.[8] Other medicines have been used off-label, including lopinavir-ritonavir, and high doses of hydroxychloroquine.

Since the beginning of the pandemic, guidelines have drastically changed, as new treatments and data have emerged over time.[9] Additionally, clinical guidelines specifically dedicated to the pregnant women population were drawn from information collected in the general population as most studies excluded pregnant women.[10] Information on the safety of several repurposed medicines to treat COVID-19 in pregnancy is scarce and insufficient to draw conclusions about potential risks.

The use of the anti-interleukin 6 (anti-IL6), tocilizumab and the antiviral remdesivir remains reassuring but extremely limited in pregnant women.[11,12] Corticosteroids have been well studied during the late pregnancy period[13] but first trimester administration raised questions about the potential increased risk of cleft lips and gestational diabetes incidence, but no evidence exists to rule this out.[14] Recommendations for COVID-19 have been drawn from the RECOVERY trial reporting a decreased mortality in the general population requiring oxygen and was first reported on 16 June 2020.[15,16] The use of lopinavir/ritonavir has been studied in pregnant patients outside COVID-19 (e.g., Human Immunodeficiency Viruses or Hepatitis B virus), and no concerns have been raised to date.[17] Chloroquine/hydroxychloroquine has been used during pregnancy for treating lupus or rheumatoid arthritis with contradictory results regarding birth defects.[18,19] There is insufficient evidence on the safety of the use of ivermectin for treating parasitosis during pregnancy.[20] The majority of observational studies regarding azithromycin use in pregnancy have not found an increased risk of major congenital anomalies.[21] However, due to their lack of efficacy and potential side effects, chloroquine/hydroxychloroquine alone or combined with azithromycin, or ivermectin are no longer recommended for the treatment of COVID-19.[22,23]

It is therefore important to assess how pregnant women were exposed to COVID-19-related medicines given the complexity and the evolving evidence and recommendations during this pandemic. In this study, we aimed to describe the use of COVID-19-related medicines during pregnancy from March 2020 until July 2021 using the COVI-PREG international registry.[24]

What is already known about this subject

- Pregnant women are at high risk of severe forms of COVID-19 leading to higher risks of preterm birth.
- Repurposed drugs have been used to treat COVID-19 even with scarce safety information.
- Pregnant women have been excluded from the majority of COVID-19 clinical trials.

What this study adds

- COVID-19 medicine use in pregnancy increased with disease severity.
- The management of COVID-19 in pregnancy has changed over time, with a decrease in the use of medicines which are no longer recommended, and an increase in the use of corticosteroids, especially for cases requiring oxygen, which is recommended.
- Further studies are urgently needed to assess the effectiveness and safety of COVID-19 medicines in pregnancy.

2 | METHODS

2.1 | Design and settings

This study used the data collected from 24 March 2020 to 1 July 2021 in the COVI-PREG registry database which is a prospective cohort study aiming to assess the impact of SARS-CoV-2 infection in pregnant women and their fetuses/newborns.[24] Pregnant women tested for SARS-CoV-2 during pregnancy, with the exception of those under 18 or declining/not able to consent, were eligible in this multicentre international study. Any health facility with an antenatal clinic or labour ward worldwide was able to contribute to the registry. The study was approved by both the Swiss Ethical Board (CER-VD-2020-00548) and the local ethics boards at each participating centre.

2.2 | Data collection

At the time of a positive SARS-CoV-2 test, patients were included in the study if they agreed to participate. The local investigator completed the enrolment form regarding patient's baseline basic characteristics, medical history (defined as a condition present before pregnancy) and information about SARS-CoV-2 exposure and testing, using the REDCap (Research Electronic Data Capture) secure web application hosted at Lausanne University Hospital data centre. They completed the natural history form regarding the course of COVID-19 at the end of the COVID-19 event or eventually at the end of the pregnancy, using individual medical records. They also completed the pregnancy and neonatal outcome form after the patient was discharged from maternity. Only de-identified data were recorded in the online database. No dedicated clinical visits were planned for the study.

2.3 | Participants, inclusion and exclusion criteria

Pregnant patients who tested positive for SARS-CoV-2 with a history of symptoms, potential virus exposure or universal screening performed depending on local guidelines, who presented to one of the participating health care facilities during pregnancy, were eligible for inclusion in the study. Confirmed infection was defined as a patient presenting a positive test at any time during pregnancy regardless of its indication. Patients who were not tested or had a negative or unknown test result were excluded from the analysis. Confirmed positive SARS-CoV-2 diagnosis was defined as a positive nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR) or antigen test during pregnancy. Patients with a positive serology but no positive nasopharyngeal RT-PCR or antigen test were not included in the study. History of COVID-19 before pregnancy and COVID-19 vaccination details were not requested in the COVI-PREG registry for patients infected with COVID-19 during the study period.

2.4 | Exposure to COVID-19-related medicines

The exposure of interest was defined as any of the medicines reported to treat a COVID-19 event during pregnancy, without a dose or duration threshold. Information about medicine exposure was collected by local investigators based on individual medical records (either extracted from pregnancy follow-up visit documents, hospital discharge letters and/or maternity discharge letters). The following medicine categories were collected: antibiotics, antivirals, hydroxychloroquine (HCQ), corticosteroids (for maternal indication), anti-IL6 and immunoglobulins (an exhaustive list of substance names is included in Table S1). Symptomatic treatments defined as any medicine not intended to treat directly COVID-19, such as antipyretic and antithrombotic treatments, were not recorded. No information was available on the timing of COVID-19-related medicine intake.

2.5 | Co-variables

Sociodemographic characteristics of patients such as marital status, ethnicity, region of the world and educational level were collected. Maternal age was divided into five categories ≤25, 26–30, 31–35, 36–40 and >40 years. Medical information such as medical history, maternal body mass index (BMI) at inclusion, maternal alcohol or tobacco consumption, obstetrical history, previous pregnancy complications and ongoing pregnancy complications before exposure to SARS-CoV-2 was also collected. Trimesters of pregnancy were defined as trimester 1: the period between the last menstrual period (LMP) and gestational week (GW) 13 plus 6 days; trimester 2: the period between GW 14 and 27 plus 6 days; and trimester 3: the period starting at GW 28.

2.5.1 | Maternal COVID-19 severity

Severity of COVID-19 disease was divided into severity levels based on the National Institute of Health (NIH) treatments guidelines: level (0) asymptomatic patients, (1) mild to moderate illness, not hospitalized, (2) hospitalized patient without oxygen support, (3) hospitalized patient requiring standard oxygen support, (4) high flow oxygen support requirement (including high flow cannula and non-invasive ventilation), (5) mechanical ventilation requirement and (6) maternal death.[22]

2.5.2 | Early and later pandemic period

The pandemic period was divided into two periods corresponding to the early (24 March 2020 to 30 June 2020) and later (1 July 2020 to 1 July 2021) pandemic periods. June 2020 corresponds to the end of the first infection wave in Europe, and coincides with a key change in the NIH clinical guidelines against the use of hydroxychloroquine for COVID-19 patients, and recommendation for the use of

dexamethasone in the light of RECOVERY trial preliminary results.[16,25] Patients were stratified into early and late period according to the recorded date of the onset of their COVID-19-related symptoms. For asymptomatic patients and those missing dates of onset of symptoms, the date of their SARS-CoV-2 positive test was used instead.

2.6 | Statistical analysis

Descriptive statistics were used to present baseline demographics and characteristics of the study population. Prevalence of reported medicine use for the COVID-19 event overall and stratified by pregnancy trimesters was categorized by early or late pandemic period, and by severity level of maternal COVID-19. Prevalence of medicine use was defined as the proportion of patients exposed to at least one medication, divided by the total number of included pregnancies. The 95% confidence intervals (95% CI) were calculated for each reported prevalence using the exact Clopper-Pearson method. Statistical analyses were performed using Stata 16 (StataCorp., College Station, TX, USA).

3 | RESULTS

3.1 | Demographics

The study population included 1964 pregnant patients who had a confirmed SARS-CoV-2 diagnosis during pregnancy. A description of cases included by country is presented in Table S2. The median age was 32 years, with 53.0% ($n = 1040$) of positive diagnoses in trimester 3, 31.9% ($n = 627$) in trimester 2 and 13.8% ($n = 272$) in trimester 1. White ethnicity represented 53.5% ($n = 1050$) of patients and 21.3% ($n = 418$) had a BMI greater than 30 kg/m^2. A total of 32.6% ($n = 640$) patients were nulliparous. Thyroid imbalance (5.1%, $n = 100$), pulmonary disease (3.1%, $n = 60$) and hypertensive disorder (2.7%, $n = 53$) were the most frequent comorbidities. Gestational diabetes and pre-eclampsia were respectively diagnosed before positive SARS-CoV-2 tests in 9.6% ($n = 189$) and in 1.9% ($n = 37$) of women (Table 1).

3.2 | Exposure to COVID-19-related medicines

A description of patient characteristics with and without exposure to COVID-19-related medicines is presented in Table S3. The complete description of COVID-19-related medication use among pregnant women who tested positive for SARS-CoV-2 during the whole study period is presented in Table 2. Overall, 10.4% ($n = 205/1964$) of pregnant women received at least one COVID-19-related medicine. Antibiotics (8.6%, $n = 169$) were the most frequently used medicine category, mostly represented by azithromycin (40.2%; 68/169), amoxicillin clavulanic acid (31.4%; 53/169), ceftriaxone (17.2%; 29/169) and amoxicillin (10.7%; 18/169), followed by corticosteroids (3.2%; 62/1964), mostly dexamethasone (62.9%; 39/62) and methylprednisolone (19.4%; 12/62). Antivirals were used by 2.0% (39/1964) of pregnant women, mostly lopinavir associated with ritonavir (33.3%; 13/39), oseltamivir (33.3%; 13/39) and remdesivir (25.6%; 10/39). Finally, HCQ was used by 1.4% (27/1964) of patients, anti-IL6 (tocilizumab) by 0.3% (5/1964) and no one was exposed to immunoglobulins. Among all medicine categories, antibiotics represented 56.0% (169/302), corticosteroids 20.5% (62/302), antivirals 12.9% (39/302), hydroxychloroquine 8.9% (27/302) and anti-IL-6 1.7% (5/302) (Figure 1).

The prevalence of exposure to COVID-19-related medicines by pregnancy trimester is reported in Table S4. The proportion of patients who received a COVID-19-related medicine was 6.6% (18/72), 11.2% (70/627) and 10.8% (112/1040) in trimesters 1, 2 and 3, respectively. The prevalence of exposure to COVID-19-related medicines by world regions is presented in Table S5.

3.3 | Medicine use by COVID-19 severity

Stratified by severity, the use of at least one COVID-19-related medicine was 3.1% (12/381) in asymptomatic patients, 4.2% (52/1233) in level 1 patients, 19.7% (46/233) in level 2 patients, 72.1% (44/61) in level 3 patients, 95.7% (22/23) in level 4 patients, 96.2% (25/26) in level 5 patients and 57.1% (4/7) among patients who died. The use of corticosteroids was 0.2% (2/1233) for level 1 patients, 3.9% (9/233) for level 2 patients, 34.4% (21/61) for level 3 patients, 56.5% (13/23) for level 4 patients, 57.7% (15/26) for level 5 patients and 14.3% (1/7) in patients who died. No corticosteroids were recorded for asymptomatic patients. The description of other medicine categories by level of severity is presented in Table 3. Individual medicine names are presented in Table S6. When stratified by trimester of infection, 1.5% (4/272) of patients infected in the first trimester required standard oxygen (level 3 or more). This figure increased to 6.9% (43/627) and 6.5% (67/1040) patients in second and third trimester infections, respectively.

3.4 | Early *vs.* late pandemic period

A total of 592 pregnant women tested positive in the early pandemic period and 1358 in the late pandemic period. Patients with no information about the period of exposure were excluded ($n = 14$). Patient characteristics according to the period of the pandemic are described in Table S7. A description of pregnant patients who tested positive for SARS-CoV-2 over time is presented in Figure S1. COVID-19-related medicine use over time is presented in Figure S2 and shows a decrease in the recorded use of medicines over time. The proportion of patients who received at least one medicine to treat COVID-19 during the early period was higher (16.7%, 95% CI 13.8–20.0) compared to the late period (7.7%, 95% CI 6.3–9.2) (Table 4). Antibiotics (14.7%, 95% CI 11.9–17.8 *vs.* 5.9%, 95% CI 4.7–7.3), antivirals (4.9%, 95% CI 3.3–7.0 *vs.* 0.7%, 95% CI

TABLE 1 Description of pregnant persons tested positive for SARS-CoV 2

	Pregnant women tested positive $n = 1964$		
	Median		**IQR**
Age (years); median	32		28–35
	n	**%**	95%CI
Age category			
≤ 25 years old (y.o.)	291	**14.9**	13.3-16.5
26–30 y.o.	554	**28.3**	26.3-30.4
31–35 y.o.	661	**33.8**	31.7-35.9
36–40 y.o.	357	**18.2**	16.6-20.0
≥ 41 y.o.	94	**4.8**	3.9-5.8
Trimester of pregnancy at infection			
Trimester 1	272	**13.8**	12.4-15.5
Trimester 2	627	**31.9**	29.9-34.0
Trimester 3	1040	**53.0**	50.7-55.2
Unknown trimester	25	**1.3**	0.8 1.9
Baseline characteristics			
Marital status			
- Married or domestic partnership	1625	**82.7**	81.0-84.4
- Single never married	165	**8.4**	7.2-9.7
- Divorced or separated	14	**0.7**	0.4-1.2
- Widowed	2	**0.1**	0.0-0.4
- Unknown	90	**4.6**	3.7-5.6
Ethnicity			
- White	1050	**53.5**	51.2-55.7
- Hispanic or Latino	316	**16.1**	14.5-17.8
- Black or African American	196	**10.0**	8.7-11.4
- Asian or Pacific islander	98	**5.0**	4.1-6.0
- Other	121	**6.2**	5.1-7.3
- Unknown	96	**4.9**	4.0-5.9
Region of the world			
Europe	1310	**66.7**	64.6-68.8
Asia	262	**13.3**	11.9-14.9
South/Central America	344	**17.5**	15.9-19.3
North America	48	**2.4**	1.8-3.2
Education level			
- University or college or equivalent	489	**24.9**	23.0-26.9
- Intermediate	193	**9.8**	8.5-11.2
- Secondary school	302	**15.4**	13.8-17.0
- Primary school or less	104	**5.3**	4.3-6.4
- Unknown	684	**34.8**	32.7-37.0
Maternal BMI (kg/m^2)			
BMI more than 30	418	**21.3**	19.5-23.2
BMI more than 35	160	**8.1**	7.0-9.4
Maternal addiction	70	**3.6**	2.8-4.5
- Drug	7	**0.4**	0.1-0.7
- Tobacco	64	**3.3**	2.5-4.1
- Alcohol	8	**0.4**	0.2-0.8

TABLE 1 (Continued)

	Pregnant women tested positive $n = 1964$		
	Median		IQR
Obstetrical history			
Nulliparous	640	**32.6**	30.5-34.7
Previous caesarean section	353	**18.0**	16.3-19.7
Medical history			
- Pulmonary	60	**3.1**	2.3-3.9
- Cardiac	28	**1.4**	0.9-2.1
- Hypertensive	53	**2.7**	2.0-3.5
- Diabetes	36	**1.8**	1.3-2.5
- Immunosuppression	12	**0.6**	0.3-1.1
- Neurological	17	**0.9**	0.5-1.4
- Digestive	23	**1.2**	0.7-1.8
- Renal	14	**0.7**	0.4-1.2
- Urological	5	**0.3**	0.1-0.6
- Oncological	12	**0.6**	0.3-1.1
- Thyroid imbalance	100	**5.1**	4.2-6.2
- Other	229	**11.7**	10.3-13.2
Previous pregnancy complications			
- Preeclampsia	39	**2.0**	1.4-2.7
- Intra uterine growth restriction	33	**1.7**	1.2-2.4
- Fetal malformation	16	**0.8**	0.5-1.3
- Preterm birth	34	**1.7**	1.2-2.4
- Postpartum haemorrhage	37	**1.9**	1.3-2.6
- Other	121	**6.2**	5.1-7.3
Ongoing pregnancy			
- Singletons	1902	**96.8**	96.0-97.6
Pregnancy condition (before exposure to the virus)			
- Preeclampsia	37	**1.9**	1.3-2.6
- Gestational diabetes	189	**9.6**	8.4-11.0
- Intra-uterine growth restriction	40	**2.0**	1.5-2.8
- Abnormal fetal Doppler	12	**0.6**	0.3-1.1
- Macrosomia	17	**0.9**	0.5-1.4
- Threatened preterm labour	32	**1.6**	1.1-2.3
- Placenta praevia	9	**0.5**	0.2-0.9
- PPROM	20	**1.0**	0.6-
- Other	174	**8.9**	7.6-10.2

Abbreviations: BMI, body mass index; IQR, interquartile range; PPROM, preterm premature rupture of membranes.

0.4–1.4) and HCQ (4.1%, 95% CI 2.6–6.0 *vs*. 0.1%, 95% CI 0.0–0.5) had a lower rate of reported use in the later period compared to the early one. The use of corticosteroids increased from 2.4% (95% CI 1.3–3.9) to 3.5% (95% CI 2.6–4.7) whereas anti-IL6 use was 0.5% (95% CI 0.1–1.5) *vs*. 0.1% (95% CI 0.0–0.5) during the early and late periods, respectively (Table 4).

A stratified analysis by severity of the disease is also reported in Table 4.

Corticosteroid use increased in the late pandemic period compared to the early period in level 2 (8/143; 5.6%; 95% CI 2.4–10.7 *vs*. 4/90; 1.1%; 95% CI 0.0–0.60), level 3 (19/37; 51.4%; 95% CI 34.4–68.1 *vs*. 2/24; 8.3%; 95% CI 1.0–27.0), level 4 (9/11; 81.8%; 95% CI 48.2–97.7 *vs*. 4/90; 1.1%; 95% CI 0.0–0.60), level 5 (10/17; 58.8%; 95% CI 32.9–81.6 *vs*. 5/9; 55.6%; 95% CI 21.2–86.3) and level 6 (1/3; 33.3%; 95% CI 0.8–90.6 *vs*. 1/4; 25.0%; 95% CI 0.6–80.6).

TABLE 2 COVID-19 medicines use in pregnant women tested positive for SARS-CoV-2

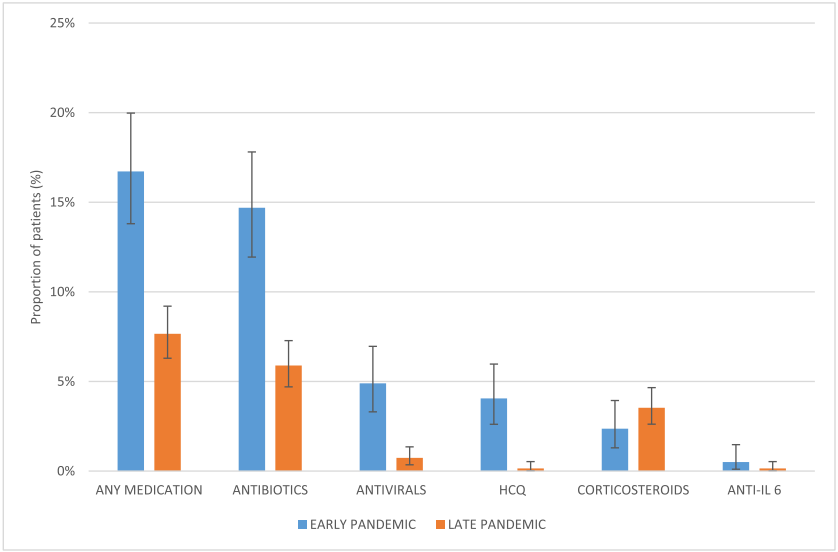
	Overall population *n* = 1964		
	n	**%**	**95% CI**
ANY MEDICATION	**205/1964**	**10.4**	**9.1–11.9**
ANTIBIOTICS	**169/1964**	**8.6**	**7.4–9.9**
Amoxicillin	18/169	10.7	6.4–16.3
Amoxicillin clavulanic acid	53/169	31.4	24.5–38.9
Ampicillin	11/169	6.5	3.3–11.3
Ampicillin sulbactam	2/169	1.2	0.1–4.2
Azithromycin	68/169	40.2	32.8–48.0
Cefalexin	1/169	0.6	0.0–3.3
Cefalotin	2/169	1.2	0.1–4.2
Cefazolin	5/169	3.0	1.0–6.8
Cefepime	11/169	6.5	3.3–11.3
Cefotaxime	13/169	7.7	4.2–12.8
Ceftazidime	3/169	1.8	0.4–5.1
Ceftriaxone	29/169	17.2	11.8–23.7
Cefuroxime	4/169	2.4	0.6–5.9
Ciprofloxacin	3/169	1.8	0.4–5.1
Clarithromycin	8/169	4.7	2.1–9.1
Clindamycin	6/169	3.6	1.3–7.6
Cloxacillin	1/169	0.6	0.0–3.3
Gentamicin	8/169	4.7	2.1–9.1
Imipenem cilastatin	2/169	1.2	0.1–4.2
Meropenem	5/169	3.0	1.0–6.8
Metronidazole	7/169	4.1	1.7–8.3
Moxifloxacin	1/169	0.6	0.0–3.3
Nitrofurantoïn	1/169	0.6	0.0–3.3
Piperacillin tazobactam	9/169	5.3	2.5–9.9
Pristinamycin	1/169	0.6	0.0–3.3
Rifamycin	1/169	0.6	0.0–3.3
Roxithromycin	2/169	1.2	0.1–4.2
Spiramycin	3/169	1.8	0.4–5.1
Teicoplanin	1/169	0.6	0.0–3.3
Vancomycin	8/169	4.7	2.1–9.1
ANTIVIRALS	**39/1964**	**2.0**	**1.4–2.7**
Atazanavir	1/39	2.6	0.1–13.5
Darunavir	1/39	2.6	0.1–13.5
Gancicolovir	1/39	2.6	0.1–13.5
Lopinavir	1/39	2.6	0.1–13.5
Lopinavir + ritonavir	13/39	33.3	19.1–50.2
Oseltamivir	13/39	33.3	19.1–50.2
Remdesivir	10/39	25.6	13.0–42.1
Ribavirin	1/39	2.6	0.1–13.5
Ritonavir	1/39	2.6	0.1–13.5
HCQ	**27/1964**	**1.4**	**0.9–2.0**
CORTICOSTEROIDS	**62/1964**	**3.2**	**2.4–4.0**
Dexamethasone	39/62	62.9	49.7–74.8

TABLE 2 (Continued)

	Overall population $n = 1964$		
	n	**%**	**95% CI**
Hydrocortisone	2/62	3.2	0.4–11.2
Methylprednisolone	12/62	19.4	10.4–31.4
Prednisolone	2/62	3.2	0.4–11.2
Prednisone	4/62	6.5	1.8–15.7
ANTI-IL6	**5/1964**	**0.3**	**0.1–0.6**
Tocilizumab	5/5	100.0	47.8–100
IMMUNIOGLOBULIN	**0/1964**	**0.0**	**0.0–0.2**

Abbreviations: ANTI-IL6, anti-interleukin 6; HCQ, hydroxychloroquine.

FIGURE 1 Medicine categories use between early and later pandemic period



4 | DISCUSSION

To our knowledge, this is one of the first studies to report use of COVID-19-related medicines among pregnant women who tested positive for SARS-CoV-2.[26] More than 10% of pregnant women in our study population used at least one COVID-19-related medicine. Antibiotics were the most prescribed medicine category (8.6%) followed by corticosteroids (3.2%), antivirals (2.0%), HCQ (1.4%) anti-IL6 (0.3%).

Despite the lack of robust safety and efficacy information for antivirals in pregnancy, 39 patients (2%) were exposed to this medicine category. Remdesivir, the only antiviral treatment recommended to be used for COVID-19 on a 'case by case' basis according to the NIH[22] and not recommended by the WHO,[23] was the third most frequently used antiviral, accounting for 25.6% (10/39) of antiviral use in our study. Lopinavir/ritonavir and oseltamivir, neither of which are recommended in the treatment of COVID-19 due to the lack of evidence of efficacy, were more frequently used. HCQ was initially suggested then no longer recommended for the treatment of COVID-19 due to the lack of benefit in severe COVID-19 and its potential cardiac toxicity in the general population. Still, 1.4% (27/1964) of patients received this medicine but mostly at the beginning of the pandemic (24/27) when the RECOVERY data were not yet known.[15]

COVID-19-related medicine use was similar among second and third trimester infections, with approximately 11% of women using at least one COVID-19-related medicine in each of these trimester infections. Medication use was lower in the first trimester infections, with 6.6% of patients using at least one COVID-19-related medicine. The first trimester is a challenging period as it is the period at risk of potential teratogenicity as this is the fetal organogenesis period, especially considering medications with scarce safety data (e.g., COVID-19 medicine). However, the disease severity level for first trimester infections was lower, and thus may not have required COVID-19 medicine use. Our results are limited to a small group of first trimester infections.

Recorded medicine use decreased over time. The recorded use of at least one COVID-19-related medicine overall, as well as antibiotics and antivirals, were significantly lower in the late period (July 2020–June 2021) compared to the early period of COVID-19. Use of corticosteroids increased in the late period (2.8%, 95% CI; 1.9–3.1 *vs.*

TABLE 3 COVID-19 related medicine use stratified by level of severity

	Asymptomatic *n* = 381			LEVEL 1 Outpatient management *n* = 1233			LEVEL 2 Hospitalized without O2 *n* = 233			LEVEL 3 Hospitalized with standard O2 *n* = 61		
	n	%	95% CI	*n*	%	95% CI	*n*	%	95% CI	*n*	%	95% CI
Any medication	12/381	3.1	1.6–5.4	52/1233	4.2	3.2–5.5	46/233	19.7	14.8–25.4	44/61	72.1	59.2–82.9
Antibiotics	11/381	2.9	1.4–5.1	47/1233	3.8	2.8–5.0	41/233	17.6	12.9–23.1	29/61	47.5	34.6–60.7
Antivirals	0/381	0.0	-	6/1233	0.5	0.2–1.1	9/233	3.9	1.8–7.2	8/61	13.1	5.8–24.2
HCQ	1/381	0.3	0.0–1.5	7/1233	0.6	0.2–1.2	6/233	2.6	1.0–5.5	5/61	8.2	2.7–18.1
Corticoids	0/381	0.0	-	2/1233	0.2	0.0–0.6	9/233	3.9	1.8–7.2	21/61	34.4	22.7–47.7
Anti-IL6	0/381	0.0	-	0/1233	0.0	-	0/233	0.0	-	0/61	0.0	-
Immunoglobulins	0/381	0.0	-	0/1233	0.0	-	0/233	0.0	-	0/61	0.0	-

Abbreviations: ANTI-IL6, anti-interleukin 6; O2, oxygen; High Flow O2, high flow oxygen canula and/or non-invasive ventilation; HCQ: hydroxychloroquine.
[a]Two patients died before ICU admission and one refused hospital admission.

TABLE 3 (Continued)

	LEVEL 4 High flow O2 *n* = 23			LEVEL 5 Mechanical ventilation *n* = 26			LEVEL 6 Maternal death[a] *n* = 7[a]		
	n	%	95% CI	*n*	%	95% CI	*n*	%	95% CI
Any medication	22/23	95.7	78.1–99.9	25/26	96.2	80.4–99.9	4/7	57.1	18.4–90.1
Antibiotics	14/23	60.9	38.5–e80.3	24/26	92.3	74.9–99.1	3/7	42.9	9.9–81.6
Antivirals	7/23	30.4	13.2–52.9	6/26	23.1	9.0–43.6	3/7	42.9	9.9–81.6
HCQ	4/23	17.4	5.0–38.8	3/26	11.5	2.4–30.2	1/7	14.3	0.4–57.9
Corticoids	13/23	56.5	34.5–76.8	15/26	57.7	36.9–76.6	2/7	28.6	3.7–71.0
Anti-IL6	2/23	8.7	1.1–28.0	2/26	7.7	0.9–25.1	1/7	14.3	0.4–57.9
Immunoglobulins	0/23	0.0	-	0/26	0.0	-	0/7	0.0	-

Abbreviations: ANTI-IL6, anti-interleukin 6; O2, oxygen; High Flow O2, high flow oxygen canula and/or non-invasive ventilation; HCQ: hydroxychloroquine.
[a]Two patients died before ICU admission and one refused hospital admission.

TABLE 4 Medicine use comparing early to later period after beginning of the COVID-19 pandemic

		EARLY PANDEMIC $n = 592$			LATE PANDEMIC $n = 1358$		
		n	Proportion	95% CI	*n*	Proportion	95% CI
TOTAL		**592**	**100.0%**		**1358**	**100.0%**	
	Any medication	99/592	16.7%	13.8–20.0	104/1358	7.7%	6.3–9.2
	Antibiotics	87/592	14.7%	11.9–17.8	80/1358	5.9%	4.7–7.3
	Antivirals	29/592	4.9%	3.3–7.0	10/1358	0.7%	0.4–1.4
	HCQ	24/592	4.1%	2.6–6.0	2/1358	0.1%	0.0–0.5
	Corticoids	14/592	2.4%	1.3–3.9	48/1358	3.5%	2.6–4.7
	Anti-IL6	3/592	0.5%	0.1–1.5	2/1358	0.1%	0.0–0.5
	Immunoglobulin	0/592	0.0%	-	0/1358	0.0%	-
LEVEL 0		**87**	**14.7%**		**293**	**21.6%**	
	Any medication	5/87	5.7%	1.9–12.9	7/293	2.4%	1.0–4.9
	Antibiotics	4/87	4.6%	1.3–11.4	7/293	2.4%	1.0–4.9
	Antivirals	0/87	0.0%	-	0/293	0.0%	-
	HCQ	1/87	1.1%	0.0–6.2	0/293	0.0%	-
	Corticoids	0/87	0.0%	-	0/293	0.0%	-
	Anti-IL6	0/87	0.0%	-	0/293	0.0%	-
	Immunoglobulin	0/87	0.0%	-	0/293	0.0%	-
LEVEL 1		**367**	**62.0%**		**853**	**62.8%**	
	Any medication	27/367	7.4%	4.9–10.5	23/853	2.7%	1.7–4.0
	Antibiotics	25/367	6.8%	4.5–9.9	20/853	2.3%	1.4–3.6
	Antivirals	4/367	1.1%	0.3–2.8	2/853	0.2%	0.0–0.8
	HCQ	4/367	1.1%	0.3–2.8	2/853	0.2%	0.0–0.8
	Corticoids	1/367	0.3%	0.0–1.5	1/853	0.1%	0.0–0.7
	Anti-IL6	0/367	0.0%	-	0/853	0.0%	-
	Immunoglobulin	0/367	0.0%	-	0/853	0.0%	-
LEVEL 2		**90**	**15.2%**		**143**	**10.5%**	
	Any medication	25/90	27.8%	18.9–38.2	21/143	14.7%	9.3–21.6
	Antibiotics	23/90	25.6%	16.9–35.8	18/143	12.6%	7.6–19.2
	Antivirals	8/90	8.9%	3.9–16.8	1/143	0.7%	0.0–3.8
	HCQ	6/90	6.7%	2.5–13.9	0/143	0.0%	-
	Corticoids	1/90	1.1%	0.0–6.0	8/143	5.6%	2.4–10.7
	Anti-IL6	0/90	0.0%	-	0/143	0.0%	-
	Immunoglobulin	0/90	0.0%	-	0/143	0.0%	-
LEVEL 3		**24**	**4.1%**		**37**	**2.7%**	
	Any medication	19/24	79.2%	57.8–92.9	25/37	67.6%	50.2–82.0
	Antibiotics	15/24	62.5%	40.6–81.2	14/37	37.8%	22.5–55.2
	Antivirals	5/24	20.8%	7.1–42.2	3/37	8.1%	1.7–21.9
	HCQ	5/24	20.8%	7.1–42.2	0/37	0.0%	-
	Corticoids	2/24	8.3%	1.0–27.0	19/37	51.4%	34.4–68.1
	Anti-IL6	0/24	0.0%	-	0/37	0.0%	-
	Immunoglobulin	0/24	0.0%	-	0/37	0.0%	-
LEVEL 4		**12**	**2.0%**		**11**	**0.8%**	
	Any medication	12/12	100.0%	73.5–100.0	10/11	90.9%	58.7–99.8
	Antibiotics	10/12	83.3%	51.6–97.9	4/11	36.4%	10.9–69.2
	Antivirals	6/12	50.0%	21.1–78.9	1/11	9.1%	0.2–41.3
	HCQ	4/12	33.3%	9.9–65.1	0/11	0.0%	-

(Continues)

TABLE 4 (Continued)

		EARLY PANDEMIC $n = 592$			LATE PANDEMIC $n = 1358$		
		n	Proportion	95% CI	*n*	Proportion	95% CI
	Corticoids	4/12	33.3%	9.9–65.1	9/11	81.8%	48.2–97.7
	Anti-IL6	2/12	16.7%	2.1–48.4	0/11	0.0%	-
	Immunoglobulin	0/12	0.0%	-	0/11	0.0%	-
LEVEL 5		**9**	**1.5%**		**17**	**1.3%**	
	Any medication	8/9	88.9%	51.8–99.7	17/17	100.0%	80.5–100.0
	Antibiotics	8/9	88.9%	51.8–99.7	16/17	94.1%	71.3–99.9
	Antivirals	3/9	33.3%	7.5–70.1	3/17	17.6%	3.8–43.4
	HCQ	3/9	33.3%	7.5–70.1	0/17	0.0%	-
	Corticoids	5/9	55.6%	21.2–86.3	10/17	58.8%	32.9–81.6
	Anti-IL6	0/9	0.0%	-	2/17	11.8%	1.5–36.4
	Immunoglobulin	0/9	0.0%	-	0/17	0.0%	-
LEVEL 6		**4**	**0.7%**		**3**	**0.2%**	
	Any medication	3/4	75.0%	19.4–99.4	1/3	33.3%	0.8–90.6
	Antibiotics	2/4	50.0%	6.8–93.2	1/3	33.3%	0.8–90.6
	Antivirals	3/4	75.0%	19.4–99.4	0/3	0.0%	-
	HCQ	1/4	25.0%	0.6–80.6	0/3	0.0%	-
	Corticoids	1/4	25.0%	0.6–80.6	1/3	33.3%	0.8–90.6
	Anti-IL6	1/4	25.0%	0.6–80.6	0/3	0.0%	-
	Immunoglobulin	0/4	0.0%	-	0/3	0.0%	-

Note: Severity levels are defined as: Level (0) Asymptomatic patients, (1) Mild to moderate illness, not hospitalized, (2) Hospitalized patient without oxygen support, (3) Hospitalized patient requiring standard oxygen support, (4) High flow oxygen support requirement (including high flow cannula and non-invasive ventilation), (5) Mechanical ventilation requirement and (6) Maternal death.
Abbreviations: HCQ, hydroxychloroquine; ANTI-IL6, anti-interleukin 6.

3.9%, 95% CI; 2.6–5.5) especially in the level 2 and more severe cases (Table 4). These results are consistent with data from the hospitalized general population in the United States, where hydroxychloroquine use decreased and corticosteroid use increased over time.[27] This reflects the accumulating evidence supporting corticosteroids, especially dexamethasone, as a beneficial and safe treatment for second phase COVID-19, which is now clearly recommended in official guidelines for patients requiring oxygen support.[22,28] In our study, corticosteroid use was reported in the majority of patients who required oxygen support, which is consistent with current guidelines.[22,28] Use of medicines stratified by maternal infection severity level shows that medicine use increased with the severity of the disease, from 3.1% in asymptomatic patients to 96.4% of patients requiring mechanical ventilation exposed to at least one COVID-19-related medicine. The SARS-CoV-2 delta variant has been reported to increase severity in pregnant women.[29] However, it is unlikely that this factor influenced COVID-19-related medicine use over time as no patient was tested positive during the delta variant predominant period in our study (data extracted from GISAID).[30]

Some limitations of our study should be considered. First, we did not report on other medicines administered to prevent COVID-19 complications, such as antithrombotic medicines, as these were not indicated at the beginning of the pandemic and therefore not systematically recorded in the registry. Prophylactic anticoagulation is recommended in pregnant women hospitalized for COVID-19 but with a low evidence rating.[31] The CONSIGN work package 1 is currently analysing antithrombotic treatment for COVID-19 in pregnancy.[32]

Second, a selection bias towards symptomatic patients cannot be excluded as different strategies have been adopted by centres such as universal screening at admission, symptom-based testing or contact to a positive case history testing. These different strategies have also changed over time as available resources and sanitary situation have changed, which possibly affects the recruitment of patients. Routine systematic screening was not always possible, thereby preventing the recruitment of all asymptomatic positive patients and leading to a possible overestimation of symptomatic patients, more likely to receive a COVID-19-related medicine. Unfortunately, we did not have access to the different testing strategies adopted in every institution participating in the study. Mild to moderate COVID-19 patients were also more likely to be managed in the outpatient setting without reaching a hospital participating in the study. This selection bias might have overestimated the use of COVID-19 medicines. Similarly, severely affected patients were very likely to be tested for SARS-CoV-2 and included in the study. Additionally, COVID-19-related medicine use

differed across geographical regions, potentially due to different local protocols for screening and/or patient management. Third, due to its design, this study cannot estimate the safety and efficacy of COVID-19-related medicines among pregnant women and this needs to be urgently assessed in this population at high risk from severe COVID-19.

This study brought evidence that pregnant women were not spared from the COVID-19 pandemic and specific recommendations regarding pregnancy were crucial in this public health crisis situation. Lessons learned from this pandemic should support the development of rapid clinical practice guidelines specific to this special population in the future.[33]

5 | CONCLUSION

Medicine use in pregnant women was low but increased with the levels of severity of symptoms. The observed decrease in use of medicines that were not recommended for the treatment of COVID-19 after the publication of the first scientific evidence (e.g., antivirals, hydroxychloroquine) and the tendency for an increased use of corticosteroids seem to be aligned with the evolution of guidelines. Finally, there is a large lack of evidence regarding the effectiveness and safety of COVID-19-related medicines in pregnant women, which calls for further and large studies in different settings that are able to stratify by severity.

COVIPREG group

Eran Hadar, Rabin Medical Center, Helen Schneider Hospital for Women and the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; Anna Goncé, Karen Castillo and Eduard Gratacós, Maternal-Fetal Medicine Department. BCNatal—Fetal Medicine Research Center (Hospital Clínic and Hospital Sant Joan de Déu), Universitat de Barcelona, Barcelona, Spain; Christophe Poncelet, Service de Gynécologie-Obstétrique, Centre Hospitalier René Dubos, Pontoise, France; Fernanda Surita, Amanda Dantas-Silva, Adriana Luz, Carolina Ribeiro-do-Valle and Carolina Borrelli, Department of Obstetrics and Gynecology, State University of Campinas, Campinas, Brazil; Thibaud Quibel, Department of Obstetrics, Maternité Poissy Saint Germain, Poissy, France; Begoña Martinez de Tejada, Sonia Campelo and Véronique Othenin-Girard, Obstetrics Division, Department of Pediatrics, Gynecology, and Obstetrics, Geneva University Hospitals, Geneva, Switzerland; Najeh Hcini and Veronique Lambert, West French Guiana Hospital Center, University of French Guiana, Saint Laurent du Maroni, French Guiana; Leonhard Schäffer and Anett Hernadi, Division of Obstetrics, Baden Cantonal Hospital, Baden, Switzerland; Albaro José Nieto-Calvache, Stiven Ernesto Sinisterra-Díaz, Juliana Maya, Paola Marsela Pérez and Adriana Messa Bryon, Fundación Valle del Lili, Cali, Colombia; Marco de Santis and Carmen de Luca, Telefono Rosso, Teratology Information Service, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; Adolfo Etchegaray and Juliana Moren, Fetal Medicine Unit, Hospital Universitario Austral, Pilar, Buenos Aires, Argentina; Sayed Hamid Mousavi, Shohra Qaderi and Mohammad Delsoz, Department of Research, Afghanistan National Charity Organization for Special Diseases (ANCOSD), Kabul, Afghanistan; Beatrice Eggel, Obstetrics and Gynecology Unit, Sion Hospital, Sion, Switzerland; Michael Geary, Jennifer Donnelly, Maria Kennelly, Fadi-Tamas Salameh, Claire McCarthy and Brian Cleary, Department of Obstetrics and Gynaecology, Rotunda Hospital, Dublin, Ireland and Department of Pharmacy, Rotunda Hospital, Dublin, Ireland; Romina Capoccia Brugger, Département de gynécologie-obstétrique, RHNE, Neuchâtel, Switzerland; Albert Ko, Uma Reddy and Olga Grechukhina, Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, United States; Javiera Fuenzalida and Jorge Carvajal, Maternal-Fetal Medicine, Department of Obstetrics, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile; Johann Silke, Department of Gynecology and Obstetrics, Hospital of the Upper Valais, Visp, Switzerland; Daniel Surbek, Anda-Petronela Radan and Luigi Raio, Department of Obstetrics and Feto-maternal Medicine, University Hospital of Bern, University of Bern, Bern, Switzerland; Monya Todesco Bernasconi and Mirjam Moser, Department of Obstetrics, Cantonal Hospital Aarau, Aarau, Switzerland; Jan Deprest and Jute Richter, Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium; Pedro Viana Pinto and Marina Moucho, Department of Obstetrics, S. João University Hospitalar Center, Porto, Portugal; Johana Sichitiu, Yves Ville, Laurent Salomon and Julien Stirnemann, Necker-Enfants Malades Hospitals, Department of Obstetrics, Paris, France; Augusto Rojas Martinez, Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Mexico; Karina Krajden Haratz, Division of Ultrasound in Obstetrics and Gynecology, Lis Maternity Hospital, Tel Aviv, Israel; Gustavo Malinger, Division of Ultrasound in Obstetrics and Gynecology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; Ann-Christin Tallarek and Kurt Hecher, Department of Obstetrics and Prenatal Medicine, University Hospital Hamburg Eppendorf, Hamburg, Germany; Lavinia Schuler-Faccini, Maria Teresa Vieira Sanseverino and Mariana Horn Scherer, Departamento de Genética, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Maria Celeste Osorio Wender and Maria Lucia Da Rocha Oppermann, Maternity Ward, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Betania Bohrer, and Luciana Friedrich, Pediatra e Neonatologista, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Camilia Giuliani, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Mary F. Higgins, UCD Perinatal Research Centre, Obstetrics and Gynaecology, National Maternity Hospital, Dublin, Ireland; Andrea Papadia, Maria Luisa Gasparri, Antonilli Morena, Christian Polli and Edoardo Taddei, Department of Gynecology and Obstetrics Ente Ospedaliero Cantonale, Lugano, Switzerland; Karin Nielsen-Saines, Mary Catherine Cambou, Rashmi Rao, Thalia Mok and Viviana Fajardo, Department of Pediatrics, Division of Infectious Diseases, David Geffen UCLA School of Medicine, Los Angeles, United States;

Nicolas Mottet, Department of Obstetrics and Gynecology, Besançon University Hospital, Besançon, France; Charles Garabedian and Louise Ghesquiere, CHU Lille, Department of Obstetrics, Lille, France; Christian R. Kahlert and Tina Fischer, Infectious Diseases and Hospital Epidemiology, Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland; Claudia Grawe, Department of Obstetrics, Gynecology Stadtspital Triemli Zürich, Zurich, Switzerland; Cora Alexandra Voekt, Department of Obstetrics, Grabs Hospital, Grabs, Switzerland; Sophie Defert and Jérôme Dimet, Department of Gynecology, Mont-de-Marsan Hospital, Mont-de-Marsan, France; Paul Böckenhoff and Brigitte Strizek, Department of Obstetrics and Prenatal Medicine, University Hospital Bonn, Bonn, Germany; Loïc Sentilhes, Amaury Brot, Aurélien Mattuizzi and Clémence Houssin, Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France; Dirk Bassler, Department of Obstetrics, University Hospital Zurich and Neonatal Department, University of Zurich, Zurich, Switzerland; Brigitte Weber, Department of Obstetrics and Gynecology, Obwald Cantonal Hospital, Sarnen, Switzerland; Marie-Claude Rossier, Department of Obstetrics and Gynecology, Hospital Riviera Chablais, Rennaz, Switzerland; Jérôme Mathis, Edouard Ha and Caroline Eggemann, Department of Obstetrics and Gynecology, Centre hospitalier Bienne, Bienne, Switzerland; Andrea Bloch, Obstetrics and Gynecology Unit, Hopital du Jura, Delemont, Switzerland; Roberta Netto, Department of Anesthesia, Intensive Care, and Out-of-Hospital Emergency, AUSL Aosta, Aosta, Italy; Martin Kaufmann, Department of Obstetrics, Spital Bülach, Bülach, Switzerland; Otto Henrique May Feuerschuette, Departamento de Ginecologia e Obstetrícia, Hospital Universitário Polydoro Ernani de São Thiago, HU-UFSC, Florianópolis, Brazil; Bénédicte Breton, Department of Obstetrics and Gynecology, Annecy Genevois Hospital Centre, Annecy, France; Arnaud Toussaint, Department of Gynecology and Obstetrics, Intercantonal Hospital of Broye, Payerne, Switzerland; Renato Augusto Moreira de Sa, Maternal and Infant Department, Federal Fluminense University, Clinical Research Department, Fernandes Figueira Institut - FIOCRUZ, Perinatal Rede D'or, Rio de Janeiro, Brazil; Mohamed Elbahnasawy and Sherief Abd-Elsalam, Emergency Medicine and Traumatology Department, Tanta University Faculty of Medicine, Tanta, Egypt; Guillaume Ducarme, Department of Obstetrics and Gynecology, Centre Hospitalier Departemental de Vendée, La-Roche-sur-Yon, France; Hélène Pelerin, Clinical Research Department, Centre Hospitalier Départemental de Vendée, La-Roche-sur-Yon, France; Ahmed Nafea, Shatby Hospital for Gynecology and Obstetrics, Alexandria, Egypt; Gaetan Plantefeve, Cecile Le Parco and Mohamed Derouich, Victor Dupouy Hospital, Argenteuil, France; Anis Feki and Gaston Grant, Département de gynécologie et obstétrique-HFR, Fribourg, Switzerland; Ina Hoffmann, Department of Obstetrics and Gynecology, Olten Cantonal Hospital, Olten, Switzerland; Kathryn Denize, Ottawa Hospital Research Institute, Ottawa, Canada; Manuel Guerra Canales, Medicina Materno Fetal, Hospital San José, Santiago, Chile; Carina Britschgi and Panagiotis Kanellos, Department of Gynecology and Obstetrics, Kantonal Hospital of Uri, Altdorf, Switzerland; Elke Barbara Prentl and Jessica Maisel, Department of Obstetrics and Gynecology, Winterthur Cantonal Hospital, Winterthur, Switzerland; Irene Hoesli and Cécile Monod, Department of Obstetrics, Basel, University Hospital, Basel, Switzerland; Grit Vetter and Brigitte Frey Tirri, Department of Obstetrics, Kantonsspital Baselland, Liestal, Switzerland; Carolin Blume and Stylianos Kalimeris, Kantonsspital Graubünden, Frauenklinik Fontana, Chur, Switzerland; Anne-Claude Muller Brochut, GynEcho private practice, Fribourg, Switzerland; Lucie Sedille, Department of Obstetrics and Gynecology, La Rochelle Hospital, La Rochelle, France; Inês Martins and Diogo Ayres dos Camps, Department of Obstetrics, Gynecology and Reproductive Medicine, Santa Maria University Hospital, Lisbon, Portugal; Michel Boulvain, Pôle Department of Gynecology and Obstetrics, GHOL Hôpital de Nyon, Nyon, Switzerland; Steffi Leu, Department of Obstetrics and Gynecology, Nidwald Cantonal Hospital, Stans, Switzerland; Kathrin Bütikofer, Department of Obstetrics and Gynecology, Olten Cantonal Hospital, Olten, Switzerland; Lisandra Stein Bernardes, Cristina Nunes dos Santos, Bruna Hipólito Micheletti, Jéssica Mosello, and Natálya Gonçalves Pereira, Department of Obstetrics and Neonatology, São Paulo University, São Paulo, Brazil; Stefanie Sturm, Frauenpraxis Schaffhausen, Schaffhausen, Switzerland; Manggala Pasca Wardhana, Obstetrics and Gynecology Department, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo Academic General Hospital, Surabaya, Indonesia; Irida Dajti, Department of Obstetrics Gynecology "Koco Gliozheni" University Hospital, Tirana, Albania; Feras Al Kharouf, Department of Obstetrics and Gynecology, King Abdulaziz Medical City, Ministry of National Guard-health Affairs, Riyad, Saudi Arabia; Chloé Moreau, Clinical Research Department, Centre Hospitalier Départemental de Vendée, La-Roche-sur-Yon, France; Mingzhu Yin, Hunan Engineering Research Center of Gynecology and Obstetrics Disease, Xiangya Hospital, Chansha, China; Annina Haessig, Department of Obstetrics and Gynecology, Zuger Kantonsspital, Zug, Switzerland; Sandrine Ackermann, Masset & Ackermann private practice, Prilly, Switzerland; Olivia Hernandez, Hospital Felix Bulnes Cerda, Santiago, Chile; Karoline Aebi-Popp, Department of Infectious Diseases, University Hospital Bern, Bern, Switzerland; Sophie Masmejan and Karine Lepigeon, Materno-fetal and Obstetrics Research Unit, Department "Femme-Mère-Enfant", University Hospital, Lausanne, Switzerland; Eric Giannoni, Clinic of Neonatology, Department Mother-Woman-Child, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

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COMPETING INTERESTS

The authors declare no conflict of interest.

CONTRIBUTORS

G.F., L.P., D.B. and A.P. conceived and designed the study. G.F., E.M., M.S. and A.P. analysed the data. All authors interpreted the data.

G.F. and E.G. drafted the manuscript. E.M., M.S. and A.P. critically revised the manuscript. A.P. provided supervision and mentorship. The COVI-PREG group contributed to data collection. Each author made a contribution in reviewing the manuscript drafting or revision and accepts accountability for the overall work. All authors approved the final version of the report.

DATA AVAILABILITY STATEMENT

Data are available through joint research agreements from the corresponding authors.

ORCID

Guillaume Favre https://orcid.org/0000-0001-6181-3126
Alice Panchaud https://orcid.org/0000-0001-6086-2401

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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