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Manuscript title: COVID-19 related medicine utilization study in pregnancy – the COVI-PREG cohort

Short running title: COVID-19 medicine use in pregnancy

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What is already known about this subject:

- Pregnant women are at high risk of severe form 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 was increasing 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.

ABSTRACT

OBJECTIVE: The aim 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 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 medicine were 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 July 1 2020).

FINDINGS: We included 1,964 pregnant patients, 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, 4.2% (52/1233) in outpatients, 19.7% (46/233) in inpatients without oxygen, 72.1% (44/61) in requiring standard oxygen, 95.7% (22/23) in requiring high flow oxygen, 96.2% (25/26) in intubated 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 lately.

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

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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 June 16, 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]

METHODS

Design and settings

This study used the data collected from March 24th, 2020, to July 1st, 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 multicenter international study. Any health facility with an antenatal clinic or labor ward worldwide was able to participate 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 center.

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 enrollment 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 center. 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.

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.

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's 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 – supplementary materials). Symptomatic treatments defined as any medicine not intended to treat directly the COVID-19, such as antipyretic and antithrombotic treatments, were not recorded. No information was available on the timing of COVID-19 related medicine intake.

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 5 categories ≤ 25 years (y), 26-30 y, 31-35y, 36-40 y, and > 40 y. 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: as the period between the last menstrual period (LMP) and gestational week (GW) 13 plus 6 days, trimester 2 defined as the period between GW 14 and 27 plus 6 days and trimester 3 as the period starting at GW 28.

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]

Early and later pandemic period

The pandemic period was divided into two periods corresponding to the early (March 24th 2020 – June 30th 2020) and later (July 1st 2020 – July 1st 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.

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, 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. 2015. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP).

RESULTS:

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 diagnosis 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 preeclampsia were respectively diagnosed before positive SARS-CoV-2 tests in 9.6% (n=189) and in 1.9% (n=37) of women (table 1).

Exposure to COVID-19 related medicines

A description of patients' characteristics with and without exposure to COVID-19 related medicines is presented in supplementary materials 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 medicines 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 – supplementary materials. 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 stable S5 – supplementary materials.

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 medicines categories by level of severity is presented in table 3. Individual medicine names are presented in table S6 (supplementary materials). 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.

Early versus late pandemic period

A total of 592 pregnant women who 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). Patients' characteristics according to the period of the pandemic are described in table S7 (supplementary materials). A description of pregnant patients tested positive for SARS-CoV-2 over time is presented in figure S1 (supplementary materials). COVID-19 related medicine use over time is presented in figure S2 (supplementary materials) 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 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.

Corticosteroids use increased in the late pandemic period compared to the early 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).

DISCUSSION:

To our knowledge, this is one of the first studies to report COVID-19 related medicines use 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) patients received this medicine but mostly in 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 have not 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 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 hospitalized general population in the United States, where hydroxychloroquine decreased and corticosteroids 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 Delta variant predominant period in our study (data extracted from GISAID)[30]

Some limitations 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 analyzing 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 centers 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, severe 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 need to be urgently assessed in this population at high risk of severe COVID-19.

This study brought evidence that pregnant women were not spared from 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]

CONCLUSION:

Medicines 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 seems 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 call for further and large studies in different settings that are able to stratify by severity.

Authors' contribution
GF, LP, DB, and AP conceived and designed the study. GF, EM, MS, and AP analyzed the data. All authors interpreted the data. GF and EG drafted the manuscript. EM, MS, and AP critically revised the manuscript. AP 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.

Declaration of interests
Authors declare no conflicts of interest.

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Data availability statement

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

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Ethics statement

This research project was reviewed and approved the Swiss Ethical Board (CER-VD-2020-00548).

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Figure 1: Medicine categories use between early and later pandemic period.
Proportion of patients with reported medicine use (%) with 95% confidence interval (I)
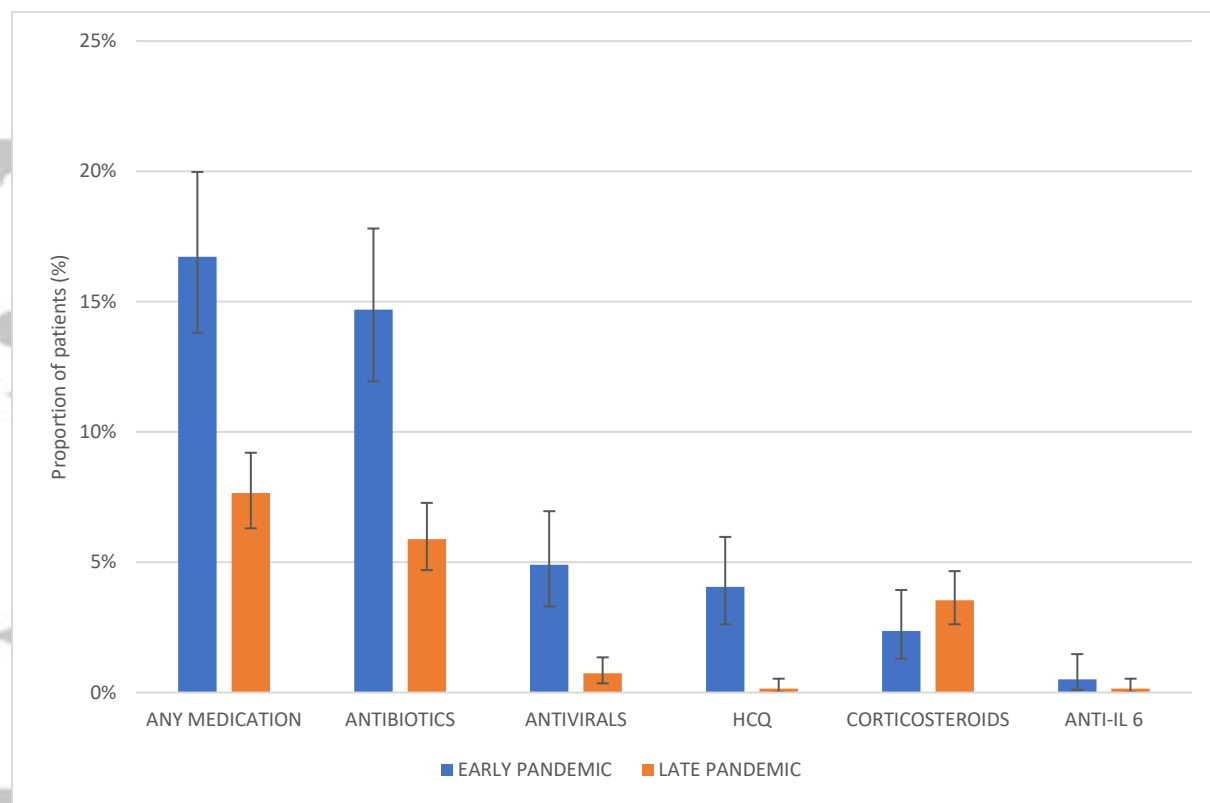
Table 1: Description of pregnant persons tested positive for SARS-CoV 2

	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
Obstetrical history			
Nulliparous	640	**32.6**	30.5 -34.7
Previous cesarean 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 hemorrhage	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 labor	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

IQR: interquartile interval
BMI: body mass index
PPROM: Preterm Premature Rupture of Membranes

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
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**

HCQ: hydroxychloroquine
ANTI-IL6: anti-interleukin 6

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	-

	LEVEL 4 High Flow O2 n = 23			LEVEL 5 Mechanical ventilation n = 26			LEVEL 6 Maternal death* n = 7*		
	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	38.5-80.3	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	-

O2: oxygen
High Flow O2: high flow oxygen canula and/or non-invasive ventilation
* 2 patients died before ICU admission and 1 refused hospital admission
HCQ: hydroxychloroquine
ANTI-IL6: anti-interleukin 6

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%	-
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%	-

HCQ: hydroxychloroquine
ANTI-IL6: anti-interleukin 6
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.