Maternal and perinatal outcomes in high vs low risk-pregnancies affected by SARS-COV-2 infection (Phase-2): The WAPM (World Association of Perinatal Medicine) working group on COVID-19


This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc.
Maternal and perinatal outcomes in high vs low risk pregnancies affected by SARS-COV-2 infection (Phase-2): The WAPM (World Association of Perinatal Medicine) working group on COVID-19

**Short title:** Outcome of SARS-COV-2 in high vs low risk pregnancies

**Correspondence:**

Francesco D’Antonio, MD, PhD

Center for High-Risk Pregnancy and Fetal Care - Department of Obstetrics and Gynecology, University of Chieti, Italy.

Via dei Vestini 31 - 66100 Chieti, Italy. Email address: francesco.dantonio@unich.it

**Disclosure:** Authors report no conflict of interest.

**Ethical approval:** Ethical Committee of Federico II University of Naples, nr. 145/2020
The WAPM (The World Association of Perinatal Medicine) working group on COVID-19

It has been listed here accordingly to their contribution:

Francesco D’Antonio MD
Centre for High-Risk Pregnancy and Fetal Care, Department of Obstetrics and Gynecology, University of Chieti, Chieti Italy

Cihat Sen
Perinatal Medicine Foundation
Department of Perinatal Medicine, Memorial Hospital, Istanbul, Turkey

Daniele DI Mascio
Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Italy

Alberto Galindo

Cecilia Villalain

Ignacio Herraiz
Fetal Medicine Unit, Maternal and Child Health and Development Network, Department of Obstetrics and Gynecology, University Hospital 12 de Octubre, Complutense University of Madrid, Madrid, Spain

Resul Arısoy
Department of Perinatal Medicine, Memorial Hospital, Istanbul, Turkey

Ali Ovayolu

Hasan Eroğlu
Cengiz Gokcek Women's and Children's Hospital, Gaziantep, Turkey

Manuel Guerra Canales
Hospital Clinico San Jose, Chile Santiago / Chile
Subhashini Ladella
UCSF Fresno, Community Medical Centers, Fresno, California, USA

Liviu Cojocaru
Ozhan Turan
Sifa Turan
Department of Obstetrics, Gynecology and Reproductive Science, University of Maryland Medical Center, Baltimore, MD, USA

Eran Hadar
Noa A. Brzezinski-Sinai
Sarah Dollinger MD
Helen Schneider Hospital for Women, Rabin Medical Center, Petach-Tikva and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Ozlem Uyaniklar
Sakine Rahimli Ocakouglu
Zeliha Atak
Bursa City Hospital, Bursa, Turkey

Tanja Premru-Srsen
Lilijana Kornhauser-Cerar
Mirjam Druškovič
Department of Perinatology, University Medical Center, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

Liana Ples
Department of Obstetrics and Gynecology, Saint John Hospital, UMF Carol Davila Bucharest, Romania

Reyhan Gündüz
Elif Ağaçayak
Department of Obstetrics and Gynecology, University of Dicle, Diyarbakır, Turkey
Javier Alfonso Schvartzman
MERCEDES NEGRI MALBRAN
Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno", Buenos Aires, Argentina

Marco Liberati
Francesca Di Sebastiano
Ludovica Oronzi
Chiara Cerra
Danilo Buca
Centre for High-Risk Pregnancy and Fetal Care, Department of Obstetrics and Gynaecology, University of Chieti, Chieti Italy

Angelo Cagnacci
Arianna Ramone
Fabio Barra
Academic Unit of Obstetrics and Gynaecology, IRCCS Ospedale Policlinico San Martino, Genova, Italy

Andrea Carosso
Chiara Benedetto
Stefano Cosma
Department of Obstetrics and Gynecology, Sant’Anna Hospital, University of Turin, Turin, Italy

Axelle Pintiaux
Caroline Daelemans
Elena Costa
Department of Obstetrics and Gynecology, Hospital Erasme, Cliniques Universitaires de Bruxells, Brussels, Belgium

Ayşegül Özel
Murat Muhçu
Antonella Cromi
Antonio Simone Laganà
Fabio Ghezzi
Department of Obstetrics and Gynecology, “Filippo Del Ponte” Hospital, University of Insubria, Varese, Italy

Angelo Sirico
Alessandra Familiari
Giovanni Scambia
Department of Obstetrics and Gynaecology, Fondazione Policlinico Universitario A Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome, Italy

Zulfiya Khodjaeva Gennady T. Sukhikh
Ksenia A. Gorina
National Medical Research Center for Obstetrics, Gynecology and Perinatology, Moscow, Russia

Renato Augusto Moreira de Sa
Mariana Vaz
Assistência Obstétrica do Grupo Perinatal, Rio de Janeiro, Brazil

Otto Henrique May Feuerschuette
Departamento de Ginecologia e Obstetrícia, Hospital Universitário Polydoro Ernani, Santiago, Brazil

Anna Nunzia Della Gatta
Aly Youssef
Gaetana Di Donna
Department of Obstetrics and Gynecology, University of Bologna, Sant’Orsola- Malpighi University Hospital, Bologna, Italy.

Alicia Martinez-Varea
Gabriela Loscalzo
José Morales Roselló
Servicio de Obstetricia y Ginecología, Hospital Universitario y Politécnico La Fe, Valencia, Spain

Vedran Stefanovic
Irmeli Nupponen
Kaisa Nelskylä
Department of Obstetrics and Gynecology, Neonatology and Intensive Care, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

RODRIGO AYALA
ABC MEDICAL CENTER, Mexico City, Mexico

Rebeca Garrote Molpeceres
ASUNCIÓN PINO VÁZQUEZ
University Clinic Hospital Of Valladolid, Valladolid, Spain

Fabrizio Sandri
Ilaria Cataneo
Marinella Lenzi
Unit of Obstetrics and Gynecology, Ospedale Maggiore, Bologna, Italy

Esra Tustas Haberal
Hisar Intercontinental Hospital, Instanbul, Turkey

Erasmo Huertas
Amadeo Sanchez
Pedro Arango
Instituto Nacional Materno Perinatal, Lima, Peru
Amanda Bermejo
Hospital Universitario de Móstoles, Móstoles, Spain

María Monica Gonzalez Alcantara
Hospital Juan A. Fernandez, Buenos, Argentina

Gökhan Göynümer
Düzce University Medicine Faculty / Department of Perinatology, Düzce, Turkey

Erhan Okuyan
Batman Maternity and Child Health Hospital, Batman, Turkey

Ciuhodaru Madalina
Universitatea de Medicină și Farmacie Grigore T. Popa Iași, Iași, Romania

Ana Concheiro Guisan
Alvaro Cunqueiro University Hospital Of Vigo, Vigo, Spain

Alejandra Martínez Schulte
Hospital Angeles Lomas, Mexico City, Mexico

Valentina Esposito
University of Milan, Milan, Italy

Valentina De Robertis
Fetal Medicine Unit, Di Venere Hospital, Barì, Italy

Snezana Zdjelar
Milan Lackovic
Sladjana Mihajlovic
Kbc Dr Dragisa Misovic Dedinje Belgrade, Serbia

Nelly Jekova
University Hospital, Department of Neonatology, Obstetrics and Gynecology, Sofia, Bulgaria

Gabriele Saccone
Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

Mehmet Musa Aslan
Sakarya University Education and Research Hospital, Sakarya, Turkey

Maria Carmela Di Dedda
Department Gynecology and Obstetrics, Fornaroli Hospital, Magenta, Italy

Maisuri Chalid
Department of Obstetrics and Gynecology, Hasanuddin University, Makassar, Indonesia

JOSE ENRIQUE MOROS CANACHE
CENTRO MEDICO LA PAZ DE BATA, DEPARTAMENTO DE GINECOLOGIA Y OBSTETRICIA, BATA, GUINEA ECUATORIAL

George Daskalakis
Panos Antsaklis
Alexandra Hospital – National and Kapodistrian, University of Athens, Athens, Greece

Enrique Criado Vega
Hospital Clínico "San Carlos", Division of Neonatology, Madrid, Spain
Elisa Cueto
Hospital Virgen De La Luz, Cuenca, Spain

Chiara Taccaliti
Ospedale Generale Regionale “F. Miulli”, Acquaviva delle Fonti, Italy

Alicia Yeliz Aykanat
Department of Obstetrics and Gynecology, Istanbul University-Cerrahpasa Medical School, Istanbul, Turkey

Şerife Özlem Genç
Karaman Public Hospital, Karaman, Turkey

Bernd Froessler
Department of Anaesthesia, Lyell McEwin Hospital, Adelaide, Australia

Petya Angelova Radulova
University hospital of Obstetrics and Gynecology, Sofia, Bulgaria

Danila Morano
Beatrice Bianchi
Maria Giulia Lombana Marino
Department of Medical Sciences, Section of Obstetrics and Gynecology, Azienda Ospedaliera-Universitaria Sant' Anna, University of Ferrara, Ferrara, Italy

Gabriella Meccariello
Ostetricia e Ginecologia Universitaria - Ospedale S.Anna e S.Sebastiano, Caserta, Italy

Bindu Rohatgi
Sulochana clinic, Kolkata India
Antonio Schiattarella
Maddalena Morlando
Nicola Colacurci
Department of Woman, Child and General and Specialized Surgery, University of Campania Luigi Vanvitelli, Naples, Italy

Andrea Villasco
Nicoletta Biglia
Academic Division of Obstetrics and Gynecology, Mauriziano Umberto I Hospital, University of Turin, Turin, Italy

Ana Luiza Santos Marques
Instituto de MedFetal e Diagnóstico por Imagem do Amazonas, Manaus, Brazil

Alessandra Gatti
Daniela Luvero
Roberto Angioli
Campus Bio Medico, University of Rome, Rome, Italy

Alejandro Pittaro
Hospital Raul F. Larcade, Buenos Aires, Argentina

Albert Lila MD,66
Regional Hospital Gjakova, Kosovo, Republic of Kosovo

Blanka Zlatohlávková
Department of Obstetrics and Gynecology, Division of Neonatology, General Hospital in Prague and First Faculty of Medicine, Charles University, Prague, Czech Republic
Keywords: SARS-COV-2; COVID19; Coronavirus; infection; pregnancy

ABSTRACT

Objectives: To evaluate maternal and perinatal outcomes in high compared to low-risk pregnancies complicated by SARS-COV-2 infection.

Methods: This was a multinational retrospective cohort study including women with laboratory-confirmed SARS-COV-2 from 76 centers from 25 different countries in Europe, United States, South America, Asia and Australia from 04 April 2020 till 28 October 2020. The primary outcome was a composite measure of maternal mortality and morbidity including admission to intensive care unit (ICU), use of mechanical ventilation, or death. Secondary outcome was a composite measure of adverse perinatal outcome, including miscarriage, fetal loss, neonatal (NND) and perinatal (PND) death, and admission to neonatal intensive care unit. All these outcomes were assessed in high-risk compared to low-risk pregnancies. Pregnancies were considered as high risk in case of either pre-existing chronic medical conditions pre-existing pregnancy or obstetric disorders occurring in pregnancy. Fisher-test and logistic regression analysis were used to analyze the data.

Results: 887 singleton pregnancies tested positive to SARS-COV-2 at RT-PCR nasal and pharyngeal swab were included in the study. The risk of composite adverse maternal outcome was higher in high compared to low risk-pregnancies with an OR of 1.52 (95% CI 1.03-2.24; p= 0.035). Likewise, women carrying a high risk-pregnancies were also at higher risk of hospital admission (OR: 1.48, 95% CI 1.07-2.04; p= 0.002), presence of severe respiratory symptoms (OR: 2.13, 95% CI .41-3.21; p= 0.001), admission to ICU (OR: 2.63, 95% CI 1.42-4.88) and invasive mechanical ventilation (OR: 2.65, 95% CI 1.19- 5.94; p= .002). When exploring perinatal outcomes, high-risk pregnancies were also at high risk of adverse perinatal outcome with an OR 0f 1.78 (95% CI .15-2.72; p= 0.009). However, such association was mainly due to the higher incidence of miscarriage in high risk compared to low risk pregnancies (5.3% vs 1.6%, p= 0.008), while there was no difference as regard as the other explored outcomes between the two study groups. At logistic regression analysis, maternal age (OR: 1.12, 95% CI 1.02-1.22, p= 0.023) and the presence of a high-risk
pregnancies (OR: 4.21, 95% CI 3.90-5.11, p<0.001) were independently associated with adverse maternal outcome.

**Conclusions:** High-risk pregnancies complicated by SARS-COV-2 infection are at higher risk of adverse maternal outcome compared to low-risk gestations.
INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) infection spread towards the end of 2019 and nowadays is still a major issue of Public Health, with new cases of infection, hospitalization, admission to Intensive Care Unit (ICU) and even deaths increasing on a daily basis worldwide.¹

From the beginning of pandemic, pregnancy has been claimed to be potentially associated with a higher burden of maternal mortality and morbidity compared to the general population.³⁻⁹

The severity of SARS-COV-2 infection in the general population has been reported to be significantly influenced by the presence of different risk factors. Among these, age and comorbidities were found to be the strongest predictors of hospital admission, critical illness and mortality.¹⁰

Despite the multitude of reports published on SARS-COV-2 infection during pregnancy, only few studies were designed to ascertain whether the presence of either pre-existing or pregnancy-related conditions (i.e. those usually considered as high risk pregnancies) might increase the risk of both maternal and fetal adverse outcome.

Thus, the aim of this secondary analysis was to elucidate whether high risk pregnancies were at higher risk of adverse maternal and perinatal outcomes in a multinational cohort of pregnant women tested positive with SARS-COV-2 infection.

METHODS

Study design and participants

This was a multinational, prospective cohort study involving all pregnant women with a laboratory-confirmed SARS-COV-2 infection, diagnosed from 04 April 2020 till 28 October 2020. This study was designed as an open and web-based database study in 76 centers from 25 different countries (Argentina,
Australia, Belgium, Brazil, Colombia, Czech Republic, Finland, Germany, Greece, Israel, Italy, North Macedonia, Peru, Portugal, Republic of Kosovo, Romania, Russia, Serbia, Slovenia, Spain, Turkey, and United States) by the WAPM Covid-19 Study Group. The study was endorsed by the World Association of Perinatal Medicine. The first phase of the study has already been published which comprises the data from 04 April 2020 till 01 June 2020. After that, some additional information for the study was added into the database and reevaluated by the contributors accordingly for the new database as WAPM Covid-19 Study Phase-2. Only confirmed cases with PCR test are included in the evaluation.

SARS-COV-2 was diagnosed on the basis of The World Health Organization (WHO) interim guidance. A confirmed case of SARS-COV-2 was defined as a positive result on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens. Inclusion criteria were women tested positive for SARS-CoV-2 at RT-PCR assay of nasal and pharyngeal swab due to symptoms or exposure with infected individuals. Neonates from mother positive to SARS-COV-2 were usually tested within 24 hours after delivery with RT-PCR assay of nasal and pharyngeal swab.

Data on recent exposure history, clinical symptoms or signs, laboratory findings, maternal and perinatal outcomes were collected. All medical records were anonymized and sent to the coordinator center at University of Naples Federico II (Naples, Italy) through The World Association of Perinatal Medicine (WAPM) data platform or via an encrypted Research Electronic Data Capture (REDCap) data management platform. Data were entered into a computerized database and cross-checked. In case of missing data, requests for clarification were sent to the coordinator of each participating center.

**Outcomes**

The primary outcome of the study was to compare the incidence of a composite measure of maternal mortality and morbidity including at least one of the following: admission to intensive care unit (ICU), use of mechanical ventilation (defined as intubation, need for continuous positive airway pressure, extra-
corporal membrane oxygenation), severe respiratory symptoms (including dyspnea and shortness of
breath) or death in high vs low risk pregnancies.

Secondary outcomes were a composite score of adverse perinatal outcome, including miscarriage, intra-
uterine death, neonatal death, admission to neonatal intensive care unit and the individual components of
both primary and secondary outcomes. Miscarriage was defined as pregnancy loss before 22 weeks of
gestation, fetal loss at or after 22 weeks of gestation, while neonatal death as death of a live-born infant
within the first 28 days of life. Perinatal death was defined as fetal loss and NND.

Further details on criteria for maternal admission to ICU and neonatal admission to NICU are more
extensively described elsewhere.\textsuperscript{9}

All these outcomes were assessed in high-risk compared to low-risk pregnancies. Pregnancies were
considered as high risk in case of either pre-existing chronic medical conditions pre-existing pregnancy
(pregestational diabetes, chronic hypertension or autoimmune disease) or obstetric disorders occurring in
pregnancy (pre-eclampsia, gestational hypertension or gestational diabetes mellitus). Regarding the specific
medical complications affecting or pre-existing pregnancy, chronic hypertension was defined as
hypertension that precedes pregnancy or was present on at least two occasions before the 20th week of
gestation. Pre-eclampsia was defined as the new onset of hypertension and proteinuria or the new onset of
hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation
or postpartum in a previously normotensive woman, while gestational hypertension as a blood pressure
$\geq 140/90$ mmHg on two occasions (at least 4 hours apart) during pregnancy after 20 weeks’ gestation in a
previously normotensive patient, without the presence of proteinuria or other clinical features suggestive
of preeclampsia. Finally, gestational diabetes was defined as any degree of glucose intolerance with onset
or first recognition during pregnancy after a 75 gr or 100 gr of oral glucose tolerance test (OGTT\textsubscript{9} according
each country specific guideline.

In order to elucidate the rate of vertical transmission, all newborn form the present cohort were tested at
birth.
**Statistical analysis**

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA) and using Stata, version 13.1 (Stata Corp., College Station, TX, 2014). Continuous variables were reported as means ± standard deviation (SD), while categorical as numbers (percentage). Univariate comparisons of dichotomous data were performed with the use of the chi-square test with continuity correction. Comparisons between groups were performed with the use of the T-test to test group means by assuming equal within-group variances for parametric data, and with the use of Wilcoxon and Mann-Whitney tests for nonparametric data. Multivariate analysis was performed to evaluate potential predictors of the primary outcome. Logistic regression was reported as adjusted odd ratio (aOR) with 95% confidence interval (CI). P value <0.05 was considered statistically significant.
RESULTS

General characteristics of the included women

During the study period, 887 women with singleton viable high-risk (122 with chronic pre-existing and 86 with medical complication occurring during gestation) pregnancies at the time of assessment, positive to SARS-COV-2 at RT-PCR nasal and pharyngeal swab, in 72 centers from 22 different countries were included in the study.

General characteristic of the study population is reported in Table 1. Maternal age was high in high risk compared to low risk pregnancies (34.16±6.8 vs 31.39±5.5, p<0.001), while there was no difference in the mean gestational age at diagnosis of infection (p= 0.425), nulliparity (p= 0.313) and smoking status (p= 0.140) (Table 1). Regarding the obstetrics outcomes, women with high-risk pregnancies had a higher incidence of preterm delivery < 37 weeks of gestation compared to non-high-risk pregnancies (15.9% vs 9.0%, p= 0.007), while there was no difference between the two groups as regard the occurrence of preterm delivery < 34 weeks of gestation. Furthermore, high-risk pregnancies were more likely delivered by cesarean section compared to controls (30.3% vs 22.4%, p= 0.026). There were three cases of maternal deaths. The first maternal death occurred in a high-risk pregnancy with type II diabetes mellitus. She presented at 33 weeks of gestation with stillbirth. She was febrile and unconscious. Chest radiography showed pulmonary infiltrates and atelectasis with elevated left hemidiaphragm. The woman was admitted to ICU and intubated but died with acute kidney injury and cardiac arrest. The second and third death occurred in two non-high-risk-pregnant women age 25 and 27 years old respectively presenting to the emergency department with severe respiratory symptoms requiring admission to ICU. Details of these three maternal deaths are reported in a previous study from our group. 4

The risk of composite adverse maternal outcome was higher in high compared to low risk-pregnancies with an OR of 1.52 (95% CU 1.03-2.24; p= 0.035) (Table 2). Likewise, women carrying a high risk-pregnancies were also at higher risk of hospital admission (OR: 1.48, 95% CI 1.07-2.04; p= 0.002), presence of severe
respiratory symptoms (aOR: 2.13, 95% CI 1.41-3.21; p= 0.001), admission to ICU (aOR: 2.63, 95% CI 1.42-4.88) and invasive mechanical ventilation (OR: 2.65, 95% CI 1.19- 5.94; p= .002).

When exploring perinatal outcomes, high-risk pregnancies were also at high risk of adverse perinatal outcome with an aOR 0f 1.78 (95% CI .15-2.72; p= 0.009). However, such association was mainly due to the higher incidence of miscarriage in high risk compared to low-risk pregnancies (5.3% vs 1.6%, p= 0.008), while there was no difference in the occurrence of either fetal loss (p= 0.334), NND (p= 1.000), PND (p= 0.516) and admission to NICU (p= 0.772) between high- and low-risk pregnancies complicated by Covid-19 infection.

At logistic regression analysis, maternal age (aOR: 1.12, 95% CI 1.01-1.22 per 10 year increase, p= 0.023) and the presence of a high risk pregnancies (aOR: 4.21, 95% CI 3.90-5.11, p<0.001) were independently associated with adverse maternal outcome, while maternal age (aOR: 1.33, 95% CI 1.19-1.47 per 10 year increase, p= 0.019) was the only factor associated with adverse perinatal outcome.
DISCUSSION

Main findings

This secondary analysis of the WAPM study - a multinational cohort study including 388 pregnant women with confirmed SARS-CoV-2 from 72 different centers – showed that in high risk pregnancies the rates composite adverse maternal outcome, severe respiratory symptoms and invasive ventilation are significantly higher, compared with low risk pregnancies. Conversely, no difference was found when assessing fetal outcomes in high compared with low risk pregnancies.

Strengths and limitations

Strength and limitation of this analysis are essentially those inherent in the primary analysis. The enrollment of only of women with laboratory-confirmed SARS-CoV-2, the large sample, the inclusion of both University Hospitals and Community Hospitals from different countries, and multitude of outcomes explored, represented the major strengths of the study. The major limitation was that the study population came mostly from women referred for suspected SARS-CoV-2 infection, due to symptoms or exposure, and consequently tested with RT-PCR nasal and pharyngeal swab, thus leading to an intuitively lower percentage of asymptomatic women in the study cohort. More importantly, inclusion of women mainly presenting with symptoms or being tested positive for close contact with infected people represents an inclusion bias and it may be entirely possible that the rate of adverse outcomes reported in women with high-risk pregnancy from the present series may represent an overestimation of the actual occurrence of these outcomes in the overall general population of pregnant women with SARS-CoV-2 infection. Another major limitation was represented by the fact that we could not stratified the analysis according to the specific pregnancy or pre-pregnancy comorbidity because the small number of cases per each sub-group category would have affected the robustness of the results. Furthermore, different income level of countries and healthcare systems, and the heterogeneity in the management of both the mother and the fetus might have independently affected perinatal outcomes. Finally, the contribution of each center in providing the data was not homogenous as well the definitions of the different pregnancy complications
(i.e. gestational diabetes mellitus). In this scenario it may be entirely possible that the present population includes the most severe spectrum of SARS-CoV-2 infection in pregnancy.

**Implications for clinical practice and research**

Since the beginning of the pandemic outbreak, pregnancy has been extensively evaluated as a potential high risk condition, due to physiological changes that might predispose pregnant women to a more severe clinical course of COVID-19, compared with non-pregnant population.⁴⁻⁵

One of the largest systematic review recently published on this topic showed that pregnant and recently pregnant women affected by COVID-19 were significantly more likely to need admission to ICU and invasive ventilation, compared with non-pregnant women of reproductive age, and that increased maternal age, higher BMI, chronic hypertension and pre-existing diabetes were all significantly associated with a more severe course of COVID-19 in pregnancy. Moreover, pre-existing maternal comorbidities represented also a risk factor for admission to ICU and for invasive ventilation.⁹

The presence of higher risk of adverse outcomes in patients affected by COVID-19 is a well-known issue also in general population and has been reported early in the beginning of the pandemic: cardiovascular diseases, diabetes mellitus, hypertension, obesity has been all shown to be strong predictors of mortality and severe morbidity in people with SARS-COV-2 infection, particularly with increasing age,¹⁴⁻¹⁷ although the strength of this association persists also when considering only young adults.¹⁸

The findings from this study confirm what previously shown both in general population and pregnant women, as the presence of either pre-existing or obstetrical conditions was associated with a significantly higher risk of composite adverse maternal outcome, severe respiratory morbidity and need for invasive ventilation. Conversely, the association between SARS-COV-2 infection and high-risk pregnancy did not significantly influence perinatal outcomes.

**Conclusions**
High risk pregnancies, complicated by SARS-COV-2 infection are at higher risk of adverse outcome, mostly respiratory, compared to low-risk gestations. Accurate risk stratification of women presenting with suspected SASR-COV-2 infection in pregnancy is warranted in order to identify a sub-set of women who may benefit of a tailored management, in order to improve maternal outcome.

REFERENCES


Mar 28;395(10229):1038] [published correction appears in Lancet. 2020 Mar 28;395(10229):1038].

e205313.
Table 1. Comparison of different characteristics in high vs low risk pregnancies complicated by SARS-COV-2 infection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High-risk pregnancies (N = 208)</th>
<th>No high-risk pregnancies (N = 679)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal and pregnancy characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age</td>
<td>34.16±6.8</td>
<td>31.39±5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age at diagnosis of infection (w)</td>
<td>30.26±9.8</td>
<td>29.65±9.6</td>
<td>0.425</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>75 (36.1%)</td>
<td>219 (32.3%)</td>
<td>0.313</td>
</tr>
<tr>
<td>Smoking before or during pregnancy</td>
<td>11 (5.3%)</td>
<td>21 (3.1%)</td>
<td>0.140</td>
</tr>
<tr>
<td>Preterm birth &lt; 37 weeks of gestation</td>
<td>33 (15.9%)</td>
<td>61 (9.0%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Preterm birth &lt; 34 weeks of gestation</td>
<td>14 (6.7)</td>
<td>27 (4.0%)</td>
<td>0.129</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>145 (69.7%)</td>
<td>527 (77.6%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>63 (30.3%)</td>
<td>152 (22.4%)</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>Clinical, radiological and laboratory findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic infection</td>
<td>106 (51.0%)</td>
<td>411 (60.5%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Asymptomatic infection</td>
<td>102 (49.0%)</td>
<td>268 (39.5%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Fever</td>
<td>50 (24.0%)</td>
<td>206 (30.3%)</td>
<td>0.081</td>
</tr>
<tr>
<td>Condition</td>
<td>Number (Percentage)</td>
<td>Reference Number (Percentage)</td>
<td>P-value</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------</td>
<td>-------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>High-grade fever</td>
<td>20 (9.6%)</td>
<td>14 (2.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cough</td>
<td>52 (25.0%)</td>
<td>185 (27.2%)</td>
<td>0.591</td>
</tr>
<tr>
<td>Myalgia</td>
<td>28 (13.5%)</td>
<td>129 (19.0%)</td>
<td>0.078</td>
</tr>
<tr>
<td>Anosmia</td>
<td>11 (5.3%)</td>
<td>47 (6.9%)</td>
<td>0.521</td>
</tr>
<tr>
<td>G.I. symptoms</td>
<td>4 (1.9%)</td>
<td>23 (3.5%)</td>
<td>0.360</td>
</tr>
<tr>
<td>Positive chest CT scan</td>
<td>34 (16.3%)</td>
<td>20 (2.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>109 (52.4%)</td>
<td>311 (45.8%)</td>
<td>0.096</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27 (13.0%)</td>
<td>31 (4.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased LDH levels</td>
<td>29 (13.9%)</td>
<td>24 (3.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Pharmacologic Treatments**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number (Percentage)</th>
<th>Reference Number (Percentage)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH</td>
<td>58 (27.9%)</td>
<td>125 (18.4%)</td>
<td>0.139</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>63 (29.3%)</td>
<td>209 (30.8%)</td>
<td>0.731</td>
</tr>
<tr>
<td>Any antiviral drug</td>
<td>69 (32.5%)</td>
<td>142 (20.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>46 (22.1%)</td>
<td>122 (18.0%)</td>
<td>0.189</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage) or as mean ± standard deviation (SD).

CT, computerized tomography; LMWH, Low molecular weight heparin; LDH, lactate dehydrogenase.

**Boldface data, statistically significant.**
Table 2. Comparison of the different maternal and fetal outcomes in high vs low risk pregnancies complicated by SARS-COV-2 infection

<table>
<thead>
<tr>
<th>Outcome</th>
<th>High-risk pregnancies (N = 208)</th>
<th>No high-risk pregnancies (N = 679)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite adverse maternal outcome</td>
<td>46 (22.1%)</td>
<td>107 (15.8%)</td>
<td>0.036</td>
</tr>
<tr>
<td>In hospital admission</td>
<td>85 (40.9%)</td>
<td>216 (31.8%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Severe respiratory symptoms</td>
<td>44 (21.2%)</td>
<td>76 (11.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission to intensive care unit</td>
<td>19 (9.1%)</td>
<td>25 (3.7%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>11 (5.3%)</td>
<td>14 (2.1%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Composite adverse fetal outcome</td>
<td>37 (17.8%)</td>
<td>74 (10.9%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>11 (5.3%)</td>
<td>11 (1.6%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Intra-uterine death</td>
<td>2 (1.0%)</td>
<td>3 (0.4%)</td>
<td>0.334</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>2 (1.0%)</td>
<td>6 (0.8%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>4 (2.0%)</td>
<td>9 (1.2%)</td>
<td>0.516</td>
</tr>
<tr>
<td>Admission to neonatal intensive care unit</td>
<td>18 (8.7%)</td>
<td>54 (8.0%)</td>
<td>0.772</td>
</tr>
</tbody>
</table>