

Daniele Di Mascio, Cihat Sen\*, Gabriele Saccone, Alberto Galindo, Amos Grünebaum, Jun Yoshimatsu, Milan Stanojevic, Asim Kurjak, Frank Chervenak, María José Rodríguez Suárez, Zita Maria Gambacorti-Passerini, María de los Angeles Anaya Baz, Esther Vanessa Aguilar Galán, Yolanda Cuñarro López, Juan Antonio De León Luis, Ignacio Cueto Hernández, Ignacio Herraiz, Cecilia Villalain, Roberta Venturella, Giuseppe Rizzo, Ilenia Mappa, Giovanni Gerosolima, Lars Hellmeyer, Josefine Königbauer, Giada Ameli, Tiziana Frusca, Nicola Volpe, Giovanni Battista Luca Schera, Stefania Fieni, Eutalia Esposito, Giuliana Simonazzi, Gaetana Di Donna, Aly Youssef, Anna Nunzia Della Gatta, Mariano Catello Di Donna, Vito Chiantera, Natalina Buono, Giulio Sozzi, Pantaleo Greco, Danila Morano, Beatrice Bianchi, Maria Giulia Lombana Marino, Federica Laraud, Arianna Ramone, Angelo Cagnacci, Fabio Barra, Claudio Gustavino, Simone Ferrero, Fabio Ghezzi, Antonella Cromi, Antonio Simone Laganà, Valentina Laurita Longo, Francesca Stollagli, Angelo Sirico, Antonio Lanzone, Lorenza Driul, Fabiana Cecchini D, Serena Xodo, Brian Rodriguez, Felipe Mercado-Olivares, Deena Elkafrawi, Giovanni Sisti, Rosanna Esposito, Antonio Coviello, Marco Cerbone, Maddalena Morlando, Antonio Schiattarella, Nicola Colacurci, Pasquale De Franciscis, Iliaria Cataneo, Marinella Lenzi, Fabrizio Sandri, Riccardo Buscemi, Giorgia Gattei, Francesca della Sala, Eleonora Valori, Maria Cristina Rovellotti, Elisa Done, Gilles Faron, Leonardo Gucciardo, Valentina Esposito, Flaminia Vena, Antonella Giancotti, Roberto Brunelli, Ludovico Muzii, Luigi Nappi, Felice Sorrentino, Lorenzo Vasciaveo, Marco Liberati, Danilo Buca, Martina Leombroni, Francesca Di Sebastiano, Luciano Di Tizio, Diego Gazzolo, Massimo Franchi, Quintino Cesare Ianniciello, Simone Garzon, Giuliano Petriglia, Leonardo Borrello, Albaro José Nieto-Calvache, Juan Manuel Burgos-Luna, Caroline Kadji, Andrew Carlin, Elisa Bevilacqua, Marina Moucho, Pedro Viana Pinto, Rita Figueiredo, José Morales Roselló, Gabriela Loscalzo, Alicia Martinez-Varea, Vincente Diago, Jesús S Jimenez Lopez, Alicia Yeliz Aykanat, Stefano Cosma, Andrea Carosso, Chiara Benedetto, Amanda Bermejo, Otto Henrique May Feuerschuetze, Ozlem Uyaniklar, Sakine Rahimli Ocakouglu, Zeliha Atak, Reyhan Gündüz, Esra Tustas Haberal, Bernd Froessler, Anupam Parange, Peter Palm, Igor Samardjiski, Chiara Taccaliti, Erhan Okuyan, George Daskalakis, Renato Augusto Moreira de Sa, Alejandro Pittaro, Maria Luisa Gonzalez-Duran, Ana Concheiro Guisan, Şerife Özlem Genç, Blanka Zlatohlávková, Anna Luengo Piqueras, Dolores Esteban Oliva, Aylin Pelin Cil, Olus Api, Panos Antsaklis, Liana Ples, Ioannis Kyvernitakis, Holger Maul, Marcel Malan, Albert Lila, Roberta Granese, Alfredo Ercoli, Giuseppe Zoccali, Andrea Villasco, Nicoletta Biglia, Cuihodaru Madalina, Elena Costa, Caroline Daelemans, Axelle Pintiaux, Elif Gül Yapar Eyi, Elisa Cueto, Eran Hadar, Sarah Dollinger, Noa A. Brzezinski Sinai, Erasmo Huertas, Pedro Arango, Amadeo Sanchez, Javier Alfonso Schwartzman, Liviu Cojocar, Sifa Turan, Ozhan Turan, Maria Carmela Di Dedda, Rebeca Garrote Molpeceres, Snezana Zdjelar, Tanja Premru-Srsen, Lilijana Kornhauser Cerar, Mirjam Druškovič, Valentina De Robertis, Vedran Stefanovic, Irmeli Nupponen, Kaisa Nelskylä, Zulfiya Khodjaeva, Ksenia A. Gorina, Gennady T. Sukhikh, Giuseppe Maria Maruotti, Silvia Visentin, Erich Cosmi, Jacopo Ferrari, Alessandra Gatti, Daniela Luvero, Roberto Angioli, Ludovica Puri, Marco Palumbo, Giusella D'Urso, Francesco Colaleo, Agnese Maria Chiara Rapisarda, Ilma Floriana Carbone, Antonio Mollo,

Giovanni Nazzaro, Mariavittoria Locci, Maurizio Guida, Attilio Di Spiezio Sardo, Pierluigi Benedetti Panici, Vincenzo Berghella, Maria Elena Flacco, Lamberto Manzoli, Giuseppe Bifulco, Giovanni Scambia, Fulvio Zullo and Francesco D'Antonio

# Risk factors associated with adverse fetal outcomes in pregnancies affected by Coronavirus disease 2019 (COVID-19): a secondary analysis of the WAPM study on COVID-19

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## Abstract

**Objectives:** To evaluate the strength of association between maternal and pregnancy characteristics and the risk of adverse perinatal outcomes in pregnancies with laboratory confirmed COVID-19.

**\*Corresponding author: Cihat Sen**, Perinatal Medicine Center, Memorial BAH Hospital and mPerinatal Medicine Foundation, Istanbul 34367, Turkey, E-mail: [cсен@perinatal.org.tr](mailto:cсен@perinatal.org.tr)  
**Daniele Di Mascio, Flaminia Vena, Antonella Giancotti, Roberto Brunelli, Ludovico Muzii and Pierluigi Benedetti Panici**, Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Rome, Italy  
**Gabriele Saccone, Rosanna Esposito, Antonio Coviello, Marco Cerbone, Giuseppe Maria Maruotti, Giovanni Nazzaro, Mariavittoria Locci, Maurizio Guida, Attilio Di Spiezio Sardo, Giuseppe Bifulco and Fulvio Zullo**, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy  
**Alberto Galindo, Ignacio Herraiz and Cecilia Villalain**, Fetal Medicine Unit, Maternal and Child Health and Development Network, University Hospital 12 de Octubre, Complutense University of Madrid Department of Obstetrics and Gynaecology, Madrid, Spain  
**Amos Grünebaum and Frank Chervenak**, Department of Obstetrics and Gynaecology, Lenox Hill Hospital, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA  
**Jun Yoshimatsu**, Department of Perinatology and Gynaecology, National Cerebral and Cardiovascular Center, Osaka, Japan  
**Milan Stanojevic and Asim Kurjak**, Department of Obstetrics and Gynaecology, Medical School University of Zagreb, Sveti Duh University Hospital, Zagreb, Croatia  
**María José Rodríguez Suárez**, Hospital Universitario Central de Asturias, Asturias, Spain  
**Zita Maria Gambacorti-Passerini**, Department of Obstetrics and Gynaecology, Ciudad Real University General Hospital, Ciudad Real, Spain  
**María de los Angeles Anaya Baz and Esther Vanessa Aguilar Galán**, Department of Obstetrics and Gynaecology, Ciudad Real University General Hospital, Ciudad Real, Spain; University of Castilla-La Mancha, Ciudad Real, Spain

**Methods:** Secondary analysis of a multinational, cohort study on all consecutive pregnant women with laboratory-confirmed COVID-19 from February 1, 2020 to April 30, 2020 from 73 centers from 22 different countries. A confirmed case of COVID-19 was defined as a positive result on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens. The primary outcome was a composite adverse fetal outcome, defined as the presence of either

**Yolanda Cuñarro López, Juan Antonio De León Luis and Ignacio Cueto Hernández**, Fetal Medicine Unit, Maternal and Child Health and Development Network, Gregorio Marañón Hospital, Complutense University of Madrid, Department of Obstetrics and Gynaecology, Madrid, Spain  
**Roberta Venturella**, Department of Obstetrics and Gynaecology, School of Medicine, Magna Graecia University of Catanzaro, Catanzaro, Italy  
**Giuseppe Rizzo**, University of Roma Tor Vergata, Division of Maternal Fetal Medicine, Ospedale Cristo Re Roma, Rome, Italy; Department of Obstetrics and Gynaecology The First I.M. Sechenov Moscow State Medical University, Moscow, Russia  
**Ilenia Mappa**, University of Roma Tor Vergata, Division of Maternal Fetal Medicine, Ospedale Cristo Re Roma, Rome, Italy  
**Giovanni Gerosolima**, Department of Obstetrics and Gynaecology, Ospedale AOSG Moscati, Avellino, Italy  
**Lars Hellmeyer, Josefine Königbauer and Giada Ameli**, Department of Gynaecology and Obstetrics, Vivantes Klinikum im Friedrichshain, Berlin, Germany  
**Tiziana Frusca, Nicola Volpe, Giovanni Battista Luca Schera and Stefania Fieni**, Department of Obstetrics and Gynaecology, University of Parma, Parma, Italy  
**Eutalia Esposito**, Department of Obstetrics and Gynaecology, Ospedale di San Leonardo, Castellammare di Stabia, Italy  
**Giuliana Simonazzi, Gaetana Di Donna, Aly Youssef and Anna Nunzia Della Gatta**, Department of Obstetrics and Gynaecology, University of Bologna, Sant'Orsola- Malpighi University Hospital, Bologna, Italy  
**Mariano Catello Di Donna, Vito Chiantera, Natalina Buono and Giulio Sozzi**, Department of Gynaecologic Oncology, University of Palermo, Palermo, Sicilia, Italy  
**Pantaleo Greco, Danila Morano, Beatrice Bianchi and Maria Giulia Lombana Marino**, Department of Medical Sciences, Section of Obstetrics and Gynaecology, Azienda Ospedaliera-Universitaria Sant' Anna, University of Ferrara, Ferrara, Italy

abortion (pregnancy loss before 22 weeks of gestations), stillbirth (intrauterine fetal death after 22 weeks of gestation), neonatal death (death of a live-born infant within the first 28 days of life), and perinatal death (either stillbirth or neonatal death). Logistic regression analysis was performed to evaluate parameters independently associated with the primary outcome. Logistic regression was reported as odds ratio (OR) with 95% confidence interval (CI).

**Results:** Mean gestational age at diagnosis was 30.6±9.5 weeks, with 8.0% of women being diagnosed in the first, 22.2% in the second and 69.8% in the third trimester of pregnancy. There were six miscarriage (2.3%), six intrauterine device (IUD) (2.3) and 5 (2.0%) neonatal deaths, with an overall rate of perinatal death of 4.2% (11/265), thus resulting into 17 cases experiencing and 226 not experiencing composite adverse fetal outcome. Neither

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**Federica Laraud, Arianna Ramone, Angelo Cagnacci, Fabio Barra, Claudio Gustavino and Simone Ferrero**, Academic Unit of Obstetrics and Gynaecology, IRCCS Ospedale Policlinico, San Martino, Genova, Italy  
**Fabio Ghezzi, Antonella Cromi and Antonio Simone Laganà**, Department of Obstetrics and Gynaecology, “Filippo Del Ponte” Hospita University of Insubria, Varese, Italy  
**Valentina Laurita Longo**, Department of Obstetrics and Gynaecology, Fondazione Policlinico Universitario A Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome, Italy; Istituto di Clinica Ostetrica e Ginecologica, Università Cattolica del Sacro Cuore, Rome, Italy; and Queen Margaret University, Institute for Global Health and Development, Edinburgh, UK  
**Francesca Stollagli and Ludovica Puri**, Istituto di Clinica Ostetrica e Ginecologica, Università Cattolica del Sacro Cuore, Rome, Italy  
**Angelo Sirico and Giovanni Scambia**, Department of Obstetrics and Gynaecology, Fondazione Policlinico Universitario A Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome, Italy  
**Antonio Lanzone**, Department of Obstetrics and Gynaecology, Fondazione Policlinico Universitario A Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome, Italy; Istituto di Clinica Ostetrica e Ginecologica, Università Cattolica del Sacro Cuore, Rome, Italy  
**Lorenza Driul, Fabiana Cecchini D and Serena Xodo**, Clinic of Obstetrics and Gynaecology, University of Udine, Udine, Italy  
**Brian Rodriguez, Felipe Mercado-Olivares, Deena Elkafrawi and Giovanni Sisti**, Department of Obstetrics and Gynaecology, New York Health and Hospitals/Lincoln Bronx, The Bronx, NY, USA  
**Maddalena Morlando, Antonio Schiattarella, Nicola Colacurci and Pasquale De Franciscis**, Department of Woman, Child and General and Specialized Surgery, University of Campania Luigi Vanvitelli, Naples, Italy  
**Ilaria Cataneo, Marinella Lenzi and Fabrizio Sandri**, Unit of Obstetrics and Gynaecology, Ospedale Maggiore, Bologna, Italy  
**Riccardo Buscemi, Giorgia Gattei, Francesca della Sala and Maria Cristina Rovellotti**, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy  
**Eleonora Valori**, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy; Hospital Castelli, Verbania, Italy  
**Elisa Done, Gilles Faron and Leonardo Gucciardo**, UZ Brussel, Universitair Ziekenhuis, Brussel, Belgium  
**Valentina Esposito**, University of Milan, Milan, Italy  
**Luigi Nappi, Felice Sorrentino and Lorenzo Vasciaveo**, Department of Obstetrics and Gynaecology, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy  
**Marco Liberati, Danilo Buca, Martina Leombroni, Francesca Di Sebastiano, Luciano Di Tizio and Francesco D’Antonio**, Centre for High Risk Pregnancy and Fetal Care, University of Chieti, Department of Obstetrics and Gynaecology, Chieti, Italy

**Diego Gazzolo**, Neonatal Intensive Care Unit, University of Chieti, Chieti Italy  
**Massimo Franchi, Quintino Cesare Ianniciello and Simone Garzon**, Department of Obstetrics and Gynaecology, AOUI Verona, University of Verona, Verona, Italy  
**Giuliano Petriglia and Leonardo Borrello**, Maternal and Child Health Department, Santa Maria Hospital, Terni, Italy  
**Albaro José Nieto-Calvache and Juan Manuel Burgos-Luna**, Fundación Valle del Lili, Tertiary Obstetric Unit, Cali, Colombia; Postgraduate Department, Universidad Icesi, Cali, Colombia  
**Caroline Kadji, Andrew Carlin and Elisa Bevilacqua**, Department of Obstetrics and Gynaecology, University Hospital Brugmann, Université Libre de Bruxelles, Brussels, Belgium  
**Marina Moucho, Pedro Viana Pinto and Rita Figueiredo**, Department of Obstetrics and Gynaecology, Centro Hospitalar e Universitário São João, Porto, Portugal  
**José Morales Roselló, Gabriela Loscalzo, Alicia Martínez-Varea and Vicente Diago**, Servicio de Obstetricia y Ginecología, Hospital Universitario y Politécnico La Fe, Valencia, Spain  
**Jesús S Jimenez Lopez**, Hospital Regional Universitario de Málaga, Málaga, Spain  
**Alicia Yeliz Aykanat**, Department of Obstetrics and Gynaecology, Istanbul University-Cerrahpasa Medical School, Istanbul, Turkey  
**Stefano Cosma, Andrea Carosso and Chiara Benedetto**, Department of Obstetrics and Gynaecology, Sant’Anna Hospital, University of Turin, Turin, Italy  
**Amanda Bermejo**, Hospital Universitario de Móstoles, Mostoles, Spain  
**Otto Henrique May Feuerschuette**, Departamento de Ginecologia e Obstetrícia, Hospital Universitário Polydoro Ernani, Santiago, Brazil  
**Ozlem Uyaniklar, Sakine Rahimli Ocakouglu and Zeliha Atak**, Bursa City Hospital, Bursa, Turkey  
**Reyhan Gündüz**, Department of Obstetrics and Gynaecology, University of Dicle, Diyarbakır, Turkey  
**Esra Tustas Haberal**, Hisar Intercontinental Hospital, Istanbul, Turkey  
**Bernd Froessler, Anupam Parange and Peter Palm**, Department of Anaesthesia, Lyell McEwin Hospital, Adelaide, Australia  
**Igor Samardjiski**, University Clinic of Obstetrics and Gynaecology, Skopje, North Macedonia  
**Chiara Taccaliti**, Ospedale Generale Regionale “F. Miulli”, Acquaviva delle Fonti, Italy  
**Erhan Okuyan**, Batman Maternity and Child Health Hospital, Batman, Turkey  
**George Daskalakis and Panos Antsaklis**, Alexandra Hospital – National and Kapodistrian, University of Athens, Athens, Greece

stillbirths nor neonatal deaths had congenital anomalies found at antenatal or postnatal evaluation. Furthermore, none of the cases experiencing IUD had signs of impending demise at arterial or venous Doppler. Neonatal deaths were all considered as prematurity-related adverse events. Of the 250 live-born neonates, one (0.4%) was found positive at RT-PCR pharyngeal swabs performed after delivery. The mother was tested positive during the third trimester of pregnancy. The newborn was asymptomatic and had negative RT-PCR test after 14 days of life. At logistic regression analysis, gestational age at diagnosis (OR: 0.85, 95% CI 0.8–0.9 per week increase;  $p < 0.001$ ), birthweight (OR: 1.17, 95% CI 1.09–1.12.7 per 100 g decrease;  $p = 0.012$ ) and maternal ventilatory support, including either need for oxygen or CPAP (OR: 4.12, 95% CI 2.3–7.9;  $p = 0.001$ ) were independently associated with composite adverse fetal outcome.

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

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

**Maria Luisa Gonzalez-Duran and Ana Concheiro Guisan**, Alvaro Cunqueiro University Hospital of Vigo, Vigo, Spain

**Şerife Özlem Genç**, Karaman Public Hospital, Karaman, Turkey

**Blanka Zlatohlávková**, Department of Obstetrics and Gynaecology, Division of Neonatology, General Hospital in Prague and First Faculty of Medicine, Charles University, Prague, Czech Republic

**Anna Luengo Piqueras and Dolores Esteban Oliva**, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain

**Aylin Pelin Cil and Olus Api**, American Hospital, Istanbul, Turkey

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

**Ioannis Kyvernitakis, Holger Maul and Marcel Malan**, Asklepios Hospital Barmbek, Hamburg, Germany

**Albert Lila**, Regional Hospital Gjakova, Kosovo, Republic of Kosovo

**Roberta Granese, Alfredo Ercoli and Giuseppe Zoccali**, Department of Obstetrics and Gynaecology, University of Messina, Messina, Italy

**Andrea Villasco and Nicoletta Biglia**, Academic Division of Obstetrics and Gynaecology, Maurizio Umberto I Hospital, University of Turin, Turin, Italy

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

**Elena Costa, Caroline Daelemans and Axelle Pintiaux**, Department of Obstetrics and Gynaecology, Hospital Erasme, Cliniques Universitaires de Bruxelles, Brussels, Belgium

**Elif Gül Yapar Eyi**, Ankara Bilkent City Hospital, Ankara, Turkey

**Elisa Cueto**, Hospital Virgen De La Luz, Cuenca, Spain

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

**Erasmus Huertas, Pedro Arango and Amadeo Sanchez**, Instituto Nacional Materno Perinatal, Lima, Peru

**Javier Alfonso Schwartzman**, Centro de Educación Médica e Investigaciones Clínicas “Norberto Quirno”, Buenos Aires, Argentina

**Conclusions:** Early gestational age at infection, maternal ventilatory supports and low birthweight are the main determinants of adverse perinatal outcomes in fetuses with maternal COVID-19 infection. Conversely, the risk of vertical transmission seems negligible.

**Keywords:** Coronavirus; perinatal mortality; perinatal morbidity.

## Introduction

Towards the end of 2019, a novel Coronavirus mutation - labelled as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) - was identified as the cause of a respiratory illness called COVID-19, that suddenly became epidemic in China, and then dramatically spread in many other countries worldwide as a global pandemic [1–9].

**Liviu Cojocar, Sifa Turan and Ozhan Turan**, Department of Obstetrics, Gynaecology and Reproductive Science, University of Maryland Medical Center, Baltimore, MD, USA

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

**Rebeca Garrote Molpeceres**, University Clinic Hospital Of Valladolid, Valladolid, Spain

**Snezana Zdjelar**, Kbc Dr Dragisa Misovic Dedinje Belgrade, Beograd, Serbia

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

**Valentina De Robertis**, Fetal Medicine Unit, Di Venere Hospital, Bari, Italy

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

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

**Silvia Visentin, Erich Cosmi and Jacopo Ferrari**, Department of Woman' and Child's Health, University of Padova, Padova, Italy

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

**Marco Palumbo, Giusella D'Urso, Francesco Colaleo and Agnese Maria Chiara Rapisarda**, Department of General Surgery and Medical Surgical Specialties, University of Catania, Catania, Italy

**Ilma Floriana Carbone**, Ospedale Maggiore Policlinico Milano, Milan, Italy

**Antonio Mollo**, University of Salerno, Salerno, Italy

**Vincenzo Berghella**, Maternal Fetal Medicine Division, Sidney Kimmel Medical College at Thomas Jefferson University, Obstetrics and Gynaecology Department, Philadelphia, PA, USA

**Maria Elena Flacco and Lamberto Manzoli**, Department of Medical Sciences, University of Ferrara, Ferrara, Italy

Despite rigorous mitigation measures adopted by governments to reduce both the virus spread and its detrimental effects on healthcare systems and therefore on the whole worldwide economy [10], COVID-19 has currently affected about five millions of people with more than 300,000 deaths [11].

Although evidence is accumulating rapidly, there are still several outstanding issues that need to be settled soon regarding the effect of COVID-19 on perinatal outcomes to guide the antenatal counselling and management of women with COVID-19 during pregnancy.

In a large multinational cohort study, we have recently shown that COVID-19 in pregnant women is associated with low rate of maternal mortality, but 11.1% rate of admission to intensive care unit (ICU) [12].

However, an accurate risk stratification of women with COVID-19 is needed to ascertain the association between different maternal characteristics or clinical findings and adverse perinatal outcomes, in order to more appropriately tailor their management.

The primary aim of this study was to report perinatal outcome in pregnancies complicated by COVID-19 infection; the secondary aim was to elucidate the strength of association between maternal and pregnancy characteristics and the risk of adverse perinatal outcome in these pregnancies.

## Materials and methods

### Study design and participants

This is a secondary analysis of the World Association of Perinatal Medicine (WAPM) study [12]. The WAPM study was a multinational, cohort study on all consecutive pregnant women with laboratory-confirmed COVID-19 from February 1, 2020 to April 30, 2020 from 73 centers from 22 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)

COVID-19 was diagnosed on the basis of The World Health Organization (WHO) interim guidance [13]. A confirmed case of COVID-19 was defined as a positive result on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens [14, 15].

The study was approved by the IRB of the University of Naples Federico II (April 2020, approval number: 145/2020).

A composite adverse fetal outcome was defined as the presence of either:

- Abortion, defined as pregnancy loss before 22 weeks of gestations,
- Stillbirth, defined as intrauterine fetal death after 22 weeks of gestation,
- Neonatal death, defined as death of a live-born infant within the first 28 days of life,
- Perinatal death, defined as either stillbirth or neonatal death.

### Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA). Continuous variables were reported as means  $\pm$  standard deviation (SD), while categorical as numbers (percentage). Univariate comparisons of dichotomous data were performed with the use of the  $\chi^2$ -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. We also planned to test the strength of association between different maternal and pregnancy characteristics, and clinical, radiological, and laboratory findings, with a composite adverse fetal outcome. Logistic regression analysis was also performed to evaluate parameters independently associated with a composite adverse fetal outcome. Logistic regression was reported as odds ratio (OR) with 95% confidence interval (CI). For the purpose of the analysis, this analysis was performed including only women with completed pregnancy. A p-value  $<0.05$  was considered statistically significant.

## Results

The WAPM study involved 388 singleton pregnancies positive to COVID-19 at RT-PCR nasal and pharyngeal swab, in 73 centers from 22 different countries.

Mean gestational age at diagnosis was  $30.6 \pm 9.5$  weeks, with 8.0% of women being diagnosed in the first, 22.2% in the second and 69.8% in the third trimester of pregnancy. Included women were asymptomatic in 24.2% of cases. The most common symptom at the time of triage was cough (52.1%), followed by fever (44.1%), while shortness of breath was complained by 60 women (15.5%). 11.1% of women were admitted to ICU, and 6.4% requiring intubation. There were three cases of maternal deaths, accounting for a maternal mortality rate of 0.8% [12].

Evaluation of the potential risk factors associated with the occurrence of the composite adverse fetal outcome was performed only in women with completed pregnancy.

Table 1 shows perinatal outcomes from the WAPM study. There were six miscarriage (2.3%), six intrauterine device (IUD) (2.3) and 5 (2.0%) neonatal deaths, with an overall rate of perinatal death of 4.2% (11/265), thus resulting into 17 cases experiencing and 248 not experiencing composite adverse fetal outcome. Neither stillbirths nor neonatal deaths had congenital anomalies found at antenatal or postnatal evaluation. Furthermore, none of the cases experiencing IUD had signs of impending demise at arterial or venous Doppler (reverse end diastolic flow in the umbilical artery, increased ductus venosus pulsatility index, absent or reverse a wave in the ductus venosus). Neonatal deaths were all considered as prematurity-related

adverse events. Of the 250 live-born neonates, one (0.4%) was found positive at RT-PCR pharyngeal swabs performed after delivery. The mother was tested positive during the third trimester of pregnancy. The newborn was asymptomatic and had negative RT-PCR test after 14 days of life. Unfortunately, amniotic fluid was not tested, and specimens from placenta were not obtained, thus questioning whether the infection occurred *in utero* (antenatal vertical transmission) or after immediately prior or after birth (perinatal vertical transmission).

When exploring maternal and pregnancy characteristics, gestational age at diagnosis was lower ( $23.2 \pm 10.9$  vs.  $35.0 \pm 4.6$ ,  $p < 0.001$ ) in fetuses with composite adverse outcome, while there was no difference in maternal age at the infection between the two study groups. Similarly, the incidence of composite adverse fetal outcome was significantly higher when the infection occurred in the first trimester (35.3 vs. 2%,  $p < 0.001$ ). The incidence of composite adverse fetal outcome was significantly higher in fetuses with lower birthweight ( $2007 \pm 1014$  g vs.  $2939 \pm 755$ ,  $p < 0.001$ ), while it was similar in nulliparous women, women smoking during pregnancy or with chronic, pre-existing conditions, women undergone flu vaccination, and those with a positive CT scan.

When focusing on clinical, radiological and laboratory findings, maternal need for oxygen (41.2 vs. 17.3%,  $p = 0.02$ ) and CPAP (29.4 vs. 8.5%,  $p = 0.02$ ) were significantly associated with composite adverse fetal outcome

Finally, no difference was found when evaluating the effect different pharmacologic treatments (LMWH, azithromycin, antiviral drugs or hydroxychloroquine) on composite adverse fetal outcome

At logistic regression analysis, gestational age at diagnosis (OR: 0.85, 95% CI 0.8–0.9 per week increase;  $p < 0.001$ ), birthweight (OR: 1.17, 95% CI 1.09–1.12.7 per 100 g decrease;  $p = 0.012$ ) and maternal ventilatory support, including either need for oxygen or CPAP (OR: 4.12, 95% CI 2.3–7.9;  $p = 0.001$ ) were independently associated with composite adverse fetal outcome.

## Discussion

### Summary of the main findings

The findings from this study showed that, in pregnancies complicated by COVID-19 infection, the rate of perinatal death was about 4%, mainly related to prematurity. Early

**Table 1:** Perinatal outcomes from the WAPM study [12].

Women with completed pregnancies (n=266)		% (95% CI)
Elective termination of pregnancy	3	1.1 (0.4–3.3)
Stillbirth	6	2.3 (1.0–4.8)
Perinatal death	11	4.1 (2.3–7.3)
IUGR	10	3.8 (2.1–6.8)
Preterm birth	70	26.3 (21.4–31.9)
Live-born infants	251	94.4 (90.9–96.6)
Women with live-born infants (n=251)		% (95% CI)
Possible vertical transmission	1	0.4 (0.07–2.2)
Neonatal death <sup>a</sup>	5	2.0 (0.9–4.6)
Admission to NICU	69	27.5 (22.3–33.3)
Breastfeeding	101	40.2 (34.4–46.4)
Skin to skin	69	27.5 (22.3–33.3)
Low birth weight	52	20.7 (16.2–26.2)
Cesarean delivery	136	54.2 (48.0–60.2)
Spontaneous first-trimester abortion <sup>b</sup>	6/31	19.4 (9.2–36.3)
Gestational age at delivery, years, mean $\pm$ SD		37.2 $\pm$ 3.9
Birth weight, grams, mean $\pm$ SD		2919 $\pm$ 772

Data are presented as number (percentage) or as mean  $\pm$  standard deviation (SD). NICU, neonatal intensive care unit; LBW, low birth weight; IUGR, intrauterine growth restriction.

<sup>a</sup>Including only live-born infants. <sup>b</sup>Including only women with first trimester infection.

gestational age at diagnosis, gestational age at diagnosis, birthweight and maternal ventilatory support were the only factors independently associated with adverse fetal outcome. Finally, the risk of vertical transmission was negligible.

### Strengths and limitations

To our knowledge, this may be the largest cohort of COVID-19 during pregnancy published so far. Strengths and limitations of this secondary analysis are those inherent in the WAPM study. The enrollment of only of women with laboratory-confirmed COVID-19 and the inclusion of both University Hospitals and Community Hospitals from different countries represent the major strengths of this study. The major limitation of the study is the incidence of the composite adverse perinatal outcome in the overall population is low, thus making our sample size potentially underpowered to draw any convincing evidence. Another limitation is the inclusion of only high-income and middle-income countries, and therefore we acknowledge that in low-income countries perinatal outcomes might be even worse [3].

## Implications for clinical practice and research

COVID-19 has brought the scientific community into unprecedented times and currently represents the major global public health issue. Despite the growing number of reports published so far [16–18], evidence is still limited particularly when focusing on vulnerable conditions, such as pregnancy.

We have recently shown that COVID-19 in pregnant women is associated with low rate of maternal mortality, but 11.1% rate of admission to ICU. Furthermore, earlier gestational age at presentation, shortness of breath as presenting symptom, and increased lactate dehydrogenase (LDH) levels were independently associated with composite adverse maternal outcome including either admission to intensive care unit, use of mechanical ventilation or death [12].

In this secondary analysis, we planned to ascertain whether different maternal and pregnancy characteristics; clinical, laboratory or radiological findings and pharmacological treatments could be associated with serious adverse perinatal outcomes, including stillbirths and neonatal deaths, and we found that earlier gestational age at diagnosis, birthweight and maternal ventilatory support were independently associated with a composite adverse perinatal outcome.

Gestational age at diagnosis is a peculiar issue when assessing pregnancies affected by viral infections and the occurrence of the infection earlier in pregnancy is usually associated with worse fetal outcomes. In a large meta-analysis of cohort and case-control studies, maternal seasonal influenza or influenza-like illness in the first trimester was associated with a significantly higher risk of congenital abnormalities, such as cleft lip, neural tube defects, hydrocephaly, and congenital heart defects [19]. Moreover, recent data on women with a primary Cytomegalovirus infection and an infected child aged at least 1 year at the time of the analysis show that the infection can be severe only when the virus hits the fetus in the embryonic or early fetal period [20]. Alongside the high burden of fetal morbidity, parvovirus B19 infection in the first trimester of pregnancy was associated with an increased risk of fetal loss [21] and fetal death is generally observed when the infection occurs before the completed 20 weeks of gestation [22].

These data are concordant with our results, as COVID-19 infection in the first trimester was significantly associated with the occurrence of a composite adverse fetal outcome, while there was no difference when the infection occurred during the second and the third trimester of pregnancy.

Therefore, longitudinal evaluation of pregnancies affected with COVID-19 is recommended to rule out any potential factor that may significantly impact short and long-term prognosis. In this scenario, the use of neurosonography and fetal magnetic resonance imaging (MRI), that has significantly spread in the past few years in several fields of maternal fetal medicine [23, 24], might be judiciously considered as useful imaging techniques for a complete fetal assessment.

Perinatal death is certainly one of the main concern of maternal fetal specialists. So far, the rate of both stillbirths and neonatal deaths has been reported to be slightly increased, although the majority of neonatal deaths are considered to be related to prematurity or to critically ill mothers [3, 25, 26].

COVID-19 may predispose the general population to a thrombotic condition, both in the venous and arterial circulations, due to inflammation, platelet activation, endothelial dysfunction, and stasis [27, 28]. This COVID-19 related hypercoagulability state might intuitively assume an important role in pregnancy due to its inherent prothrombotic state, and might represent a possible cause of the small increase of the rate of stillbirths compared with the baseline population [29–32].

However, we acknowledge that the sample size potentially underpowered for this outcome and the lack of effect of low molecular weight heparin cast some doubt on this hypothesis and do not allow to obtain robust evidence on the risk of stillbirth in pregnancies affected by COVID-19.

## Conclusions

Early gestational age at infection, maternal ventilatory supports and low birthweight are the main determinants of adverse perinatal outcomes in fetuses with maternal COVID-19 infection. Conversely, the risk of vertical transmission seems negligible.

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**Informed consent:** Informed consent was obtained from all individuals included in this study.

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