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On the cutting edge: key findings on maternal and neonatal outcomes in women with COVID-19 in a study by the World Association of Perinatal Medicine

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Abstract

The World Association of Perinatal Medicine (WAPM) study on the COrona VIrus Disease 2019 (COVID-19) was an international, retrospective cohort study that included pregnant women tested positive with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection between February and April 2020. The study involved 73 centers from 22 countries. The WAPM study included 388 singletons, viable pregnancies, positive to SARS-CoV-2 at real-time reverse-transcriptase-polymerase-chain-reaction nasal and pharyngeal swab. The majority of the included women were symptomatic. The occurrence of maternal adverse events was significantly higher in symptomatic, compared with asymptomatic pregnant women. Women carrying high-risk pregnancies (either preexisting chronic medical conditions in pregnancy or obstetrical disorders occurring in pregnancy) were at a higher risk of hospital admission, presence of severe respiratory symptoms, admission to the intensive care unit, and invasive mechanical ventilation. As per maternal outcomes, the occurrence of fetal and neonatal adverse events was significantly higher in symptomatic, compared with asymptomatic pregnant women. The incidence of a composite adverse fetal outcome was significantly higher when the infection occurred in the first trimester, and in fetuses with lower birthweight.

Keywords: COVID-19; SARS-CoV-2; pregnancy; respiratory morbidity; maternal mortality; adverse outcomes
MeSH terms:
PREGNANCY COMPLICATIONS, INFECTIOUS – DIAGNOSIS
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На переднем крае: основные выводы исследования Всемирной ассоциации перинатальной медицины о материнских и неонатальных показателях у беременных с COVID-19

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Аннотация

В международном ретроспективном когортном исследовании по новой коронавирусной инфекции (COVID-19), проведенном в период с февраля по апрель 2020 года Всемирной ассоциацией перинатальной медицины (WAPM – The World Association of Perinatal Medicine), приняли участие беременные женщины с положительным результатом теста на коронавирус тяжелого острого респираторного синдрома – 2 (SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2). В исследовании участвовали 73 центра из 22 стран мира. Исследование WAPM включало 388 женщин с одноплодными прогрессирующими беременностями, положительных на SARS-CoV-2 по данным полимеразной цепной реакции с обратной транскрипцией в реальном времени мазков из носа и глотки. У большинства включенных женщин были симптомы заболевания. Частота неблагоприятных событий со стороны матери была значительно выше у беременных женщин с симптомами заболевания по сравнению с бессимптомными беременными. Женщины с беременностью высокого риска (с ранее выявленными хроническими заболеваниями, акушерскими осложнениями) чаще госпитализировались в стационар, имели тяжелые респираторные симптомы, госпитализировались в отделение интенсивной терапии и нуждались в механической инвазивной вентиляции легких. Аналогично материнским показателям, частота осложнений со стороны плода и новорожденного была значительно выше у женщин с симптомами заболевания по сравнению с бессимптомными случаями. Совокупный неблагоприятный исход для плода был значительно выше при инфицировании в первом триместре беременности, а также у плодов с более низкой массой тела при рождении.

Ключевые слова: COVID-19; SARS-CoV-2; беременность; респираторные заболевания; материнская смертность; неблагоприятные исходы
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НОВОРОЖДЕННЫЙ, БОЛЕЗНИ – ДИАГНОСТИКА
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List of abbreviation

aOR – adjusted odds ratio
CI – confidence interval
COVID-19 – COrona VIrus Disease 2019
ICU – intensive care unit
OR – odds ratio
RT-PCR – real-time reverse-transcriptase-polymerase-chain-reaction
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
WAPM – World Association of Perinatal Medicine

HIGHLIGHTS	КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ
The occurrence of maternal adverse events was significantly higher in symptomatic, compared with asymptomatic pregnant women.	Частота неблагоприятных исходов со стороны матери была значительно выше у беременных женщин с симптомами заболевания по сравнению с бессимптомным течением.
As per maternal outcomes, the occurrence of fetal and neonatal adverse events was significantly higher in symptomatic, compared with asymptomatic pregnant women.	Так же как и материнские показатели, частота осложнений со стороны плода и новорожденного была значительно выше у женщин с симптомами заболевания по сравнению с бессимптомными случаями.
The incidence of a composite adverse fetal outcome was significantly higher when the infection occurred in the first trimester, and in fetuses with lower birthweight.	Совокупный неблагоприятный исход для плода был значительно выше при инфицировании в первом триместре беременности, а также у плодов с более низкой массой тела при рождении.
Women carrying high-risk pregnancies (either preexisting chronic medical conditions in pregnancy or obstetrical disorders occurring in pregnancy) were at higher risk of hospital admission.	Женщины с беременностями высокого риска (с ранее выявленными хроническими заболеваниями, акушерскими осложнениями) чаще госпитализировались в стационар.
Women carrying high-risk pregnancies also experienced the presence of severe respiratory symptoms, admission to the intensive care unit, and invasive mechanical ventilation.	У женщин с беременностью высокого риска чаще наблюдались тяжелые респираторные симптомы, госпитализация в отделение интенсивной терапии и необходимость инвазивной механической вентиляции.

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

Since the beginning of pandemic, it has been claimed that pregnancy is potentially associated with a higher burden of maternal mortality and morbidity compared to the general population due to the peculiar cardiovascular and respiratory maternal adaptations occurring during pregnancy [2, 3].

Coronaviruses are enveloped, non-segmented positive-sense RNA belonging to the Nidovirales order [2]. Even though responsible for generally mild infections, Coronavirus have caused two important epidemics in the last decade: the severe acute respiratory syndrome and the Middle East respiratory syndrome, also known as SARS and MERS, respectively.

Pregnant women are at an increased risk of severe illness from respiratory infections due to physiological cardiopulmonary adaptive changes occurring during pregnancy that can increase

[1] https://covid19.who.int/ Accessed July 29th, 2021.

the risk of hypoxemia and worsen the clinical course.

Several cohort studies and systematic reviews evaluating the course of SARS-CoV-2 infection in terms of both maternal and perinatal outcomes have already been published [4–10], and the World Association of Perinatal Medicine (WAPM) working group on COrona VIrus Disease 2019 (COVID-19) in pregnancy has been among the first collaborative groups providing data on COVID-19 and pregnancy from several centers in Asia, Europe, Oceania and North and South America [3, 4, 11].

In this paper, we critically review the findings from this large collaborative study.

THE ORGANIZATION OF THE STUDY

The WAPM study on COVID-19 is an international, retrospective cohort study that included pregnant women tested positive with SARS-CoV-2 infection between February and April 2020. The study involved 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) (fig.1) [3]. The authors only included infected women diagnosed antepartum, while they excluded from the study women with a positive test before conception or during post-partum. SARS-CoV-2 infection was diagnosed with a positive result on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens.

CHARACTERISTICS OF THE STUDY POPULATION

The WAPM study included 388 singleton, viable pregnancies, positive to SARS-CoV-2 at RT-PCR nasal and pharyngeal swab, with a mean gestational age at diagnosis of 30.6 ± 9.5 weeks. The women included were mainly in the third trimester of pregnancy (69.8%), compared with second (22.2%) and first (8.0%) trimester.

Most of the included women were symptomatic, and cough and fever, followed by shortness of breath were the most common symptoms at the time of triage. The rate of asymptomatic women was 24.2%.

As the study was conducted at the beginning of pandemic, there was a huge heterogeneity in the choice for treatment: the most used pharmacologic therapy was hydroxychloroquine that was used in 23.2% of cases, and then antiviral drugs used in 18.6% of women, mostly with the combination of Lopinavir/Ritonavir.

MATERNAL OUTCOMES

Regarding maternal outcomes, the primary outcome of the study was a composite maternal adverse

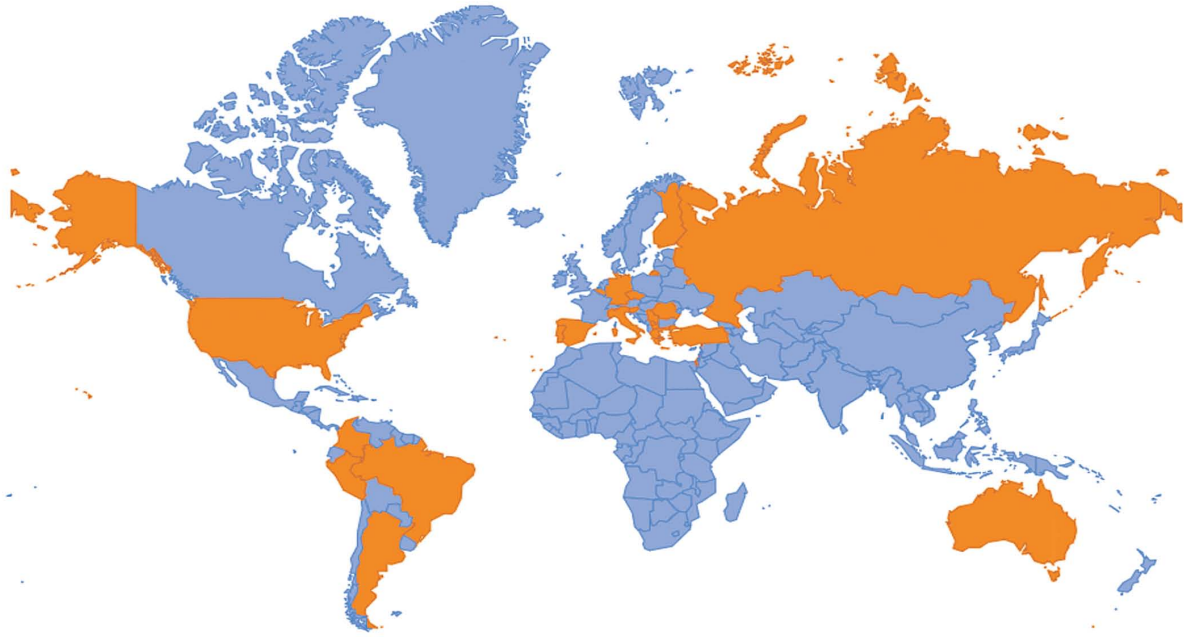

FIG. 1. Map of countries participating in World Association of Perinatal Medicine (WAPM) study.
РИС. 1. Карта стран – участниц исследования Всемирной ассоциации перинатальной медицины (WAPM).

Note: the participating countries are marked in orange.
Примечание: оранжевым цветом обозначены страны-участницы.

outcome defined as the presence of maternal mortality and morbidity including at least one of the following: admission to ICU, use of mechanical ventilation, or death. Figure 2 shows results of maternal outcomes of the WAPM study [3].

The primary outcome was reported in 12.1% of women, and of these, 11.1% were admitted to ICU, and 9.3% required some type of mechanical ventilation.

Intubation and extracorporeal membrane oxygenation were required in 6.4% and 0.5% of cases, respectively. Maternal deaths occurred in 0.8% of cases.

As shown in figure 2, the occurrence of maternal adverse events was significantly higher in symptomatic, compared with asymptomatic pregnant women.

At the multivariable analysis was only restricted to women with completed pregnancy, the independent predictors of the above-mentioned primary outcome were the presence of symptoms at the time of triage (adjusted odds ratio [aOR] 5.11; 95% confidence interval [CI] 1.11–23.6), increased levels of lactate dehydrogenase (aOR 4.13; 95% CI 1.54–11.1) and shortness of breath at presentation (aOR 3.68; 95% CI 1.58–8.58), with no statistically significant differences when stratifying the analysis according to different world region.

In a phase-2 analysis published a few months after the WAPM study with the aim of evaluating maternal and perinatal outcomes in high- and low-risk pregnancies, the authors found that women carrying high-risk pregnancies (either preexisting chronic medical conditions in pregnancy or obstetrical disorders occurring in pregnancy) had a higher risk of hospital admission, presence of severe respiratory symptoms, admission to the ICU, and invasive mechanical ventilation [11].

FETAL AND NEONATAL OUTCOMES

Figure 3 shows the fetal and neonatal outcomes of the WAPM study [3]. Out of the 388 women included in the study, 122 were still pregnant at the time of the study data analysis. Among the other 266 women, 6 had stillbirth, 6 had spontaneous first-trimester abortion and 3 had elective termination of pregnancy, and another 251 delivered a live-born infant.

The mean gestational age at delivery was 37.2 ± 3.9 weeks of gestation in women with liveborn infants. Cesarean delivery was performed in 54.2% of these women. Preterm birth at less than 37 weeks of gestation occurred in 26.3%, mostly (80.0%) iatrogenic deliveries. In 40.2% of cases, mothers were able to breastfeed and skin to skin was allowed in 27.5% of cases.

The rate of intrauterine growth restriction was 3.8% in completed pregnancies, and low birth weight neonates were 20.7% in women with liveborn infants. Admission rates to neonatal intensive care unit was 27.5%. Neonatal death occurred in 2.0% of cases, all considered as prematurity-related events.

Among the 266 women with completed pregnancies, the overall number of perinatal deaths was 11 (4.1%). Ten of the mothers had COVID-19 symptoms at presentation, and one was asymptomatic.

In women with liveborn infant who had symptoms at the time of triage, the gestational age at delivery was significantly lower than in asymptomatic women: 36.6 ± 4.3 weeks vs. 38.6 ± 2.2 weeks, respectively ($p < 0.001$). Also, symptomatic women had less birth weight 2821 ± 846 g vs. 3149 ± 496 g ($p = 0.004$).

As per maternal outcomes, the occurrence of fetal and neonatal adverse events was significantly higher in symptomatic, compared with asymptomatic pregnant women.

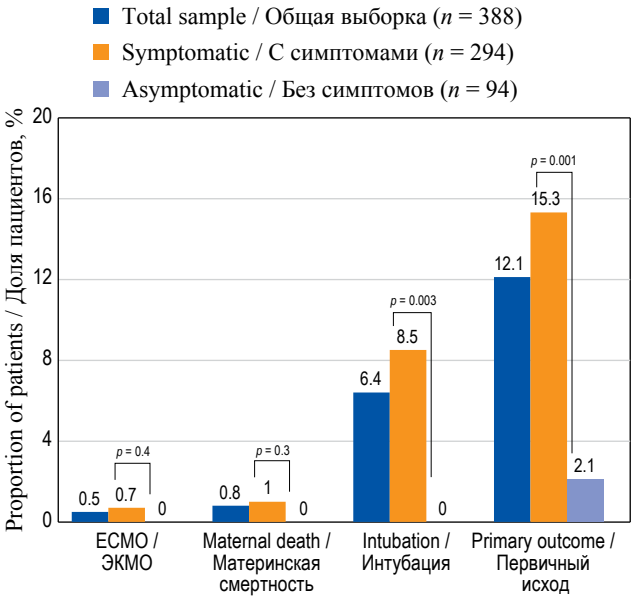

FIG. 2. Maternal outcomes in total sample, in symptomatic patients at the time of triage and asymptomatic patients (Diagram based on published WAPM study data [3]).
РИС. 2. Материнские показатели в общей выборке, у пациенток с симптомами во время госпитализации и у бессимптомных пациенток (диаграмма основана на опубликованных данных исследования WAPM [3]).

Note: ECMO – extracorporeal membrane oxygenation.
Примечание: ЭКМО – экстракорпоральная мембранная оксигенация.

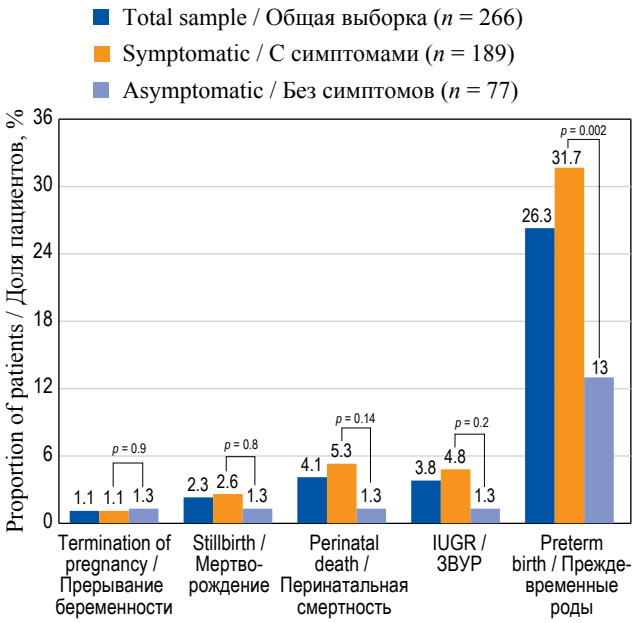

FIG. 3. Fetal and neonatal outcomes (women with completed pregnancies) in total sample, in symptomatic patients at the time of triage and asymptomatic patients (Diagram based on published WAPM study data [3]).
РИС. 3. Показатели плода и новорожденного (женщины с завершенной беременностью) в общей выборке, у пациенток с симптомами во время включения в исследование и у бессимптомных пациенток (диаграмма основана на опубликованных данных исследования WAPM [3]).

Note: IUGR – intrauterine growth restriction.
Примечание: ЗВУР – задержка внутриутробного развития.

In a secondary analysis of the WAPM study, the authors found that the incidence of a composite adverse fetal outcome (defined as the presence of either abortion, stillbirth, neonatal death, or perinatal death) was significantly higher when the infection occurred in the first trimester, and in fetuses with lower birthweight [5].

At logistic regression analysis, gestational age at diagnosis (odds ratio [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 continuous positive airway pressure (CPAP) (OR: 4.12; 95% CI 2.3–7.9; $p = 0.001$) were independently associated with the above-mentioned composite adverse fetal outcome [4].

STRENGTHS AND LIMITATIONS

The WAPM study has been among the first published studies on SARS-CoV-2 infection during pregnancy [3]. The inclusion of only women with laboratory-confirmed SARS-CoV-2, the large sample size coming from both University Hospitals and Community Hospitals from different countries, and the different outcomes explored can be considered as the major strengths of the study. In this scenario, the WAPM study has been among the first attempts to answer to several urgent questions raised by specialists dealing with COVID-19 during pregnancy and to provide data that could soon settle a multitude of outstanding issues that were raising daily.

The major limitations of the study were the lack of a control group, the inclusion of only high-income and middle-income countries, and the heterogeneity in the management that was limited by the non-randomized approach. Furthermore, the study population mostly came from women referred for suspected COVID-19, due to symptoms or exposure, and consequently tested with RT-PCR nasal and pharyngeal swab, thus leading to a lower percentage of asymptomatic women, compared with women receiving universal screening for SARS-CoV-2.

CONCLUSIONS

The WAPM study has been one of the first cohorts published on SARS-CoV-2 infection in pregnancy in the literature. Data from the WAPM study helped physicians in the early period of pandemic in 2020, and are an outstanding example of scientific collaboration among centers from all across the world during pandemic time.

AUTHOR CONTRIBUTIONS

Daniele Di Mascio and Francesco D'Antonio participated in writing the text of the manuscript and its interpretation. Giuseppe Rizzo developed the general concept of the article and supervised its writing. All authors participated in the discussion and editing of the work. All authors approved the final version of the publication.

ВКЛАД АВТОРОВ

Д. Ди Масцио и Ф. Д'Антонио участвовали в написании текста рукописи и его интерпретации. Д. Риццо разработал общую концепцию статьи и руководил ее написанием. Все авторы участвовали в обсуждении и редактировании работы. Все авторы одобрили окончательную версию публикации.

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