PERINATAL JOURNAL

Original Article

Perinatal Journal 2021;29(1):71–78

Maternal and perinatal outcomes in women with advanced maternal age affected by SARS-CoV-2 infection (Phase-2): The WAPM (World Association of Perinatal Medicine) Working Group on COVID-19

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Abstract

Objective: To elucidate the role of advanced maternal age (AMA) in determining the outcome of pregnancies complicated by SARS-CoV-2 infection.

Methods: Multinational cohort study included women with laboratory-confirmed SARS-CoV-2 infection from 76 centers in 27 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 (defined as intubation, need for continuous positive airway pressure, extra-corporeal membrane oxygenation), severe respiratory symptoms (including dyspnea and shortness of breath) or death.

Results: Eight hundred and eighty seven pregnant women were included in the study who were positive SARS-CoV-2 results by RT-PCR (reverse transcriptase-polymerase chain reaction) on their nasal and pharyngeal swab specimens (235 with and 652 with no AMA). The risk of composite adverse maternal outcome was higher in AMA group compared to that of under 35 years of age group, with an OR of 1.99 (95% CI 1.4–2.9; p=0.002). Likewise, women >35 years were also at higher risk of hospital admission (OR: 1.88, 95% CI 1.4–2.5; p<0.001), presence of severe respiratory symptoms (OR: 1.53, 95% CI 1.0–2.3; p=0.04) and/or admission to ICU (OR: 2.00, 95% CI 1.1–3.7; p=0.003); however, no difference was observed in terms of perinatal outcome risk.

Conclusion: Advanced maternal age is an independent risk factor for adverse maternal outcome in pregnancies complicated by SARS-CoV-2 infection. Accurate risk stratification of women presenting with suspected SARS-CoV-2 infection in pregnancy is warranted in order to identify a subset of women who may benefit from a personalized management, including elective hospitalization and/or prolonged surveillance in order to improve maternal outcome.

Keywords: SARS-CoV-2, COVID-19, Coronavirus, infection, pregnancy.

Özet: SARS-CoV-2 enfeksiyonundan etkilenmiş ileri anne yaşına sahip kadınlarda maternal ve perinatal sonuçlar (Faz 2): WAPM (Dünya Perinatal Tıp Birliği) COVID-19 Çalışma Grubu

Amaç: SARS-CoV-2 enfeksiyonu ile komplike gebeliklerin sonucunu belirlemede ileri anne yaşının (İAY) rolüne ışık tutmak.

Yöntem: Çok uluslu kohort çalışmasına, 4 Nisan 2020 ile 28 Ekim 2020 tarihleri arasında Avrupa, ABD, Güney Amerika, Asya ve Avustralya'daki 27 farklı ülkede bulunan 76 merkezden laboratuvar teyitli SARS-CoV-2 enfeksiyonlu kadınlar dahil edildi. Primer sonuç, yoğum bakım ünitesine (YBÜ) yatış, mekanik ventilasyon kullanımı (entübasyon, sürekli pozitif hava yolu basıncı ihtiyacı, ekstrakorporeal membran oksijenizasyonu olarak tanımlanmıştır), şiddetli respiratuvar semptomlar (dispne ve nefes darlığı dahil) veya ölüm dahil maternal mortalite ve morbiditenin bileşik ölçümüydü.

Bulgular: Çalışmaya, nazal ve faringeal sürüntü örneklerinde RT-PCR (ters transkriptaz polimeraz zincir reaksiyonu) ile pozitif SARS-CoV-2 sonuçlarına sahip 887 gebe çalışmaya dahil edildi (ileri anne yaşına sahip olan 235 olgu ve ileri anne yaşına sahip olmayan 652 olgu). Bileşik advers maternal sonuç riski, 35 yaş altındaki gruba kıyasla 1.99 OR (olasılık oranı) ile (%95 CU 1.4–2.9; p=0.002) İAY grubunda daha yüksekti. Benzer şekilde 35 yaşından büyük kadınlarda da hastaneye yatış (OR: 1.88, %95 GA 1.4–2.5; p<0.001), şiddetli respiratuvar semptom varlığı (OR: 1.53, %95 GA 1.0–2.3; p=0.04) ve/veya YBÜ'ye yatış (OR: 2.00, %95 GA 1.1–3.7; p=0.003) riski daha yüksekti, ancak perinatal sonuç riski bakımından hiçbir fark bulunmadı.

Sonuç: İleri anne yaşı, SARS-CoV-2 enfeksiyonuyla komplike gebeliklerde advers maternal sonuç için bağımsız bir risk faktörüdür. Maternal sonucu iyileştirebilmek için, elektif hospitalizasyon ve/veya uzun süreli takip dahil kişiselleştirilmiş bir yönetimden faydalanabilecek kadınların alt kümesini tespit edebilmek amacıyla gebelikte SARS-CoV-2 enfeksiyonu olduğundan şüphelenilen kadınlarda doğru risk sınıflandırması gereklidir.

Anahtar sözcükler: SARS-CoV-2, COVID-19, Koronavirüs, enfeksiyon, gebelik.

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e-mail: dantoniofra@gmail.com / **Received:** February 1, 2021; **Accepted:** March 9, 2021
How to cite this article: D'Antonio F, Şen C, Di Mascio D, Galindo A, Villalain C, Herraiz I, et al.; WAPM (World Association of Perinatal Medicine) Working Group on COVID-19. Maternal and perinatal outcomes in women with advanced maternal age affected by SARS-COV-2 infection (Phase-2): The WAPM (World Association of Perinatal Medicine) Working Group on COVID-19. Perinatal Journal 2021;29(1):71–78. doi:10.2399/prn.21.0291011
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Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection spread towards the end of 2019 and is still a major public health problem. New cases of infection, hospitalization, admission to Intensive Care Unit (ICU) and death toll are increasing on a daily basis worldwide.[1,2] From the beginning of pandemic, pregnancy has been claimed to be potentially be 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.[3,4]

Several cohort studies and systematic reviews evaluating the course of SARS-CoV-2 in pregnancy for maternal and perinatal outcomes have been published so far.[5–8] Despite the reassuring low rates of maternal-perinatal mortality and vertical transmission, in pregnancy, the risk of maternal admission to ICU appears to be higher, than that of age-matched non-pregnant women.[8–10]

The severity of SARS-CoV-2 infection in pregnancy has been reported to be associated with several risk factors. Among these, maternal age has been found to be an independent additional risk for adverse maternal outcome.[9] Still, the data for the relation between maternal age and outcome of pregnancies complicated by this infection is inconsistent. The aim of this study was to report the outcome of SARS-CoV-2 infection in pregnancies with AMA in a multinational cohort of pregnant women who were tested positive for SARS-CoV-2 infection.

Methods

This was a multinational, prospective cohort study involving pregnant women with a laboratory-confirmed SARS-CoV-2 infection, diagnosed from April the 4th, 2020 till October 28th, 2020. This study was designed as an open and web-based database study in 76 centers from 27 different countries (Argentina, Australia, Belgium, Brazil, Bulgaria, Colombia, Czech Republic, Chile, Finland, Germany, Greece, Equatorial Guinea, India, Israel, Italy, Mexico, North Macedonia, Peru, Portugal, Republic of Kosovo, Romania, Russia, Serbia, Slovenia, Spain, Turkey, and The United States) by the World Association of Perinatal Medicine (WAPM) COVID-19 Study Group. The study was endorsed by WAPM. Ethical approval for the study was obtained from the Ethical Committee of Federico II University of Naples (nr.145/2020). The first phase of the study has already been published and comprised the data from April 4th, 2020 till June 1st, 2020.[4] Then, additional data (more details for fetal and neonatal outcome) was added and reevaluated by contributors for WAPM COVID-19 Study Phase-2 new database. Only confirmed cases with PCR were included in the evaluation. The cases with clinical diagnosis without positive PCR test were excluded.

SARS-CoV-2 was diagnosed on the basis of The World Health Organization (WHO) interim guidance.[11] 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.[11,12]

In the included centers, women were tested with RT-PCR of nasal and pharyngeal swab mostly because of having symptoms or history of exposure.

Neonates of mothers with positive SARS-CoV-2 results were usually tested within 24 hours after delivery by oro-nasopharyngeal swab RT-PCR. 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 WAPM data 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.

The primary outcome was to compare the rates of maternal mortality and morbidity (admission to intensive care unit [ICU], use of mechanical ventilation [defined as intubation, need for continuous positive airway pressure, extra-corporeal membrane oxygenation], severe respiratory symptoms [including dyspnea and shortness of breath]). Secondary outcomes were a composite score of adverse perinatal outcome, including miscarriage, intrauterine death (IUD), neonatal death (NND), perinatal death (PND), admission to neonatal intensive care unit. Miscarriage was defined as pregnancy loss before 22 weeks of gestation, IUD as fetal loss at or after 22 weeks of gestation, while NND as death of a live-born infant within the first 28 days of life. PND was defined as IUD or NND.

Further details on criteria for maternal admission to ICU and neonatal admission to NICU are more extensively described elsewhere.[4]

All outcomes of AMA group were compared to that of non-AMA group. For the purpose of the analysis, AMA was defined as age >35 years. Subgroup analysis considering women >40 years was also performed.

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, USA, 2014). Continuous variables were reported as means ± standard deviation (SD), while categorical variables as percentage. Univariate comparisons of dichotomous data were performed with the use of the Fisher's exact test with continuity correction. Comparisons between groups were performed with the use of the Student's t-test to analyze by assuming equal within-group variances for parametric data, and with the use of Mann-Whitney U tests for nonparametric data. Multivariate analysis was performed to evaluate potential predictors of the primary outcome. Logistic regression was reported as odds ratio (OR) and adjusted OR (aOR) with 95% confidence interval (CI). A p-value <0.05 was considered statistically significant.

Results

During the study period, 887 singleton viable pregnancies from 76 centers in 27 different countries, who were tested positive for SARS-CoV-2 by nasopharyngeal swab RT-PCR were included. Among these, 652 were <35 years old of age, 235>35 and 67>40 years. General characteristic of the study population is reported in **Table 1**.

Table 1. Comparison of different characteristics in pregnant women with those with no advanced age.

Characteristic	<35 years (n=652)	≥35 years (n=235)	p-value	≥40 years (n=67)	p-value
Maternal and pregnancy characteristics					
Gestational age at diagnosis of infection (weeks)	25.41±8.1	26.35±8.9	0.134	30.78±8.9	**<0.001**
Nulliparity	30.5 (199)	44.7 (105)	**0.001**	43.3 (29)	**0.039**
Smoking before or during pregnancy	4.6 (30)	0.9 (2)	**0.007**	1.5 (1)	0.349
High-risk pregnancies	17.3 (113)	(95)	**<0.001**	67.1 (45)	**<0.001**
Clinical, radiological and laboratory findings					
Symptomatic infection	56.1 (366)	64.3 (151)	**0.039**	58.2 (39)	0.797
Respiratory symptoms	32.7 (213)	44.7 (105)	0.719	40.3 (27)	0.701
Non-respiratory symptoms	30.7 (200)	34.0 (80)	0.368	31.3 (21)	0.601
Only non-respiratory symptoms	22.5 (147)	19.6 (46)	0.358	17.9 (12)	0.442
Fever	28.1 (183)	31.1 (73)	0.402	23.9 (16)	0.567
Cough	23.5 (153)	35.7 (84)	**0.001**	44.8 (30)	**0.001**
Myalgia	16.0 (104)	22.6 (53)	**0.028**	47.8 (32)	**0.001**
Anosmia	5.4 (35)	9.8 (23)	**0.030**	7.5 (5)	0.409
Gastrointestinal symptoms	3.5 (23)	1.7 (4)	0.190	1.5 (1)	0.717
Lymphopenia	48.6 (317)	43.8 (103)	0.223	55.2 (37)	0.308
Thrombocytopenia	6.0 (39)	8.1 (19)	0.282	9.0 (6)	0.297
Increased LDH levels	5.7 (37)	6.8 (16)	0.523	11.9 (8)	0.059
Pharmacologic treatments					
LMWH	17.5 (114)	29.4 (69)	**<0.001**	50.7 (34)	**<0.001**
Antibiotics	27.5 (179)	38.7 (91)	**0.002**	67.2 (45)	**<0.001**
Any antiviral drug	20.6 (134)	31.9 (75)	**0.001**	58.2 (39)	**<0.001**
Hydroxychloroquine	15.5 (99)	29.4 (69)	**<0.001**	53.7 (36)	1.00

LDH: lactate dehydrogenase; **LMWH:** low molecular weight heparin.

There was no difference in mean gestational age at the diagnosis of the infection between AMA group and non-AMA group (25.4±8.1 vs 26.4±8.9, respectively; p=0.134). The incidence of nulliparity (44.7% vs 30.5%, p=0.001) and high-risk pregnancies (i.e. pre-existing or gestational medical conditions complicating the pregnancy) (40.4% vs 17.3%, p<0.0001) was higher in AMA group when compared to no-AMA group. When exploring the different clinical, radiologic and laboratory findings, women in AMA group were more likely to present with a symptomatic infection (64.3% vs 56.1%, p=0.039), while there was no difference in the occurrence of respiratory or non-respiratory symptoms, fever, lymphopenia, thrombocytopenia or increased serum LDH levels between the two study groups (**Table 1**).

The risk of composite adverse maternal outcome was higher in women with AMA compared to those <35 years (OR: 1.99, 95% CI 1.4–2.9; p<0.001) (**Table 2**). Likewise, women were also at higher risk of hospital admission (OR: 1.88, 95% CI 1.4–2.5; p<0.001), presence of severe respiratory symptoms (OR: 1.53, 95% CI 1.0–2.3; p=0.045), and admission to ICU (OR: 2.00, 95% CI 1.1–3.7; p=0.035) while there was no difference in the risk of adverse perinatal outcome between the two groups.

When restricting the analysis to women over 40 years of age, the risk of composite adverse maternal outcome was higher in women >40 compared to those <40 years of age (OR: 2.53, 95% CI 1.4–4.5; p=0.006). Likewise, women >40 had also a higher risk of in hospital admission (OR: 1.89, 95% CI 1.1–3.1; p=0.016), development of severe respiratory symptoms (OR: 2.28, 95% CI 1.2–4.2, p=0.012), admission to ICU (OR: 3.26, 95% CI 1.4–7.5; p=0.010) and/or need for invasive ventilation (OR: 4.18, 95% CI 1.6–11.2; p=0.009). At logistic regression analysis, AMA >35 (OR: 3.12, 95% CI 2.2–5.7; p=0.002), presence of a high-risk pregnancies (OR: 4.12, 95% CI 3.1–6.311; p=0.001) and nulliparity (OR: 3.11, 95% CI 2.9–6.2; p=0.001) were independently associated with adverse maternal outcome.

Discussion

This secondary analysis of the WAPM's multinational cohort study on pregnant women with SARS-CoV-2 from 76 different centers, showed that risks of composite adverse maternal outcome, severe respiratory symptoms and admission to ICU are higher in pregnant women with AMA than youngers.

To our knowledge, this is the first study extensively assessing the role of AMA on the outcome of pregnancies complicated by SARS-CoV-2 infection. The WAPM study was one of the largest cohort of pregnant women with SARS-CoV-2 infection, with data collected from the beginning of the pandemic. Major strengths of the study are the enrollment of only confirmed SARS-

Table 2. Comparison of the different maternal and fetal outcomes in pregnant women with those without advanced age.

	<35 years (n=652)	≥35 years (n=235)	p-value	≥40 years (n=67)	p-value
Composite adverse maternal outcome	14.4 (94)	25.1 (59)	**<0.001**	30.0 (20)	**0.006**
In hospital admission	35.3 (230)	50.6 (119)	**<0.001**	50.7 (34)	**0.016**
Severe respiratory symptoms	12.1 (79)	17.4 (41)	**0.045**	23.9 (16)	**0.012**
Admission to intensive care unit	4.0 (26)	7.7 (18)	**0.035**	11.9 (8)	**0.010**
Invasive ventilation	2.3 (15)	4.3 (10)	0.165	9.0 (6)	**0.009**
Maternal death	0.3 (2)	0.4 (1)	1.000	1.5 (1)	0.255
Composite adverse fetal outcome	11.2 (73)	13.2 (31)	0.410	14.9 (10)	0.420
Miscarriage	2.5 (16)	2.6 (6)	1.000	6.0 (4)	0.107
Intra-uterine death	0.5 (3)	0.9 (2)	0.612	0 (0)	1.000
Neonatal death	0.8 (5)	1.3 (3)	0.443	0 (0)	1.000
Perinatal death	1.2 (8)	2.1 (5)	0.346	0 (0)	1.000
Admission to neonatal intensive care unit	7.5 (49)	9.8 (23)	0.268	9.0 (6)	0.630
Vertical transmission	0.6 (4)	2.1 (5)	0.061	4.5 (3)	**0.021**

CoV-2 cases, large sample size, the inclusion of both tertiary centers and community hospitals from many different countries and multitude of outcomes explored.

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, thus leading to an intuitively lower percentage of asymptomatic women in the study cohort. 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.

Women who delay childbearing are at increased risk of adverse pregnancy outcome, including miscarriage, fetal anomalies, pre-eclampsia, gestational diabetes and cesarean delivery compared to getting pregnant at younger age.[13,14] The reason for such association is likely to rely on the higher rate of chronic morbidities potentially affecting a pregnancy in advanced age.

In the present study, we reported that AMA represents an independent risk factor for adverse outcomes in pregnancies complicated by SARS-CoV-2 infection, irrespective of the presence of pregestational or gestational co-morbidities. The course of SARS-CoV-2 infection in pregnancy has been widely reported with a higher risk of maternal respiratory morbidity compared to non-pregnant counterparts, due to physiologic changes of pregnancy that might predispose them to a more severe clinical course.[3–9]

One of the largest systematic reviews recently published on this topic showed that pregnant women affected by COVID-19 were significantly more likely to need admission to ICU and invasive ventilation, compared to non-pregnant women of same 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 SARS-CoV-2 infection in pregnancy.[9]

A likely explanation for the independent association between AMA and adverse pregnancy outcome may rely in the higher incidence of maternal chronic conditions in previous pregnancy of these women. However, the association between AMA and adverse maternal outcome persisted at logistic regression analysis, indicating an independent contribution of AMA in determining the outcome of pregnancies complicated by SARS-CoV-2 infection. Pregnancy induces marked changes in the respiratory and cardiovascular systems that are essential for meeting the increased metabolic demands of the mother and fetus. It is plausible that relative changes in the respiratory physiology with advancing age may predispose these women to a higher risk of developing pulmonary complications when affected by SARS-CoV-2 infection.

The findings from this study support an accurate risk stratification of pregnancies complicated by SARS-CoV-2 infection in order to maximize the maternal respiratory outcome. Pregnancies with co-morbidities and advanced age are at higher risk of developing complications.[15] A prolonged observation of women presenting with mild symptoms or elective hospital admission may represent a reasonable option in order to improve maternal outcome, although this assumption would require confirmation in randomized controlled trials.

Conclusion

Advanced maternal age represents an independent risk factor for adverse maternal outcome in pregnancies complicated by SARS-CoV-2 infection. Accurate risk stratification of women presenting with suspected SARS-CoV-2 infection in pregnancy is warranted in order to identify a subset of women who may benefit of a personalized management, including prolonged surveillance or elective hospitalization, in order to improve maternal outcomes.

The WAPM (The World Association of Perinatal Medicine) Working Group on COVID-19

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Funding: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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