DOI: 10.47093/2218-7332.2021.12.2

ISSN 2218-7332 (Print)
ISSN 2658-3348 (Online)

Первый Московский государственный медицинский университет имени И.М. Сеченова
(Сеченовский Университет)

Сеченовский вестник

SECHENOV MEDICAL JOURNAL

Том/Volume 12
№ 2, 2021

НАУЧНО-ПРАКТИЧЕСКИЙ МЕДИЦИНСКИЙ ЖУРНАЛ

SPECIAL ISSUE:
COVID-19 AND PREGNANCY

СПЕЦИАЛЬНЫЙ ВЫПУСК:
COVID-19 И БЕРЕМЕННОСТЬ

Первый Московский государственный медицинский университет имени И.М. Сеченова
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Sechenovskii vestnik

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Сеченовский Университет
НАУК О ЖИЗНИ

Цели и задачи

К основным целям журнала относятся представление актуальных научных достижений российских и зарубежных ученых в области медико-биологических наук, фундаментальной и клинической медицины, увеличение значимости и авторитета российской медицинской науки за счет повышения качества научных публикаций.

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История издания журнала: издается с 2010 г.
Периодичность: выходит 4 раза в год.
Префикс DOI: 10.47093
Свидетельство о регистрации средства массовой информации: ПИ № ФС77-78884 от 28 августа 2020 года выдано Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор).

Учредитель, издатель, редакция: федеральное государственное автономное образовательное учреждение высшего образования «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет).
Адрес: 119991, г. Москва, ул. Трубецкая, д. 8, стр. 2.
Телефон редакции: +7 (905) 517-27-99
Сайт: https://www.sechenovmedj.com/jour
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Выход в свет: 29.09.2021

Индексирование: журнал входит в перечень изданий, рекомендованных ВАК, и библиографическую базу данных РИНЦ.
Журнал представлен в Федеральной электронной медицинской библиотеке: http://www.femb.ru
Подписной индекс: в каталоге агентства «Пресса России» – 29124
Цена: свободная

Заведующая редакцией: А.В. Седова
Редакторы-корректоры: И.С. Пигулевская, Л.А. Зелексон
Верстка: О.А. Юнина
Отпечатано: ООО «БЕАН»
Адрес: 603003, Нижегородская обл, Нижний Новгород, ул. Баррикад, д. 1
Формат 60×90⅛.
Печать офсетная. Тираж 1000 экз.

Sechenov First Moscow State Medical University (Sechenov University).

Sechenov Medical Journal

SCIENTIFIC AND PRACTICAL MEDICAL JOURNAL

ISSN 2218-7332 (Print)
ISSN 2658-3348 (Online)
Vol. 12,
No. 2, 2021

Sechenov University
Life Sciences

Focus and Scope

The Sechenov Medical Journal is committed to presenting important scientific achievements in the field of biomedical sciences, fundamental and clinical medicine, increasing the authority of the Russian medical science by improving the quality of scientific publications.
The academic and clinical Sechenov Medical Journal publishes articles related to the issues of medical and biological sciences, clinical medicine. The information contained in Sechenov Medical Journal is intended for healthcare professionals only.

Founded: the journal has been published since 2010.
Frequency: quarterly
DOI Prefix: 10.47093
Mass Media Registration Certificate: PI No FS77-78884 as of 28 August 2020 issued by the Federal Service for Supervision of Communications, Information Technology and Mass Media (Roskomnadzor).
Distribution: content is distributed under Creative Commons Attribution 4.0 License
Founder, Publisher, Editorial Office: Sechenov First Moscow State Medical University (Sechenov University).
Address: 8/2, Trubetskaya str., Moscow, 119991
Editorial office phone number: +7 (905) 517-27-99
Website: https://www.sechenovmedj.com/jour
E-mail: vestnik@sechenov.ru

Published: 29.09.2021

Indexation: the Journal is included in the index of periodical publications recommended by the State Commission for Academic Degrees and Titles, and in the Russian Science Citation Index database
The Journal is available in the Federal Electronic Medical Library: http://www.femb.ru
Subscription index in the Russian Press Agency catalog – 29124.
Price: flexible

Managing Editor: Alla V. Sedova
Editors-proofreaders: Irina S. Pigulevskaya, Lev A. Zelexon
Page layout: Olga A. Yunina
Printed by LLC BEAN
Address: 603003, Russian Federation, Nizhny Novgorod region, Nizhny Novgorod, Barrikad str., 1
Format 60×90⅛. Off set print. Print run 1000 copies.

СОДЕРЖАНИЕ

CONTENT

Dear Colleagues!

The ongoing COrona VIrus Disease 2019 (COVID-19) pandemic provides the medical community with new challenges in terms of healthcare organization, treatment, vaccination, psychological care, ethics, and social policy.

During this time, significant progress has been made in understanding the pathological mechanisms of the development of severe forms of the disease and the long-term consequences.

A special issue of the Sechenov Medical Journal (No. 2 for 2020) dedicated to COVID-19, attracted great interest within the professional community with a wide range of readers, and opened up the opportunity for a productive discussion of the results obtained by leading Russian experts.

At the same time, the features of the course and treatment of COVID-19 remain poorly studied for specialist patient categories such as pregnant women and women in labor. The same is true regarding the impact of the virus on the fetus and newborn.

Therefore, the Editorial Board of the journal considered it appropriate to devote a special issue to these problems, in which leading experts from different countries summarize the world data and presented their own.

We are convinced that in this difficult time only close international cooperation along with the sharing of experience and knowledge can contribute to our common success in reducing maternal and perinatal morbidity and mortality associated with COVID-19.

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Уважаемые коллеги!

Продолжающаяся пандемия новой коронавирусной инфекции (COrona VIrus Disease 2019 – COVID-19) бросает все новые вызовы медицинскому сообществу в вопросах организации здравоохранения, лечения, вакцинации, психологической помощи, этических аспектов и социальной политики.

За это время достигнут значительный прогресс в понимании патологических механизмов развития тяжелых форм заболевания и долгосрочных последствий.

Специальный выпуск журнала «Сеченовский вестник» (№ 2 за 2020 г.), посвященный COVID-19, вызвал большой интерес профессиональной общественности и широкого круга читателей, открыл возможность продуктивного обсуждения результатов, полученных ведущими российскими специалистами.

Вместе с этим особенности течения и лечения COVID-19 у особой категории пациентов: беременных и рожениц, а также влияние вируса на плод и новорожденного – остаются малоизученными.

Поэтому редакция журнала сочла целесообразным посвятить этим проблемам специальный номер, в котором ведущие эксперты из разных стран обобщили мировые и представили свои собственные данные.

Мы убеждены, что в это непростое время только тесное международное сотрудничество, обмен опытом и знаниями могут способствовать нашему общему успеху в снижении материнской и перинатальной заболеваемости и смертности, связанных с COVID-19.

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Минздрава России (Сеченовский Университет),
Москва, Россия

Целевая статья / Target article
УДК 618.3-06:[616.98:578.834.1]-07:616-053.31-07
https://doi.org/10.47093/2218-7332.2021.12.2.5-11

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
Рубрики MeSH:
БЕРЕМЕННОСТИ ОСЛОЖНЕНИЯ ИНФЕКЦИОННЫЕ – ДИАГНОСТИКА
COVID-19 – ДИАГНОСТИКА
COVID-19 – ОСЛОЖНЕНИЯ
ПЛОДА БОЛЕЗНИ – ДИАГНОСТИКА
ПЛОДА БОЛЕЗНИ – ЭТИОЛОГИЯ
НОВОРОЖДЕННЫЙ, БОЛЕЗНИ – ДИАГНОСТИКА
НОВОРОЖДЕННЫЙ, БОЛЕЗНИ – ЭТИОЛОГИЯ
Для цитирования: Ди Масцио Д., Д'Антонио Ф., Риццо Д. На переднем крае: основные выводы исследования Всемирной ассоциации перинатальной медицины о материнских и неонатальных показателях у беременных с COVID-19. Сеченовский вестник. 2021; 12(2): 5–11. https://doi.org/10.47093/2218-7332.2021.12.2.5-11

КОНТАКТНАЯ ИНФОРМАЦИЯ:
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Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Финансирование. Исследование не имело спонсорской поддержки (собственные ресурсы).

Поступила: 30.07.2021
Принята: 10.08.2021
Дата печати: 29.09.2021

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
COVID-19 – DIAGNOSIS
COVID-19 – COMPLICATIONS
FETAL DISEASES – DIAGNOSIS
FETAL DISEASES – ETIOLOGY
INFANT, NEWBORN, DISEASES – DIAGNOSIS
INFANT, NEWBORN, DISEASES – ETIOLOGY
For citation: Di Mascio D., D'Antonio F., Rizzo G. 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. Sechenov Medical Journal. 2021; 12(2): 5–11. https://doi.org/10.47093/2218-7332.2021.12.2.5-11

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Conflict of interests. The authors declare that there is no conflict of interests.
Financial support. The study was not sponsored (own resources).

Received: 30.07.2021
Accepted: 10.08.2021
Date of publication: 29.09.2021

Список сокращений

COVID-19 – COrona VIrus Disease 2019, новая коронавирусная инфекция
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2, коронавирус тяжелого острого респираторного синдрома – 2
WAPM – World Association of Perinatal Medicine, Всемирная ассоциация перинатальной медицины
ДИ – доверительный интервал
ОИТ – отделение интенсивной терапии
ОТ-ПЦР – метод полимеразной цепной реакции с обратной транскрипцией в реальном времени
ОШ – отношение шансов
сОШ – скорректированное отношение шансов

КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ	HIGHLIGHTS
Частота неблагоприятных исходов со стороны матери была значительно выше у беременных женщин с симптомами заболевания по сравнению с бессимптомным течением.	The occurrence of maternal 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.	As per maternal outcomes, the occurrence of fetal and neonatal adverse events was significantly higher in symptomatic, compared with asymptomatic pregnant women.
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.	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.
Женщины с беременностями высокого риска (с ранее выявленными хроническими заболеваниями, акушерскими осложнениями) чаще госпитализировались в стационар.	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.
У женщин с беременностью высокого риска чаще наблюдались тяжелые респираторные симптомы, госпитализация в отделение интенсивной терапии и необходимость инвазивной механической вентиляции.	Women carrying high-risk pregnancies also experienced the presence of severe respiratory symptoms, admission to the intensive care unit, and invasive mechanical ventilation.

Инфекция, вызванная коронавирусом тяжелого острого респираторного синдрома – 2 (severe acute respiratory syndrome coronavirus 2 – SARS-CoV-2), распространяется с конца 2019 года по настоящее время и все еще является серьезной проблемой общественного здравоохранения. Ежедневно во всем мире регистрируются новые случаи инфекции, производится госпитализация, в том числе и в отделения интенсивной терапии (ОИТ), развиваются летальные случаи, число которых нарастает с каждым днем[1] [1].

С самого начала пандемии утверждалось, что беременные входят в группу высокого риска материнской смертности и заболеваемости по сравнению с остальным населением в связи с особенностями перестройки сердечно-сосудистой и дыхательной систем во время беременности [2, 3].

Коронавирусы представляют собой оболочечные несегментированные позитивно-смысловые РНК-вирусы, принадлежащие к отряду Nidovirales [2]. Несмотря на то что коронавирусы обычно вызывают легкое течение респираторного заболевания, за последнее десятилетие они запустили две пандемии: тяжелый острый респираторный синдром и ближневосточный респираторный синдром, также известные как SARS (severe acute respiratory syndrome) и MERS (Middle East respiratory syndrome) соответственно.

Беременные женщины находятся в зоне высокого риска тяжелого течения респираторных заболеваний

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

в связи с особенностями физиологической сердечно-легочной адаптации, происходящей во время беременности, увеличивающей риск гипоксии и ухудшающей клиническое течение.

К настоящему времени опубликовано несколько когортных исследований и систематических обзоров, в которых описано течение инфекции SARS-CoV-2 с точки зрения материнских и перинатальных показателей [4–10]. Рабочая группа по новой коронавирусной инфекции (COrona VIrus 2019, COVID-19) у беременных Всемирной ассоциации перинатальной медицины (World Association of Perinatal Medicine, WAPM) была одной из первых, предоставивших данные о COVID-19 во время беременности из нескольких центров в Азии, Европе, Океании, Северной и Южной Америке [3, 4, 11].

В этой статье мы критически оцениваем результаты этого крупного совместного исследования.

ОРГАНИЗАЦИЯ ИССЛЕДОВАНИЯ

WAPM-исследование по новой коронавирусной инфекции (COrona VIrus Disease 2019, COVID-19) представляет собой международное ретроспективное когортное исследование, в которое включены беременные женщины с положительным тестом на SARS-CoV-2 в период с февраля по апрель 2020 года. В исследовании участвовали 73 центра из 22 стран мира (Аргентина, Австралия, Бельгия, Бразилия, Германия, Греция, Израиль, Испания, Италия, Колумбия, Перу, Португалия, Республика Косово, Россия, Румыния, Северная Македония, Сербия, Словения, США, Турция, Финляндия, Чешская Республика) (рис. 1) [3].

Авторы включили в исследование только женщин, инфицированных на фоне прогрессирующей беременности, исключив пациенток с положительным тестом до зачатия или в послеродовом периоде. Вирус SARS-CoV-2 определяли путем анализа мазков из носа и глотки методом полимеразной цепной реакции с обратной транскрипцией в реальном времени (ОТ-ПЦР).

ХАРАКТЕРИСТИКА ИССЛЕДОВАННОЙ ПОПУЛЯЦИИ

Исследование WAPM включало 388 женщин с одноплодной прогрессирующей беременностью, имеющих положительный тест на SARS-CoV-2 при оценке методом ОТ-ПЦР мазков из носа и глотки, со средним сроком беременности на момент установления диагноза 30,6 ± 9,5 недели. Вошедшие в исследование беременные были преимущественно в третьем триместре беременности (69,8%), женщины во втором триместре составляли 22,2%, в первом – 8,0%.

У большинства беременных имелись симптомы заболевания, наиболее частыми из которых были кашель и лихорадка, за которыми по частоте следовала одышка. Доля бессимптомных женщин составила 24,2%.

Поскольку исследование проводилось в начале пандемии, терапевтическая тактика не была стандартизована: наиболее часто (в 23,2% случаев) назначался гидроксихлорохин, при этом противовирусные препараты применялись у 18,6% женщин, в основном в комбинации лопинавир/ритонавир.

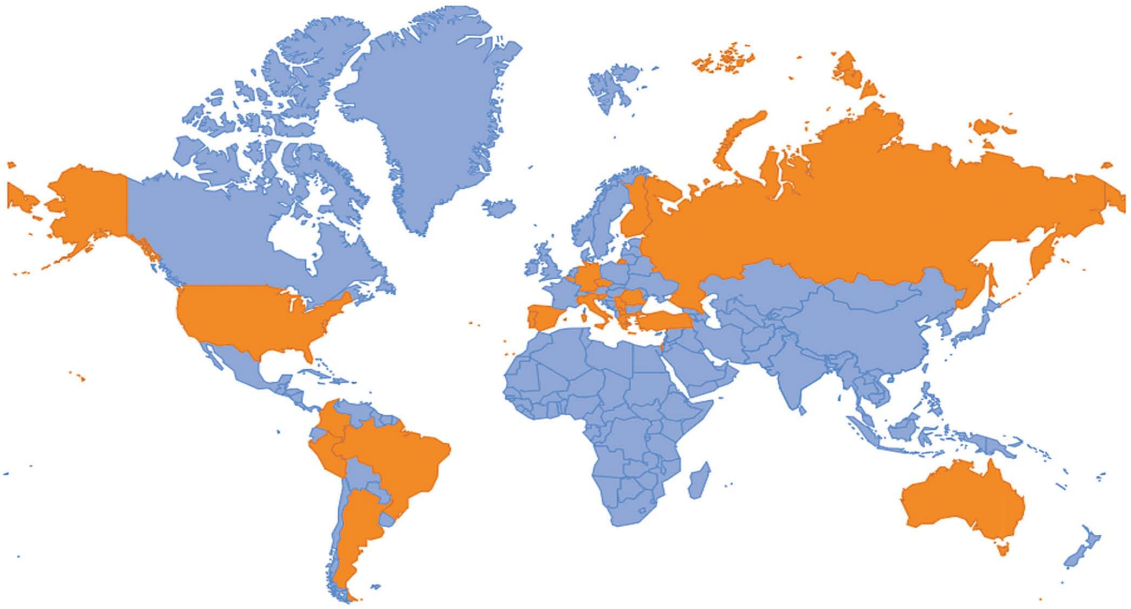

РИС. 1. Карта стран – участниц исследования Всемирной ассоциации перинатальной медицины (WAPM).
FIG. 1. Map of countries participating in World Association of Perinatal Medicine (WAPM) study.

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

МАТЕРИНСКИЕ ПОКАЗАТЕЛИ

Среди материнских исходов первичной конечной точкой был выбран комбинированный неблагоприятный исход, определяемый как минимум наличием одного из следующих: госпитализация в ОИТ, использование искусственной вентиляции легких или материнская смерть.

На рисунке 2 представлены материнские показатели исследования WAPM [3].

Первичный исход зафиксирован у 12,1% женщин. Из них 11,1% были госпитализированы в ОИТ, а в 9,3% случаев потребовался один из видов искусственной вентиляции легких.

Интубация и экстракорпоральная мембранная оксигенация потребовались в 6,4 и 0,5% случаев соответственно. Материнская смертность отмечена в 0,8% случаев.

На рисунке 2 также показано, что частота осложнений у матери была значительно выше при наличии симптомов заболевания по сравнению с бессимптомными беременными.

В многофакторном анализе, ограниченном только женщинами с завершившейся беременностью, независимыми предикторами первичного исхода установлены следующие: наличие симптомов на момент госпитализации (скорректированное отношение шансов [сОШ] 5,11; 95% доверительный интервал [ДИ] 1,11–23,6), повышенный уровень лактатдегидрогеназы (сОШ 4,13; 95% ДИ 1,54–11,1) и одышка на момент поступления (сОШ 3,68; 95% ДИ 1,58–8,58), при отсутствии статистически значимых различий при стратификации результатов из разных регионов мира.

Анализ второй фазы исследования, опубликованный через несколько месяцев после исследования WAPM, показал, что у женщин с беременностью высокого риска (ранее выявленными хроническими заболеваниями, акушерскими осложнениями) отмечено увеличение развития тяжелой одышки, госпитализации, в том числе в ОИТ, и инвазивной искусственной вентиляции легких [11].

ПОКАЗАТЕЛИ ПЛОДА И НОВОРОЖДЕННОГО

На рисунке 3 представлены результаты оценки показателей плода и новорожденного согласно исследованию WAPM [3]. Из 388 женщин, включенных в исследование, у 122 беременность еще не завершилась на этапе анализа данных. Среди оставшихся 266 женщин у 6 произошло мертворождение, у 6 – самопроизвольный аборт в первом триместре, у 3 – плановое прерывание беременности, у 251 – роды жизнеспособным плодом.

Средний срок беременности на момент родов составил 37,2 ± 3,9 недели у женщин с живорожденными детьми. Кесарево сечение выполнено в 54,2% случаев. Преждевременные роды до 37 недель беременности произошли у 26,3% женщин, большинство из них (80,0%) составили ятрогенные роды. В 40,2% случаев матери могли кормить грудью, а непосредственное прикладывание к груди было разрешено в 27,5% случаев.

У женщин с завершенной беременностью частота задержки внутриутробного развития составила 3,8%; среди живорожденных у 20,7% отмечена низкая масса тела. Госпитализация в ОИТ потребовалась 27,5% новорожденных. Неонатальная смерть наступила в 2,0% случаев, все они были связаны с недоношенностью.

Среди 266 женщин с завершенной беременностью общее число перинатальных потерь составило 11 (4,1%). В 10 из этих случаев у матерей были симптомы COVID-19, и в одном – бессимптомное течение.

У женщин с живорожденными детьми, у которых были симптомы на момент госпитализации (сортировки), срок беременности на момент родов был значительно ниже, чем у женщин без симптомов: 36,6 ± 4,3 недели против 38,6 ± 2,2 недель соответственно ($p < 0,001$). Кроме того, у женщин с симптомным течением средний вес новорожденного был ниже: 2821 ± 846 г по сравнению с 3149 ± 496 г ($p = 0,004$).

Так же как и для материнских показателей, частота нежелательных исходов у плода и новорожденного была значительно выше при наличии симптомов

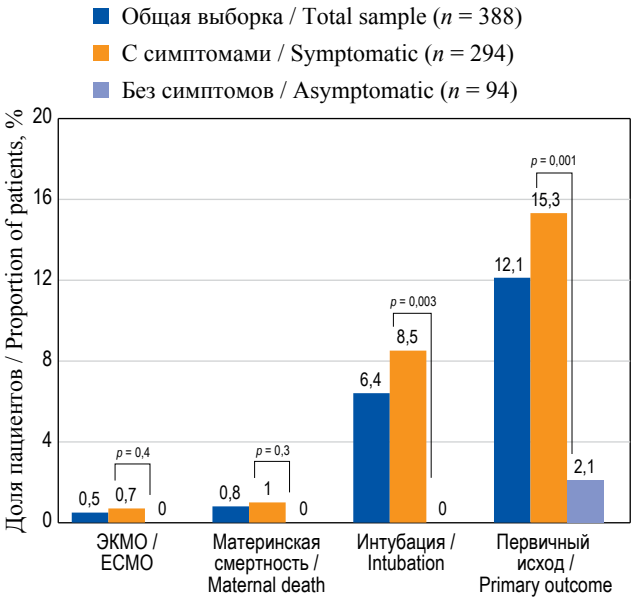

РИС. 2. Материнские показатели в общей выборке, у пациенток с симптомами во время госпитализации и у бессимптомных пациенток (диаграмма основана на опубликованных данных исследования WAPM [3]).

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]).

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

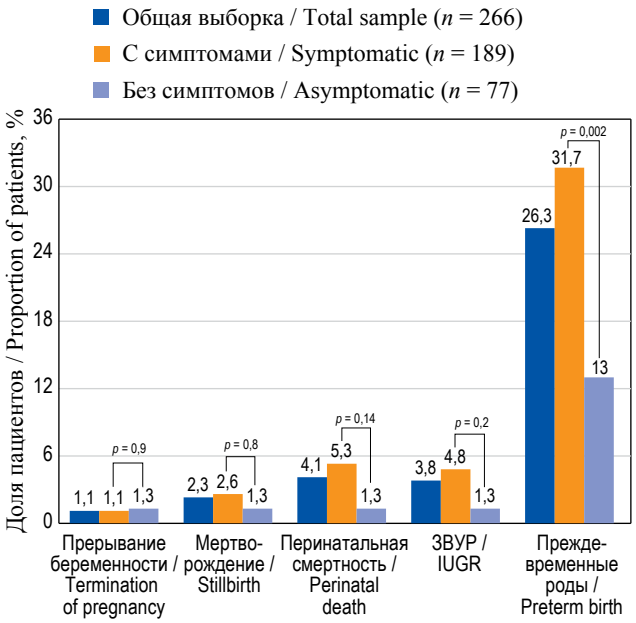

РИС. 3. Показатели плода и новорожденного (женщины с завершенной беременностью) в общей выборке, у пациенток с симптомами во время включения в исследование и у бессимптомных пациенток (диаграмма основана на опубликованных данных исследования WAPM [3]).
FIG. 3. Fetal and neonatal outcomes (women with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

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

COVID-19 у матери по сравнению с бессимптомными беременными женщинами.

При проведении вторичного анализа исследования WAPM авторами показано, что совокупный неблагоприятный показатель для плода (определяемый как самопроизвольный аборт, мертворождение, неонатальная или перинатальная гибель) был значительно выше при инфицировании матери в первом триместре беременности, а также у плодов с более низкой массой тела при рождении [5].

Логистический регрессионный анализ показал, что с вышеупомянутым совокупным неблагоприятным показателем для плода были независимо связаны: срок беременности на момент установления диагноза (отношение шансов [ОШ]: 0,85; 95% ДИ 0,8–0,9 при увеличении на неделю, $p < 0,001$), вес при рождении (ОШ: 1,17; 95% ДИ 1,09–1,12,7 при уменьшении на 100 г; $p = 0,012$) и респираторная поддержка матери, включая потребность в кислороде или режиме постоянного положительного давления в дыхательных путях (continuous positive airway pressure, CPAP) (ОШ: 4,12; 95% ДИ 2,3–7,9; $p = 0,001$) [4].

СИЛЬНЫЕ СТОРОНЫ ИССЛЕДОВАНИЯ И ЕГО ОГРАНИЧЕНИЯ

Исследование WAPM было одним из первых опубликованных исследований инфекции SARS-CoV-2 во время беременности [3]. К сильным сторонам исследования стоит отнести включение в него только женщин с лабораторно подтвержденным SARS-CoV-2, большой размер выборки, источником которой явились как университетские больницы, так и городские стационары разных стран, и широкий спектр изучаемых показателей. Исследование WAPM – одна из первых попыток ответить на несколько неотложных вопросов, поднятых специалистами, занимающимися COVID-19 во время беременности, и предоставить данные, которые могли бы быстро решить множество проблем, возникающих ежедневно.

Основными ограничениями исследования являются: отсутствие контрольной группы, включение только стран с высоким и средним доходом и различные подходы к терапии, что требовало нерандомизированного подхода. Кроме того, исследуемая выборка состояла в основном из женщин с симптомами заболевания COVID-19, направленных на тестирование путем ОТ-ПЦР мазков из носа и глотки, что привело к более низкому проценту бессимптомных женщин по сравнению с выборкой беременных, проходящих стандартный скрининг на SARS-CoV-2.

ВЫВОДЫ

Исследование WAPM – одно из первых когортных исследований, опубликованных в литературе, посвященных SARS-CoV-2 во время беременности. Данные исследования WAPM помогли врачам в начальный период пандемии в 2020 году и являются выдающимся примером научного сотрудничества между центрами со всего мира во время пандемии.

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.

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.

Перевод статьи на русский язык: Слуханчук Екатерина Викторовна, канд. мед. наук, доцент кафедры акушерства и гинекологии Клинического института детского здоровья им. Н.Ф. Филатова ФГАОУ ВО «Первый МГМУ им. И.М. Сеченова» (Сеченовский Университет).

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Short review / Краткий обзор
https://doi.org/10.47093/2218-7332.2021.12.2.12-19

Organization of an obstetrics unit during the COVID-19 pandemic: a short literature review

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has posed unprecedented challenges for the delivery of high-quality obstetric services to both SARS-CoV-2 positive and negative women. The initial epidemiological pressure, especially in the most affected areas of China and Italy, led the local health services to defining care pathways based on the organizational and logistical availability of the moment. Currently, some aspects of clinical care practices and the management of women with suspected or confirmed SARS-CoV-2 virus infection are well established. The aim of this review article is to provide an outline of the suggested organization of obstetric units during the COVID-19 pandemic, and to mention the challenges we had to face at our institution.

Keywords: pneumonia; pregnancy; delivery; antenatal care; SARS-CoV-2; COVID-19
MeSH terms:
PREGNANCY COMPLICATIONS, INFECTIOUS – THERAPY
COVID-19 – COMPLICATIONS
COVID-19 – THERAPY
DELIVERY OF HEALTH CARE – ORGANIZATION & ADMINISTRATION
MIDWIFERY – ORGANIZATION & ADMINISTRATION
For citation: Zanardini C., Papaccio M., Castellani R., Orabona R., Fratelli N., Fichera A., Franceschetti L., Ferrari F., Odicino F.E., Sartori E., Prefumo F. Organization of an obstetrics unit during the COVID-19 pandemic: a short literature review. Sechenov Medical Journal. 2021; 12(2): 12–19. https://doi.org/10.47093/2218-7332.2021.12.2.12-19

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Conflict of interests. The authors declare that there is no conflict of interests.
Financial support. The study was not sponsored (own resources).

Received: 20.08.2021
Accepted: 29.08.2021
Date of publication: 29.09.2021

УДК 618.3-06:[616.9:578.834.1]}:614.2

Организация работы акушерского отделения во время пандемии COVID-19: краткий обзор литературы

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Аннотация

Пандемия новой коронавирусной инфекции (COVID-19) создала беспрецедентные проблемы для оказания высококачественной акушерской помощи женщинам как с положительным, так и с отрицательным результатом на SARS-CoV-2. В наиболее пострадавших от первой волны эпидемии районах Китая и Италии местные службы здравоохранения определили пути оказания помощи в зависимости от организационных возможностей и материально-технической оснащенности на тот момент времени.

В настоящее время хорошо изучены некоторые аспекты оказания медицинской помощи и ведения женщин с подозрением или подтвержденной вирусной инфекцией SARS-CoV-2. Цель этой обзорной статьи – представить схему организации работы акушерских отделений во время пандемии COVID-19 и упомянуть проблемы, с которыми нам пришлось столкнуться в нашем учреждении.

Ключевые слова: пневмония; беременность; роды; дородовый уход; SARS-CoV-2; COVID-19

Рубрики MeSH:

БЕРЕМЕННОСТИ ОСЛОЖНЕНИЯ ИНФЕКЦИОННЫЕ – ТЕРАПИЯ
COVID-19 – ОСЛОЖНЕНИЯ
COVID-19 – ТЕРАПИЯ
МЕДИЦИНСКОЙ ПОМОЩИ ОКАЗАНИЕ – ОРГАНИЗАЦИЯ И УПРАВЛЕНИЕ
АКУШЕРСТВО ПРАКТИЧЕСКОЕ – ОРГАНИЗАЦИЯ И УПРАВЛЕНИЕ

Для цитирования: Занардини К., Папаччо М., Кастеллани Р., Орабона Р., Фрателли Н., Фичера А., Франческетти Л., Феррари Ф., Одичино Ф.Э., Сартори Э., Префумо Ф. Организация работы акушерского отделения во время пандемии: краткий обзор литературы. Сеченовский вестник. 2021; 12(2): 12–19. https://doi.org/10.47093/2218-7332.2021.12.2.12-19

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Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Финансирование. Исследование не имело спонсорской поддержки (собственные ресурсы).

Поступила: 20.08.2021
Принята: 29.08.2021
Дата печати: 29.09.2021

List of abbreviations

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

HIGHLIGHTS	КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ
The SARS-CoV-2 has had major effects on the provision of healthcare services worldwide.	Инфекция SARS-CoV-2 оказала серьезное влияние на оказание медицинской помощи во всем мире.
Before accessing health services, pregnant women should be triaged to detect any symptoms or exposure suggesting risk of SARS-CoV-2 virus infection.	Перед обращением за медицинскими услугами беременные женщины должны пройти сортировку для выявления любых симптомов или факторов, указывающих на риск заражения вирусом SARS-CoV-2.
The antenatal visits and screening ultrasound examinations recommended in low-risk pregnancy must be performed with the timing and modalities suggested by local or international guidelines both in asymptomatic patients, and in patients with suspected/confirmed SARS-CoV-2 infection.	Посещения медицинских учреждений в дородовом периоде и скрининговые ультразвуковые исследования, рекомендуемые при беременности с низким уровнем риска, должны проводиться в сроки и в условиях, рекомендованных местными или международными рекомендациями, как у бессимптомных пациентов, так и у пациентов с подозреваемой или подтвержденной инфекцией SARS-CoV-2.
In the event of confirmed or suspected SARS-CoV-2 infection, a multidisciplinary team including obstetrician, anesthetist, midwife, neonatologist, pediatric nurse and infectious disease specialist should take care of the woman and her infant.	В случае подтвержденной или подозреваемой инфекции SARS-CoV-2 о женщине и ее младенце должна позаботиться мультидисциплинарная бригада, в которую входят акушер, анестезиолог, фельдшер-акушер, неонатолог, детская медсестра и инфекционист.
The mode of delivery should not be affected by the presence of COVID-19 unless the woman's respiratory conditions require urgent delivery.	Наличие COVID-19 не должно влиять на способ родоразрешения, за исключением тяжелого поражения дыхательной системы, требующего срочного родоразрешения.
Specific training and planning should be dedicated to the management of obstetric emergencies in SARS-CoV-2 infected women.	Необходимо проводить специальное обучение и планирование по оказанию неотложной акушерской помощи у женщин, инфицированных SARS-CoV-2.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, a global public health emergency, has had major effects on the provision of healthcare services worldwide. It also had a major impact on obstetric services. From the very beginning of the pandemic, it became clear that care pathways and the assistance network of pregnant women, mothers, fathers and newborns needed a timely review and reorganization. In January-March 2020, however, the scientific evidence was still scarce and often ambiguous. The initial epidemiological pressure, especially in the most affected areas of China and Italy, led the local health services to defining care pathways based on the organizational and logistical availability of the moment. Currently, some aspects of clinical care practices and the management of women with suspected or confirmed SARS-CoV-2 virus infection are well established. The aim of this article is to provide an outline of the suggested organization of obstetric units during the coronavirus disease 2019 (COVID-19) pandemic, and to mention the challenges we had to face at our Institution.

ANTENATAL CARE

The presence of asymptomatic or paucisymptomatic (subclinical) SARS-CoV-2 virus positive subjects has been documented in both the general population and pregnant women, many of whom generally have mild or moderate symptoms [1]. The prevalence and clinical manifestations of COVID-19 disease in pregnancy appear to be substantially similar to the general population. All women, even those positive for the SARS-CoV-2 virus, should be enabled to participate in the choices related to their care, in line with the principles of informed consent [2]. Assistance must be centered on women, respectful and qualified in order to preserve dignity, privacy and confidentiality and allow an informed choice. The presence of a person chosen by the woman must also be guaranteed throughout the birth process. In case of low-risk pregnancy it is recommended to maintain the minimum prenatal visits in presence according to local guidelines and, when possible, to include the visit, the ultrasound examination, and any other diagnostic tests in a single appointment, taking care to involve the least possible number of healthcare professionals. In the event of a high-risk pregnancy, some women, due to their medical or obstetric clinical conditions, comorbidities or complications, may require a greater number of visits and multidisciplinary assistance [2].

At the end of each appointment, it is advisable to book the next appointment and its modality (in presence or remotely). Multidisciplinary assistance must include anesthetic evaluation, which is also useful for providing comprehensive information on the safety of the care pathway and to offer analgesia at childbirth. There should be a recovery system for women who are unable to attend appointments for more than three consecutive weeks. Before accessing health services, women should be triaged to detect any symptoms suggestive of SARS-CoV-2 virus infection, including their household members. Several triage checklists have been suggested [3, 4]. Pregnant women who have had contact with a person with confirmed SARS-CoV-2 infection should be carefully monitored considering the possibility of transmission from asymptomatic individuals.

ULTRASOUND EXAMINATIONS

The screening ultrasound examinations recommended in low-risk pregnancy must be performed with the timing and modalities suggested by local or international guidelines [5–7], both in asymptomatic patients and in patients with suspected/confirmed SARS-CoV-2 infection or with reported close contacts with individuals with confirmed or suspected infection within the last 14 days. Non-urgent and/or deferrable ultrasound examinations in patients with suspected/confirmed SARS-CoV-2 infection or with reported close contacts in the last 14 days should be postponed for 14 days.

In areas with a high incidence of SARS-CoV-2 infection, the planning of ultrasound activities must be reviewed on a weekly basis and possibly rescheduled taking into consideration the epidemiological situation, the availability/unavailability of operators and the gestational age and indication of the ultrasound examinations. In the event that the planning manager deems it advisable to defer a non-urgent ultrasound examination, the patient must be informed by telephone that the postponement of the examination does not substantially change the monitoring of pregnancy, and that the choice to defer the ultrasound examination is dictated by the need to protect the pregnant woman and the fetus from the ongoing epidemic. The ultrasound planning must provide sufficient time for the spacing of the appointments so that each ultrasound examination can probably be concluded before the starting time of the next examination (minimum 30 – max 60 minutes depending on the type of ultrasound examination and the clinical indication) to minimize the possibility of waiting for more than one patient in the common areas. The scheduling/rescheduling of appointments should be done by phone, e-mail or electronic messaging. The woman must be contacted by phone one day before the scheduled appointment to verify the absence of symptoms and close contacts with individuals with confirmed or suspected SARS-CoV-2 infection in the last 14 days. Table summarizes the changes to ultrasound scheduling in low-risk pregnancies according to SARS-CoV-2 status as suggested by the International Society for Ultrasound in Obstetrics and Gynecology [8].

Table. **Modification of routine sonographic examinations in women at low obstetric risk, according to whether they are asymptomatic for COVID-19 or symptomatic and/or screen-positive for TOOC factors (reproduced with permission from [8])**

Таблица. **Модификация сроков проведения рутинных ультразвуковых исследований у женщин с низким акушерским риском в зависимости от того, являются ли они бессимптомными по COVID-19 или имеют симптомы и/или факторы риска TOCC (воспроизведено с разрешения [8])**

Scan / Исследование	Asymptomatic / Бессимптомные	Symptomatic and/or screen-positive for TOCC / Наличие симптомов и/или положительные результаты скрининга на факторы риска TOCC
11 + 0 to 13 + 6 weeks (also for dating) / с 11 + 0 до 13 + 6 недель (также для определения срока беременности)	• Combined test • Offer NIPT • Комбинированный тест • Предлагается НИПТ	• Reschedule combined test in 2 weeks if still within gestational-age window[a] (unless local protocols differ) • Offer NIPT/serum screening and detailed scan in 3–4 weeks after quarantine • Комбинированный тест переносится на 2 недели позже, если все еще в пределах окна гестационного возраста[a] (если местные протоколы не отличаются) • Предлагается НИПТ / скрининг маркеров сыворотки и подробное сканирование через 3–4 недели после карантина
18 + 0 to 23 + 0 weeks / С 18 + 0 до 23 + 0 недель	• Anatomical scan • Анатомическое сканирование	• Reschedule after quarantine in 2–3 weeks[b] • Перенести исследование на срок после карантина через 2–3 недели[b]
Fetal growth scan in third trimester / Сканирование развития плода в третьем триместре	• Do not perform, unless clinically indicated • Не проводится, если нет клинических показаний	• Do not perform, unless clinically indicated • Не проводится, если нет клинических показаний

Note: TOCC – 14 days before onset of symptoms: Travel, High-risk Occupation (e.g. laboratory worker, healthcare worker, wild-animal-related work), History of unprotected Contact with a person with confirmed COVID-19; clustering of influenza-like illness / pneumonia (≥2 affected person).
NIPT – non-invasive prenatal testing. [a] – the scan at 11–13 weeks is not advisable unless the gestational age allows for it to be performed after 2 weeks. [b] – in countries where there is a legal gestational-age limit for termination of pregnancy, the time limit and its implications should be explicitly explained to the patients prior to rescheduling the appointment.
If a patient presents close to the gestational-age legal limit, consider offering a scan using appropriate personal protective equipment or defer for 2–3 weeks.
Примечание: TOCC – 14 дней до появления симптомов: путешествие, род занятий с высоким риском (например, работник лаборатории, медицинский работник, работа с дикими животными), история незащищенного контакта с человеком с подтвержденным COVID-19; наличие среди ближайшего окружения гриппоподобного заболевания / пневмонии (≥2 заболевших).
НИПТ – неинвазивное пренатальное тестирование. [a] – исследование на сроке 11–13 нед. не рекомендуется, за исключением случая, когда гестационный возраст не позволяет проводить его через 2 недели. [b] – в странах с установленным законом пределом гестационного возраста для прерывания беременности этот срок и последствия его переноса должны быть четко объяснены пациенткам до переноса приема.
Если у пациентки предельный гестационный возраст для прерывания беременности соответственно закону, рассмотрите возможность проведения сканирования с использованием соответствующих средств индивидуальной защиты или отсрочки на 2–3 недели.

A different approach must be taken for scans that are not part of the routine care of low-risk pregnancy but may be needed in view of an increased risk of complications (structural/genetic abnormalities; history of preterm delivery, fetal growth restriction or pre-eclampsia; maternal medical conditions). Sometimes, an ultrasound examination may be needed urgently because of actual maternal symptoms or pregnancy complications. The algorithm suggested by the International Society for Ultrasound in Obstetrics and Gynecology [8] for such cases is shown in Figure.

HOSPITAL ADMISSION (TRIAGE)

If a pregnant woman needs unplanned or urgent care, triage units should offer telephone advice, possibly providing a call-back service if the appropriate care provider is not immediately available. When medical assessment and/or hospitalization is required, local protocols are needed to ensure that women with confirmed or suspected SARS-CoV-2 infection are identified early and isolated upon arrival at the health facility. These protocols must include detailed indications for the identification, in the emergency room, of dedicated spaces, clean and protected paths, distancing and protection of accompanying persons in the waiting room. Protocols must also contain indications for the sanitation of environment and equipment, use of personal protection equipment for both the pregnant woman and staff, and instructions for the possible hospitalization and assistance offered in case of complications and/or development of critical conditions [3, 4, 9–11].

LABOUR AND DELIVERY IN SARS-COV-2 POSITIVE WOMEN

In the event of confirmed or suspected SARS-CoV-2 infection, a multidisciplinary team including obstetrician, anesthetist, midwife, neonatologist,

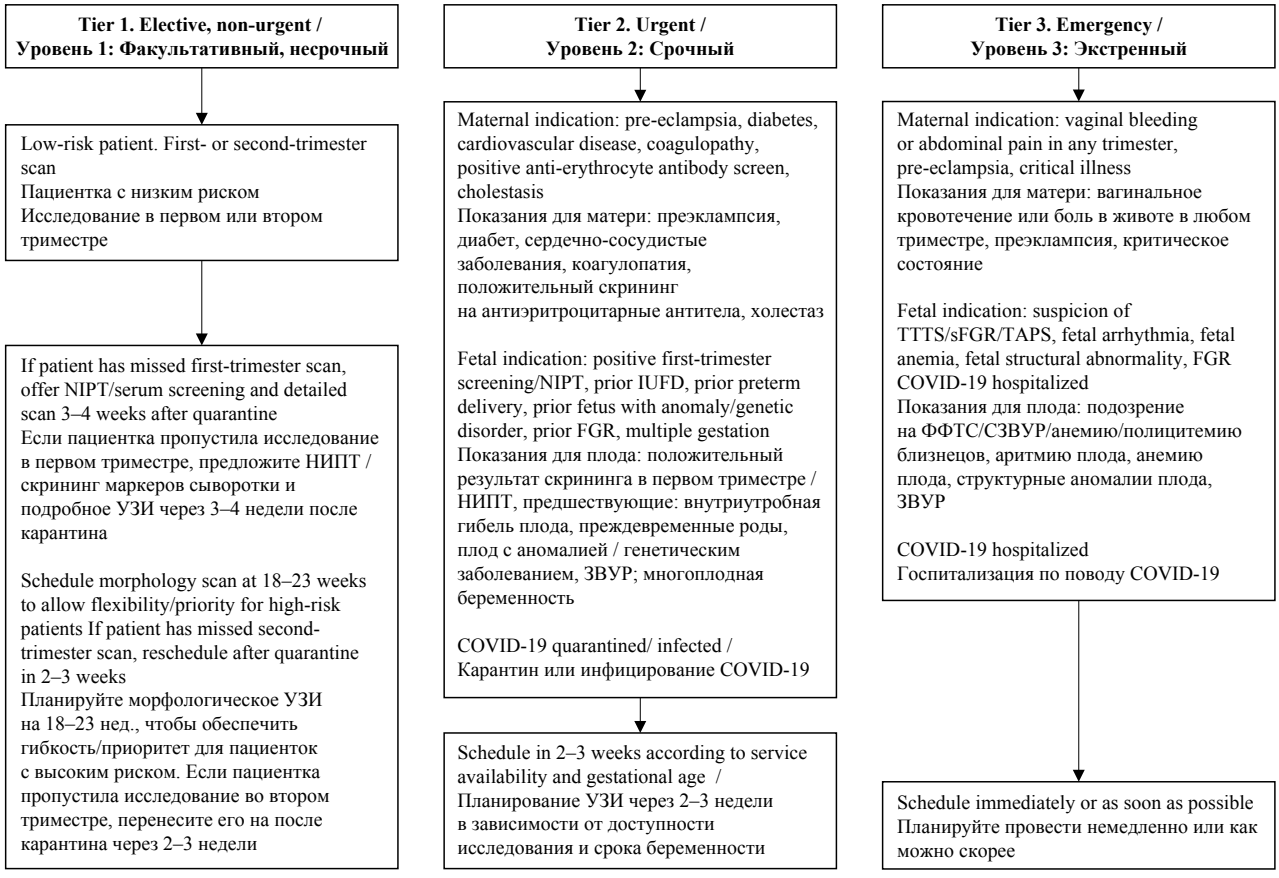

FIG. Algorithm for prioritizing appointments in obstetric ultrasound unit in context of COVID-19 pandemic (reproduced with permission from [8]).
РИС. Алгоритм приоритизации посещений акушерского отделения ультразвуковой диагностики в контексте пандемии COVID-19 (воспроизведено с разрешения [8]).

Note: FGR – fetal growth restriction; IUFD – intrauterine fetal death; NIPT – non-invasive prenatal testing; sFGR – selective fetal growth restriction; TAPS – twin anemia polycythemia sequence; TTTS – twin-to-twin transfusion syndrome.
Примечание: ЗВУР – задержка внутриутробного развития; ВГП – внутриутробная гибель плода; НИПТ – неинвазивное пренатальное тестирование; СЗВУР – селективная задержка внутриутробного роста; САП – синдром анемии/полицитемии близнецов; ФФТС – фето-фетальный трансфузионный синдром.

pediatric nurse and infectious disease specialist, should take care of the woman and her infant. A clear separation must be maintained between the pathways of negative women and those of confirmed or suspected SARS-CoV-2 infection[1]. The observation and evaluation of the woman must be carried out as usual with the addition of the oxygen saturation control to be carried out every hour with the aim of maintaining it over 94%. A designated team member should regularly update the woman's family members about her medical condition, using interpreting services when needed. In case of clinical indications, the administration of steroids for fetal pulmonary maturation is indicated as per existing protocols < 34 weeks of gestation. SARS-CoV-2 positivity does not constitute an indication for elective caesarean section[1] [3, 4].

The mode of delivery should not be affected by the presence of COVID-19, unless the woman's respiratory conditions require urgent delivery [9]. The choice of delivery method must be discussed with the woman, taking into consideration her preferences and any obstetric and anesthetic indications. Labor and water birth are not recommended in symptomatic women (cough, fever, general malaise) due to the hypothetical risk of transmission via feces and because protective equipment is not waterproof; it is not contraindicated in SARS-CoV-2 negative women. SARS-CoV-2 positivity in asymptomatic women is not, in itself, an indication for continuous monitoring of fetal heart rate by cardiotocography. Epidural analgesia is not contraindicated in case of SARS-CoV-2 infection and should be recommended to reduce the use of general anesthesia if an emergency caesarean section is required. Induction of labor must be evaluated on an individual basis, taking into account the possible risks and benefits. Pharmacological induction, oxytocin augmentation, and episiotomy or operative vaginal delivery must be performed not based on SARS-CoV-2 status but only if clinically justified and based on maternal and/or fetal conditions[1] [3, 4].

Birth attendants must wear appropriate protective equipment. The choice of birth position is subject to the same assessments as in the ordinary period, not related to the COVID-19 emergency, and considering the choices of the woman. Fluid management requires careful hourly monitoring with the aim of avoiding the risk of overload that could expose women with moderate or severe clinical manifestations to an increased risk of respiratory distress syndrome. Delayed cord clamping is recommended for known health benefits to mother and infant that outweigh theoretical and undocumented risks of SARS-CoV-2 transmission.

MANAGING OBSTETRIC EMERGENCIES

Managing obstetric emergencies in a woman with suspected or confirmed SARS-CoV-2 infection poses difficulties and challenges. Personnel facing a shoulder dystocia, or a postpartum hemorrhage needs to be clinically effective and operate in safety at the same time. The use of personal protective equipment, the obstacles of working and communicating in an isolated room may hinder the performance of the obstetric team. In 2020 Cambridge University's THIS Institute, in collaboration with the PROMPT (Practical Obstetric Multi-Professional Training) Maternity Foundation ran a rapid-response consultation involving 100 experts in human factors, obstetrics, infection prevention and control[2]. Five key areas were identified. In order to ensure appropriate teamwork, team roles should be clearly assigned, and members should help each other to get ready; it should be clear who goes in first to attend the emergency; a 'clean' member of the team should not go into the patient's room but should help colleagues to don/doff personal protective equipment, transfer equipment and laboratory samples. To improve communication between team members and with the woman and her partner, operators could wear stickers or laminated photos as role identifiers. When wearing masks, goggles/face shields and gowns, eye contact, tone of voice and body language should be emphasized to allow efficient communication. Transitions of staff and equipment between 'dirty' and 'clean' zones should be facilitated by clearly marking contaminations zones (e.g. drawing lines with red tape on the floor), using dedicated plastic bags/boxes for biological sample transfer, providing a standardized layout for personal protective equipment in the donning area supported by laminated posters showing donning/doffing steps, using wide-aperture disposal bins. Finally, the team should debrief after emergencies to provide feedback, ensure psychological safety and refine procedures.

OBSTETRIC SERVICES AT SPEDALI CIVILI DI BRESCIA

Spedali Civili di Brescia is located in the Lombardy region of Italy, which was the epicenter of the first wave of COVID-19. It is a tertiary hospital with 1,400 beds; by mid-March 2020, more than 800 beds were converted for COVID-19 inpatient care. Between the 25th February and 22nd April 2020 in Italy the incidence rate of confirmed SARS-CoV-2 infection in women who gave birth was 2.1/1,000 deliveries at national level and 6.9/1,000 in Lombardy [12]. In the period 25th February-30th June 2021, it acted as the COVID-19 obstetric hub for an area of 1.5 million inhabitants, and 288 pregnant women were admitted and/or delivered at Spedali Civili di Brescia. Common protocols were shared with the other

[1] https://www.rcog.org.uk/globalassets/documents/guidelines/2021-02-19-coronavirus-covid-19-infection-in-pregnancy-v13.pdf, Accessed Aug 11th, 2021.

[2] https://www.thisinstitute.cam.ac.uk/research-articles/covid-19-managing-an-obstetric-emergency/

Lombardy COVID-19 maternity hubs [10, 11, 13, 14] with reciprocal back up in case of bed saturation. The early surge of COVId-19 in the area led to some early observations on neonatal transmission of SARS-CoV-2 [15], co-presentation of SARS-CoV-2 with other infectious diseases [16], and positive retesting after clinical and laboratory recovery [17]. Data were shared in international prospective registries [18, 19].

CONCLUSIONS

The COVID-19 pandemic has posed unprecedented challenges for the delivery of high-quality obstetric services to both SARS-CoV-2 positive and negative women. Accurate planning, flexibility in adapting to the different phases of the epidemics, and healthcare system resilience are key factors for success.

AUTHOR CONTRIBUTIONS

All authors: Cristina Zanardini, Marta Papaccio, Roberta Castellani, Rossana Orabona, Nicola Fratelli, Anna Fichera, Laura Franceschetti, Federico Ferrari, Franco E. Odicino, Enrico Sartori, and Federico Prefumo conceived and designed the paper, acquired analysed and interpreted the data, drafted the manuscript and critically revised it for important intellectual content. All authors approved the final version of the publication.

ВКЛАД АВТОРОВ

Все авторы: К. Занардини, М. Папаччо, Р. Кастеллани, Р. Орабона, Н. Фрателли, А. Фичера, Л. Франческетти, Ф. Феррари, Ф. Э. Одичино, Э. Сартори и Ф. Префумо – придумали и разработали дизайн, получили, проанализировали и интерпретировали данные, подготовили рукопись и критически отредактировали ее с учетом важного интеллектуального содержания. Все авторы одобрили окончательную версию публикации.

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Short review / Краткий обзор
https://doi.org/10.47093/2218-7332.2021.12.2.20-25

Fetal growth and hemodynamics during SARS-CoV-2 infection: a short literature review

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a virus that, having crossed species, has caused human disease from 2019 – COrona VIrus Disease 2019 (COVID-19). Pregnant women are potentially at high risk of contracting SARS-CoV-2 infection when compared to non-pregnant matched controls. Pregnancy is also complicated with a higher risk of developing severe SARS-CoV-2, including respiratory diseases, admission to the intensive care unit and mortality, even after adjusting for confounding risk factors. Moreover, data on the effect on fetal outcome including preterm delivery and perinatal morbidity are still conflicting, the risk of vertical transmission (i.e., transmission of SARS-CoV-2 from the mother to the fetus or the newborn) is considered low but there is evidence that a significant proportion of placentas where SARS-CoV-2 occurred during pregnancy show histopathological findings suggesting placental hypoperfusion and inflammation. In this review we will present the available data on the effects of SARS-CoV-2 infection on fetal growth and maternal hemodynamics

Keywords: SARS-CoV-2-infection; COVID-19; fetal growth; uterine artery Doppler; fetal Dopplers
MeSH terms:
PREGNANCY COMPLICATIONS, INFECTIOUS – DIAGNOSIS
PREGNANCY COMPLICATIONS, INFECTIOUS – PHYSIOPATHOLOGY
SEVERE ACUTE RESPIRATORY SYNDROME – DIAGNOSIS
SEVERE ACUTE RESPIRATORY SYNDROME – COMPLICATIONS
SEVERE ACUTE RESPIRATORY SYNDROME – PHYSIOPATHOLOGY
FETUS – DIAGNOSTIC IMAGING
FETUS – PHYSIOPATHOLOGY
PLACENTAL CIRCULATION
For citation: Rizzo G., Mappa I., Maqina P., Bitsadze V.O., Khizroeva J.Kh., Makatsariya A.D. Fetal growth and hemodynamics during SARS-CoV-2 infection: a short literature review. Sechenov Medical Journal. 2021; 12(2): 20–25. https://doi.org/10.47093/2218-7332.2021.12.2.20-25

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Conflict of interests. The authors declare that there is no conflict of interests.
Financial support. The study was not sponsored (own resources).

Received: 21.08.2021
Accepted: 29.08.2021
Date of publication: 29.09.2021

УДК 618.3-06:[616.98:578.834.1](048)

Рост плода и гемодинамика при инфицировании SARS-CoV-2: краткий обзор литературы

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Аннотация

Коронавирус тяжелого острого респираторного синдрома 2 (SARS-CoV-2) – вирус, который преодолел видовой барьер и стал причиной заболевания человека с 2019 года (COrona VIrus Disease 2019, COVID-19). Беременные женщины потенциально подвержены более высокому риску заражения SARS-CoV-2 по сравнению с небеременными женщинами соответствующей контрольной группы. Беременность также ассоциирована с повышенным риском развития тяжелого SARS-CoV-2, включая заболевания дыхательной системы, госпитализацию в отделение интенсивной терапии и смертность, даже после поправки на сопутствующие факторы риска. Более того, данные о влиянии на показатели плода, включая преждевременные роды и перинатальную заболеваемость, все еще противоречивы. Риск вертикальной передачи, то есть передачи SARS-CoV-2 от матери к плоду или новорожденному, считается низким, однако есть доказательства, что в плаценте, инфицированной SARS-CoV-2, достаточно часто определяются гистопатологические признаки гипоперфузии и воспаления плаценты. В этом обзоре мы представим имеющиеся данные о влиянии инфекции SARS-CoV-2 на рост плода и гемодинамику матери.

Ключевые слова: инфекция SARS-CoV-2; COVID-19; рост плода; доплерография маточной артерии; допплерография плода

Рубрики MeSH:

БЕРЕМЕННОСТИ ОСЛОЖНЕНИЯ ИНФЕКЦИОННЫЕ – ДИАГНОСТИКА
БЕРЕМЕННОСТИ ОСЛОЖНЕНИЯ ИНФЕКЦИОННЫЕ – ПАТОФИЗИОЛОГИЯ
ТЯЖЕЛЫЙ ОСТРЫЙ РЕСПИРАТОРНЫЙ СИНДРОМ – ДИАГНОСТИКА
ТЯЖЕЛЫЙ ОСТРЫЙ РЕСПИРАТОРНЫЙ СИНДРОМ – ОСЛОЖНЕНИЯ
ТЯЖЕЛЫЙ ОСТРЫЙ РЕСПИРАТОРНЫЙ СИНДРОМ – ПАТОФИЗИОЛОГИЯ
ПЛОД – ДИАГНОСТИЧЕСКОЕ ИЗОБРАЖЕНИЕ
ПЛОД – ПАТОФИЗИОЛОГИЯ
ПЛАЦЕНТАРНОЕ КРОВООБРАЩЕНИЕ

Для цитирования: Риццо Д., Маппа И., Макина П., Бицадзе В.О., Хизроева Д.Х., Макацария А.Д. Рост плода и гемодинамика при инфицировании SARS-CoV-2: краткий обзор литературы. Сеченовский вестник. 2021; 12(2): 20–25. https://doi.org/10.47093/2218-7332.2021.12.2.20-25

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Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Финансирование. Исследование не имело спонсорской поддержки (собственные ресурсы).

Поступила: 21.08.2021
Принята: 29.08.2021
Дата печати: 29.09.2021

List of abbreviation

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

UVBF – umbilical vein blood flow

UVBF/AC – umbilical vein blood flow normalized for fetal abdominal circumference

HIGHLIGHTS	КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ
SARS-CoV-2 virus induce changes in the placenta, mainly characterized by hypoperfusion and inflammation	Вирус SARS-CoV-2 вызывает изменения плаценты, которые в основном характеризуются гипоперфузией и воспалением
These placenta changes do not seem associated with changes in fetal growth and hemodynamics	Эти изменения плаценты, по-видимому, не ассоциированы с изменениями роста плода и гемодинамики
Women experiencing SARS-CoV-2 infection should be reassured of the low risk of adverse perinatal outcome	Беременным женщинам с SARS-CoV-2 инфекцией необходимо дать информацию о низком риске неблагоприятных перинатальных исходов
An intensive fetal surveillance should be considered when other pregnancy complications are present in addition to COVID 19 infection	При наличии других осложнений беременности следует рассмотреть возможность интенсивного наблюдения за плодом

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection started and spread from the end of 2019 and up to now is still a major issue of concern for Public Health, with a daily worldwide increase of new cases of infection that may require admission to hospital and or to intensive care unit, and deaths[1] [1, 2].

Pregnancy has been reported to be an independent risk factor for adverse outcomes in women with SARS-CoV-2 infection, especially if other co-morbidities, such as diabetes or pre-eclampsia co-exist. The peculiar changes occurring in the cardiorespiratory system during pregnancy may be partially responsible for the increased burden of maternal morbidities observed in these women when compared to the non-pregnant general population [3–5].

SARS-CoV-2 infection has been reported to potentially affect the placenta. There is an increasing number of reports showing a high prevalence of placental related to hypoperfusion and inflammation in women with SARS-CoV-2 infection when compared to control pregnant population women [6–10]. The potential association between SARS-CoV-2 and impaired placental function is crucial because it might lead to changes in fetal growth, hemodynamic decompensation and increased risk of perinatal mortality and morbidity.

The objective of this review is to quantify the effects of SARS-CoV-2 infection on placental changes, fetal growth, and hemodynamics during pregnancy.

PLACENTAL CHANGES

The findings from our systematic review showed that a large proportion of pregnancies complicated by SARS-CoV-2 infection have placental histopathological abnormalities consistent with placental inflammation and hypoperfusion, while only about 17.4% of these pregnancies showed no placental anomalies. Sub-group analyses according to the presence of maternal symptoms or high-risk pregnancy showed similar results with the large majority of placenta from women with SARS-CoV-2 infection in pregnancy [11].

The recently reported association between SARS-CoV-2 infection in pregnancy and stillbirth questions whether the placenta can be a targeted host to viral infection. A population study from the United Kingdom, including more than 3000 pregnancies with laboratory confirmed SARS-CoV-2 infection, reported that stillbirth was significantly more common in women when compared to those without the infection (8.5 per 1000 vs 3.4 per 1000) with an adjusted odds ratio of 2.21 (95% confidence interval 1.58–3.11; $p < 0.001$) [12].

It has been shown that the COVID-19 virus enters into human cells by interacting with the angiotensin-converting-enzyme receptor and there is evidence that the concentrations of these receptors are increased in the pregnant uterus and placenta [11]. These findings have been subsequently confirmed by the increased prevalence of signs of decidual arteriopathy in the placenta of infected pregnant women, demonstrating a link between infection and impaired placental function. The potential mechanisms responsible for the higher risk of fetal death in the pregnancies may be explained on the basis of a direct effect of the virus on the placenta, inducing inflammation and necrosis or, alternatively, to a secondary effect due to placenta hypoperfusion induced by the compromised hemodynamic status of the mother. The results from this systematic review showed a high rate of maternal and fetal vascular malperfusion, associated with acute and chronic inflammatory pathology, potentially linking the observed increased risk of stillbirth with placental anomalies.

EFFECTS ON FETAL GROWTH

The Royal College of Obstetricians and Gynecologists (RCOG) recommends that pregnant women recovering

[1] Centers for Disease Control and Prevention (CDC) Data on COVID-19 during pregnancy: weekly COVID-19 pregnancy data (2021). https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/special-populations/pregnancy-data-on-covid-19.html. Accessed Aug 3rd, 2021.

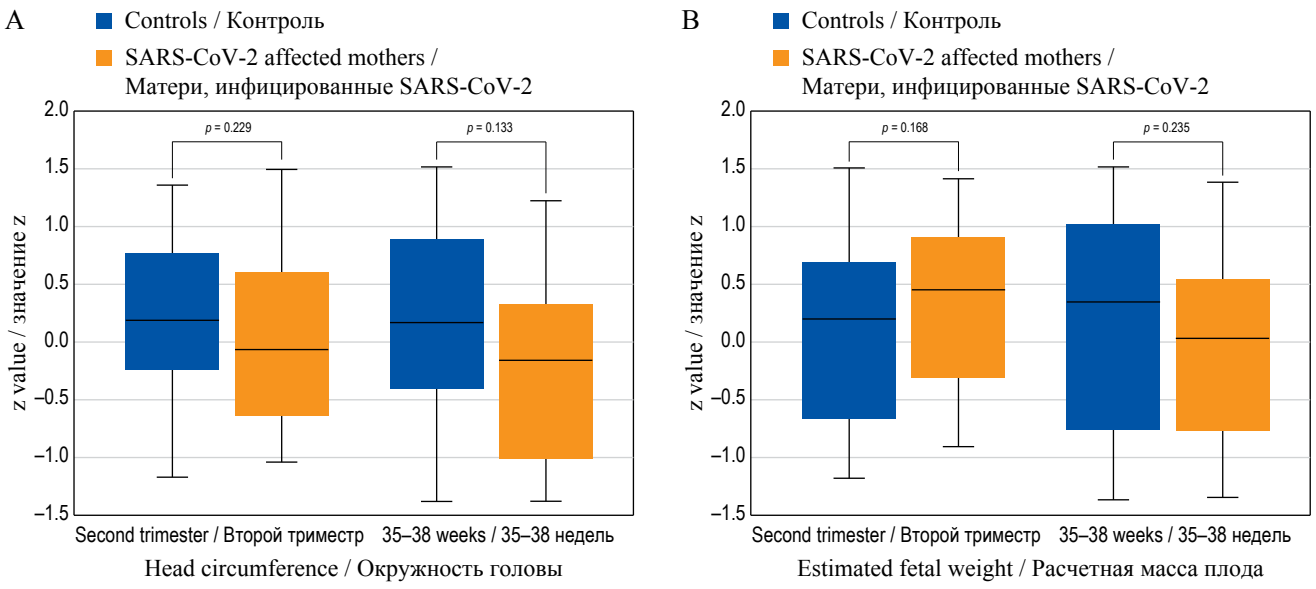

FIG. 1. Box-whisker plots of head circumference (A), and estimated fetal weight (B): z value in SARS-CoV-2 affected mothers and in control group in the second trimester, and at 35–38 weeks. (Diagram based on data from [13].)
РИС. 1. Графики окружности головы (A) и расчетной массы плода (B): значение z у матерей, инфицированных SARS-CoV-2, и в контрольной группе во втором триместре и на сроках 35–38 недель. (Диаграмма построена по данным [13].)

from SARS-CoV-2 infection should be offered a growth scan, and at least a fetal growth scan, approximately 14 days after recovering from the illness (or > 21 days from prior fetal biometry ultrasound), unless there is a pre-existing clinical reason for an earlier scan. This suggests that these pregnancies might theoretically be at a higher risk of fetal growth restriction[2].

Despite this, there is still a substantial lack of evidence on the actual role of SARS-CoV-2 infection in affecting fetal growth. We have previously reported [13] that, in women with mildly symptomatic infection, there was no difference in estimated fetal weight and fetal growth velocity in pregnancies complicated by Sars-CoV-2 infection compared to those not. However, this study was hampered by the small sample size, lack of severely symptomatic cases and heterogeneity in the gestational age at infection. Figure 1 shows the absence of effects on the z value (i.e., the number of standard deviations that the value differs from the expected mean for gestation) on head circumference and the estimated fetal weight in women experiencing SARS-CoV-2 infection.

Despite the absence of evident changes in fetal growth, it should be considered that maternal vascular hypoperfusion is potentially associated with a higher risk of impaired placental function, and stillbirth. Therefore, particular care may be necessary in pregnancies, and particularly those associated with other risk factors.

HEMODYNAMIC EFFECTS

A significant proportion of women with SARS-Cov-2 infection in pregnancy show placental histopathological abnormalities suggesting placental hypoperfusion and inflammation. Doppler ultrasonography is considered a reliable technique to evaluate hemodynamic changes in fetal and maternal circulation. We therefore tested whether SARS-CoV-2 infection can alter in maternal and fetal Dopplers [13]. There was no difference in either mean uterine artery, umbilical and middle cerebral artery pulsatility index and cerebral placental ratio z-scores [14] between pregnancies complicated and those not complicated by SARS-CoV-2 infection (Fig. 2).

We recently hypothesized that placental changes due to COVID-19 infection may lead to impaired umbilical vein blood flow (UVBF) and subsequent fetal cardiac remodeling [15]. The objective was to compare the UVBF and fetal cardiac function in pregnancies complicated and in those not complicated by COVID-19 infection in a prospective case-control study of consecutive pregnancies complicated by COVID-19 infection during the second half of pregnancy matched with unaffected women.

Measurements of UVBF normalized for fetal abdominal circumference (UVBF/AC), the atrial area (AA) and ventricular sphericity indices (SI) were assessed and compared between the two study groups. There was no difference in UVBF/AC values. Likewise, there was no difference in the left and right AA and SI suggesting that pregnancies complicated by COVID-19 infection showed no reduction in UVBF and are not at higher risk of cardiac remodeling.

CONCLUSION

In the management of pregnancies complicated by SARS-CoV-2 infection there is still debate as to whether

[2] Royal College of Obstetricians and Gynaecologists. Coronavirus (COVID-19) Infection in Pregnancy Information for healthcare professionals Version 13: Published Friday 19 February 2021 https://www.rcog.org.uk/ Accessed Aug 6th, 2021.

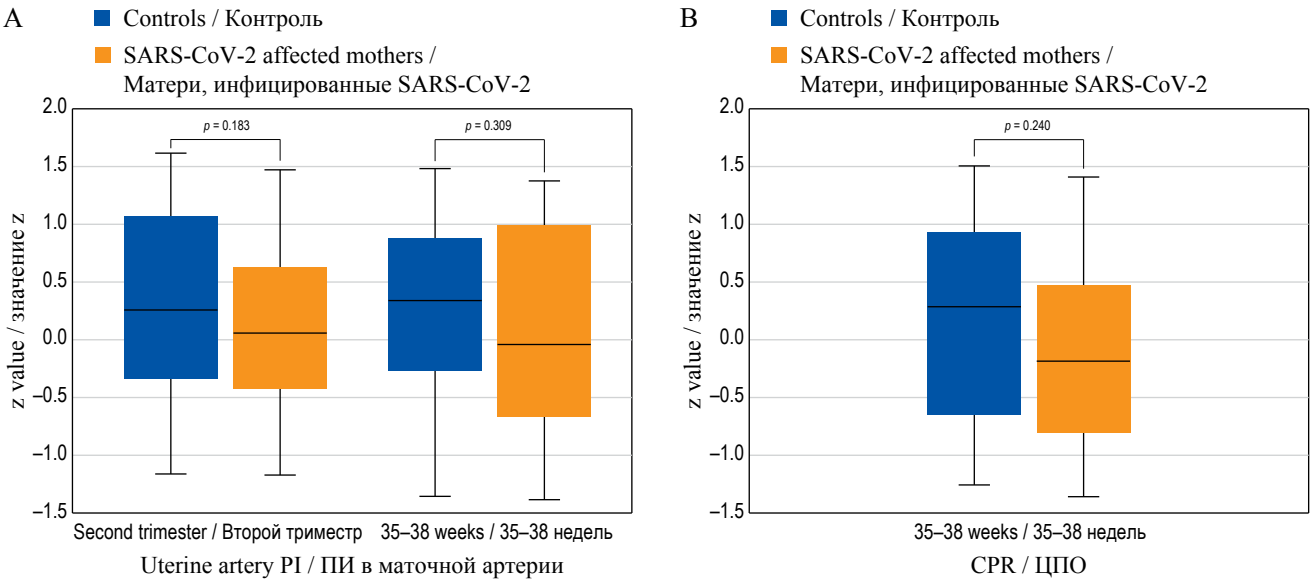

FIG. 2. Box-whisker plots of uterine artery pulsatility index (A) and cerebral placental ratio (B): z value in SARS-CoV-2 affected mothers and in control group in the second trimester and at 35–38 weeks. (Diagram based on data from [14].)
РИС. 2. Графики пульсационного индекса в маточной артерии (A) и церебро-плацентарного отношения (B): значение z у матерей, инфицированных SARS-CoV-2, и в контрольной группе во втором триместре и на сроках 35–38 недель. (Диаграмма построена по данным [14].)

Note: PI – pulsatility index. CPR – cerebral placental ratio.
Примечание: ПИ – пульсационный индекс. ЦПО – церебро-плацентарное отношение.

more frequent fetal surveillance should be applied to these women or whether they should be followed in the standard manner. The data reported in this review provide no evidence that a policy of serial ultrasonography scans to assess the velocity of fetal growth is necessary in view of the lack of association between infection and impaired fetal growth. Furthermore, in women with SARS-CoV-2 infection the risk of stillbirth has been reported to be not significantly different from that of the control pregnant population. Consequently, women with SARS-CoV-2 infection should be reassured of the low risk of experiencing adverse fetal outcomes. This concept should be emphasised since there is evidence that pregnant women with SARS-CoV-2 infection showed increased levels of anxiety due to the specific concerns about the potential negative effect of infection on their fetus and newborn [16].

Pregnancies with SARS-CoV-2 infection showed no greater risk of developing fetal growth restriction or fetal compromise. Even though sub-group analysis according to the severity of the disease and gestational age at infection could not be performed, it might be reasonable to offer women recovered from SARS-CoV-2 infection an additional growth scan in the third trimester to rule out the possibility of reduced fetal growth due to impaired placental function, and therefore, reassure the parents.

More importantly, additional ultrasound scans throughout the pregnancy might be required in women presenting with objective risk factors for growth restriction such as a previous complicated pregnancy, abnormal placental biomarkers or increased pulsatility index in the uterine arteries because in these women SARS-CoV-2 infection may worsen an already compromised placenta.

AUTHOR CONTRIBUTIONS

Giuseppe Rizzo, Ilenia Mappa and Pavjola Maquina equally contributed to the design, participated in writing the text of the manuscript and its interpretation. Victoria O. Bitsadze, Jamilya Kh. Khizroeva and Alexander D. Makatsariya 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. Риццо, И. Маппа и П. Макина в равной степени внесли свой вклад в дизайн, участвовали в написании текста рукописи и его интерпретации. В.О. Бицадзе, Д.Х. Хизроева и А.Д. Макацария разработали общую концепцию статьи и руководили ее написанием. Все авторы участвовали в обсуждении и редактировании работы. Все авторы одобрили окончательную версию публикации.

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Review / Обзор
https://doi.org/10.47093/2218-7332.2021.12.2.26-34

Lung ultrasound in COVID-19 pregnancies: a literature review

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Abstract

Lung ultrasound has been recognized as a valid imaging method for diagnosing and monitoring COVID-19 pneumonia in pregnant women. The present review aimed to summarize the main findings reported in the literature and international guidelines on the role of lung ultrasound in the care of pregnant women affected by COVID-19. A search strategy was developed and applied to PubMed, Scopus, Web of Science and EMBASE to identify previous papers reporting the utility of ultrasound in diagnosing and monitoring COVID-19 pneumonia. The search retrieved 369 articles and 23 of these were selected for analysis. The articles mainly focused on the definition of the procedure, development of training programs for obstetricians managing pregnant women with suspicion of COVID-19 and definition of scoring systems. The clinical applications of lung ultrasound in this setting have also been described. This review could encourage obstetricians to learn lung ultrasound to use during critical events like a pandemic.

Keywords: pregnancy; lung ultrasound; COVID-19; obstetrics; pulmonary; pneumonia
MeSH terms:
PREGNANCY COMPLICATIONS, INFECTIOUS – DIAGNOSIS
COVID-19 – DIAGNOSIS
COVID-19 – COMPLICATIONS
LUNG – DIAGNOSTIC IMAGING
ULTRASONOGRAPHY – METHODS
For citation: Moro F., Beneduce G., Buonsenso D., Landolfo C., Mascilini F., Scambia G., Testa A.C. Lung ultrasound in COVID-19 pregnancies: a literature review. Sechenov Medical Journal. 2021; 12(2): 26–34. https://doi.org/10.47093/2218-7332.2021.12.2.26-34

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Conflict of interests. The authors declare that there is no conflict of interest.
Financial support. The study was not sponsored (own resources).

Received: 31.07.2021
Accepted: 13.08.2021
Date of publication: 29.09.2021

УДК 618.3-06:[616.98:578.834.1]-07:616.24-073.431

Ультразвуковое исследование легких у беременных с COVID-19: обзор литературы

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Аннотация

Ультразвуковое исследование (УЗИ) легких признано обоснованным методом исследования для диагностики и мониторинга пневмонии при COVID-19 у беременных женщин. Целью настоящего обзора является обобщение основных результатов исследований, представленных в литературе и международных руководствах о роли УЗИ легких в наблюдении беременных женщин с COVID-19. Для отбора опубликованных статей об использовании УЗИ для диагностики и мониторинга пневмонии при COVID-19 была разработана стратегия поиска, которая применена в PubMed, Scopus, Web of Science и EMBASE. В результате поиска найдено 369 статей, 23 из которых выбраны для анализа. В основном статьи посвящены описанию техники проведения УЗИ легких, разработке программ обучения акушеров, ведущих наблюдение за беременными с подозрением на COVID-19, и разработке балльных систем оценки результатов исследования. Также описана клиническая применимость УЗИ легких в этих условиях. Представленный обзор может побудить акушеров изучать методику проведения и интерпретации УЗИ легких – методику, которая может использоваться в таких критических условиях, как пандемия.

Ключевые слова: беременность; ультразвуковое исследование легких; COVID-19; акушерство; легочный; пневмония

Рубрики MeSH:
БЕРЕМЕННОСТИ ОСЛОЖНЕНИЯ ИНФЕКЦИОННЫЕ – ДИАГНОСТИКА
COVID-19 – ДИАГНОСТИКА
COVID-19 – ОСЛОЖНЕНИЯ
ЛЕГКИЕ – ДИАГНОСТИЧЕСКОЕ ИЗОБРАЖЕНИЕ
УЛЬТРАСОНОГРАФИЯ – МЕТОДЫ

Для цитирования: Моро Ф., Бенедуче Дж., Буонсенсо Д., Ландольфо К., Масцилини Ф., Скамбиа Дж., Теста А.К. Ультразвуковое исследование легких у беременных с COVID-19: обзор литературы. Сеченовский вестник. 2021; 12(2): 26–34. https://doi.org/10.47093/2218-7332.2021.12.2.26-34

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Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Финансирование. Исследование не имело спонсорской поддержки (собственные ресурсы).

Поступила: 31.07.2021
Принята: 13.08.2021
Дата печати: 29.09.2021

List of abbreviation

COVID-19 – COrona VIrus Disease 2019
CT – computed tomography
LUS – lung ultrasound
SIS – sonographic interstitial syndrome

HIGHLIGHTS	КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ
Lung ultrasound could play an essential role in the management of COVID-19 pneumonia in pregnant women.	Ультразвуковое исследование легких может играть важную роль в лечении пневмонии при COVID-19 у беременных.
Pneumologists use lung ultrasound to detect pulmonary consolidations with high sensitivity and specificity.	Пульмонологи применяют ультразвуковое исследование легких для обнаружения уплотнения легочной ткани с высокой чувствительностью и специфичностью.
There are few data in the literature about the use of lung ultrasound in COVID-19 pregnant women.	В литературе мало данных об использовании ультразвукового исследования легких у беременных с COVID-19.
With the patient in a supine position, the ultrasound examiner can simply move the probe from the abdomen to the chest, scanning the anterior and lateral areas of the thorax.	В положении пациента лежа на спине специалист по ультразвуковому исследованию может просто переместить датчик с брюшной полости на грудную клетку, сканируя ее переднюю и боковую области.
Lung ultrasound is a rapid, low-cost, safe and bed-side method for pregnant women.	Ультразвуковое исследование легких – это быстрый, недорогой и безопасный метод для беременных женщин, который может использоваться у постели пациента.
Lung ultrasound is an easily learnable method that could be taught all over the world.	Ультразвуковое исследование легких – это метод легкого обучения, которому можно научить во всем мире.
To identify a standardized approach, different image scoring systems have been proposed.	Для определения стандартизированного подхода предложены различные балльные системы оценки изображений.
In developing areas like low- and middle-income countries, ultrasound may be the only useful radiological service.	В странах с низким и средним уровнем дохода ультразвуковое исследование может быть единственным полезным методом диагностики.

At the outbreak of the COrona VIrus Disease 2019 (COVID-19) pandemic, the scientific community needed to evaluate the severity of lung involvement rapidly and in a standardized way. Even if chest computed tomography (CT) is the best imaging method in the diagnosis of COVID-19 infection, lung ultrasound (LUS) was quickly recognized as a tool for the diagnosis and monitoring of pneumonia [1]. In recent years, LUS has gained a diagnostic role in acutely dyspneic patients [2].

Pneumologists use LUS to detect pulmonary consolidations with high sensitivity and specificity, to study chronic obstructive disease, asthma, pulmonary embolism and pneumothorax, with a positive predictive value ranging from 83 to 100% [3, 4]. In the pediatric fields, LUS is also used to detect typical acute respiratory distress syndrome patterns of bilateral diffuse loss of aeration, as well as several other respiratory conditions, including the commonest disorders like pneumonia and bronchiolitis [5, 6]. LUS examination represents a substitute for chest radiography or CT since it is practical, reliable, cost-effective, and safe.

Ultrasound examination can be carried out at the bedside avoiding unnecessary movement and risks for clinicians. These advantages are more important for vulnerable patients, such as pregnant women. Physiological changes during pregnancy have a significant impact on the immune system, respiratory system, cardiovascular function, and coagulation: these may have effects on COVID-19 disease progression and lung involvement.

In the literature, there are few reviews and case reports about the role of LUS in evaluating COVID-19 disease in pregnant women. The current review aims to summarize the main findings reported in both literature and international guidelines on this role.

METHODS

Review of the literature

A search strategy was developed and applied to PubMed, Scopus, Web of Science and EMBASE to identify previous studies reporting LUS as a tool for diagnosis of pregnant women with COVID-19. We used the following words for selection “covid” and “pregnancy” and “lung ultrasound”, “lung ultrasound” and “pregnancy”, “lung ultrasound” and “pregnant women”.

RESULTS

The search retrieved 369 articles, a selection from abstracts and full texts, yielded 23 publications. We found one prospective study, one retrospective study, three reviews, two case series, five case reports, nine letters, and one guideline. We divided the selected papers into three main subgroups: definition of the procedure, training program, score systems and clinical applications.

Definition of the procedure

Many authors described how to perform LUS in different settings (i.e. obstetrics, emergency, paediatrics). For example, at Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy, a practical approach has been proposed for obstetricians and gynaecologists to manage pregnant women during the COVID-19 pandemic. Obstetricians and gynaecologists represent a category of clinicians who use ultrasound during their routine practice, and it would be easy for them to extend the examination to the lungs. Therefore, LUS can be considered as an ‘extension’ of the obstetric abdominal ultrasound evaluation. Both linear and convex probes can be used, but linear ones are better for evaluating details of the pleural line and subpleural

space due to their high frequencies and resolution. With the patient in a supine position, the ultrasound examiner can simply move the probe from the abdomen to the chest, scanning the anterior and lateral areas of the thorax [6].

The examination of the lung should include the whole pulmonary area, from basal to upper zones of the thorax. Four vertical lines (right mid-axillary line, right parasternal line, left parasternal line, left mid-axillary line) can be followed to perform a systematic examination. The next step is to scan the posterior paravertebral surface of the thorax with the patient in a sitting or lateral position [7].

M. Yassa et al. also described how to perform the LUS on pregnant women: for each patient fourteen areas (3 posterior, 2 lateral, and 2 anterior) were scanned for at least 10 seconds [8].

The exam was performed in supine, right-sided and left-sided positions. Where applicable, scanning from the intercostal space is preferred.

G. Soldati et al. proposed the same standard sequence of evaluations of fourteen areas (3 posterior, 2 lateral, and 2 anterior), using landmarks on chest anatomic lines [9].

For a patient able to maintain the sitting position the sequence includes: right basal on the paravertebral line above the curtain sign; right middle on the paravertebral line at the inferior angle of the shoulder blade; right upper on the paravertebral line at the spine of the shoulder blade; left basal on the paravertebral line above the curtain sign; left middle on the paravertebral line at the inferior angle of the shoulder blade; left upper on the paravertebral line at the spine of the shoulder blade; right basal on the midaxillary line below the internipple line; right upper on the midaxillary line above the internipple line; left basal on the midaxillary line below the internipple line; left upper on the midaxillary line above the internipple line; right basal on the midclavicular line below the internipple line; right upper on the midclavicular line above the internipple line; left basal on the midclavicular line below the internipple line; and left upper on the midclavicular line above the internipple line.

Development of training program. One single experience

To date, only one standardized training experience has been reported. a research team in Rome, Italy, developed a specific single day training program to provide gynaecologists and obstetricians, already skilled in ultrasound examination, with the theoretical background for the recognition of the main LUS patterns. The program design was presented to the COVID-19 Research Ethical Committee who evaluated and approved the project [10]. The teachers were two pneumologists and one paediatrician skilled in LUS. They all have more than 10 years of experience in LUS practice, research and teaching. The teaching program is available on a dedicated website[1].

The training program consisted of three phases: a phase 1 of 15 minutes pre-test, including 10 ultrasound video clips submitted to 11 learners. Each video showed normal (pattern = 1) or typical pathological (patterns = 2–6) lung ultrasound patterns; phase 2 consisted of a theoretical lesson on LUS findings both normal and pathological; phase 3 consisted of 15 minutes post-test to verify the knowledge acquired. During post-test analysis, the ultrasound patterns were divided into two groups (pattern 1 = normal and patterns 2–6 = abnormal), 8/10 participants correctly discriminated normal from pathological patterns in all cases, 2/10 in 90% of cases, and 1/10 in 80% of cases. This experience is a useful preliminary step for teaching theoretical LUS skills [10].

During the COVID-19 emergency the University Centre for International Solidarity of Università Cattolica, in Rome, (CESI) and Fondazione Policlinico Universitario A. Gemelli, IRCCS, in Rome, promoted a distance learning project called “Fast lung ultrasound teaching program beyond Europe during COVID-19 pandemic: Africa’s reality”. Ten doctors, together with physicists and engineers from the University of Trento, prepared a training protocol to support doctors and health care workers in Africa in the use of LUS. The ultrasound equipment, available in many African hospitals to monitor pregnant women, can be converted into a COVID-19 detector[2].

Interpretation of the images. Score systems

To identify a standardized approach, different image scoring systems have been proposed. In a normal lung, at ultrasound examination, the pleura appears as a highly hyperechoic horizontal line (pleural line) and hyperechoic, parallel, horizontal artifacts (‘A-lines’) are visible [11]. A-lines indicate normal inflated peripheral lungs if combined with the ‘sliding’ of the pleural line [12].

In the cases of viral pneumonia, interstitial lung disease, pulmonary fibrosis, pulmonary oedema, lung deflation, or lung contusion, different shapes and lengths of vertical artifacts, called B-lines, are generated [13]. Another typical pattern of viral pneumonia is the “white lung”, where white is visible, and the pleural line is irregular and thickened. The distribution of the white area can be monofocal or multifocal, patchy, surrounded by spared areas and with no gravitational distribution. This pattern is common during the early stage of COVID-19 when no A or B-lines are visible [12]. If any consolidation (hypoechoic areas) appears, there is loss of lung aeration and a transition of these areas towards acoustic properties like soft tissue. Below these irregular hypoechoic areas, vertical artifacts are generally found [14].

A standardized approach to optimize the use of LUS in patients with COVID-19 has been proposed. In the setting of COVID-19, wireless transducers and tablets represent the most appropriate ultrasound

[1] https://covid19.disi.unitn.it/iclusdb/login

[2] https://centridiateneo.unicatt.it/solidarieta-internazionale-studi-e-ricerche-fast-lung-ultrasound-teaching-program

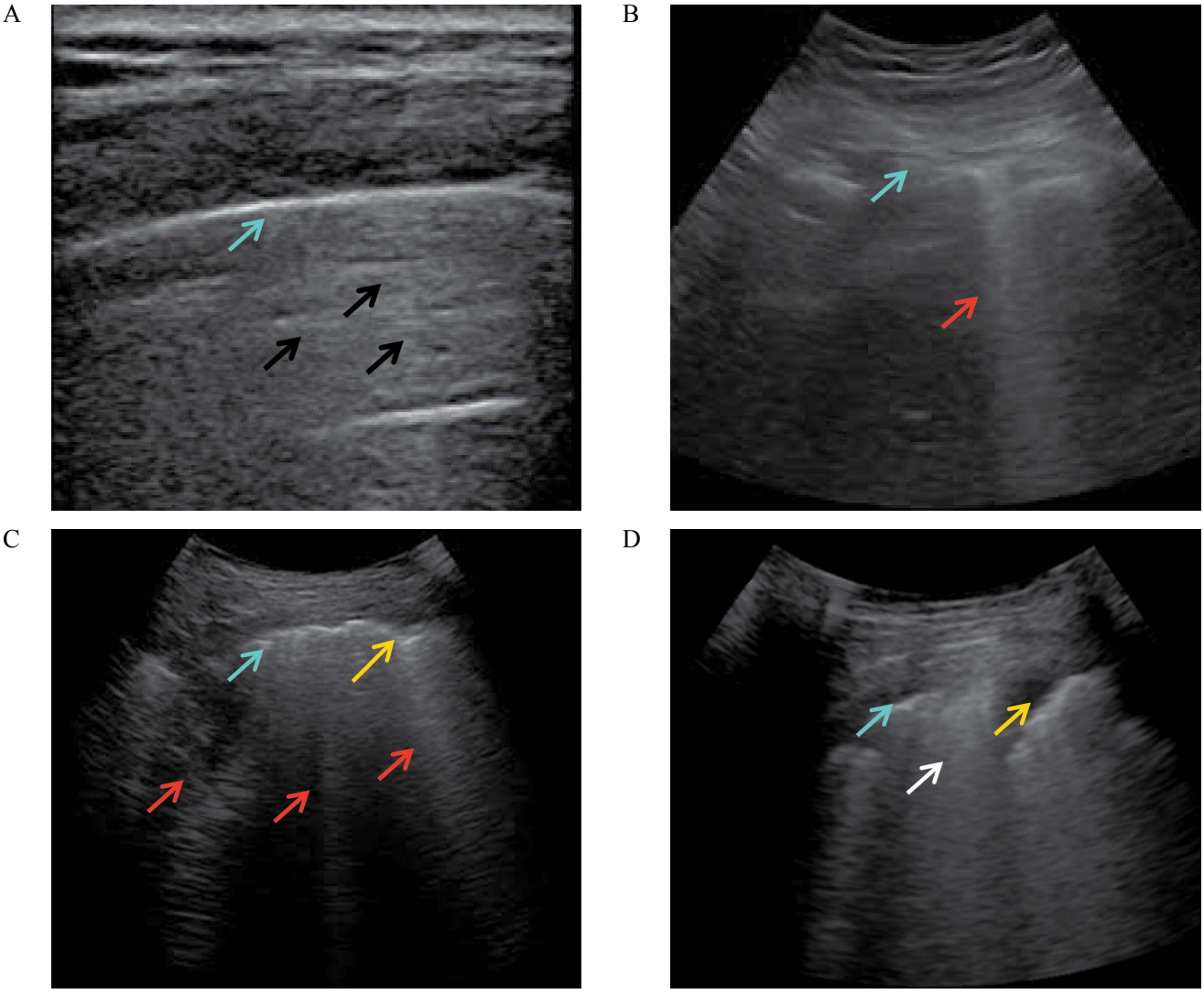

FIG. Lung ultrasound imaging and the scoring system (A–D). (A) Score 0: a regular pleural line (blue arrow) and A-lines (black arrows); (B) Score 1: an irregular pleural line (blue arrow) and an isolated B-line (red arrow); (C) Score 2: an irregular pleural line (blue arrow), multiple B-lines (red arrows), and consolidations (yellow arrow); (D) Score 3: an irregular pleural line (blue arrow), large area of white lung (white arrow) and subpleural consolidations (yellow arrow).

РИС. Ультразвуковое исследование легких и балльная система (A–D). (A) 0 баллов: непрерывная плевральная линия (голубая стрелка) и А-линии (черные стрелки); (B) 1 балл: прерывистая плевральная линия (синяя стрелка) и единичная В-линия (красная стрелка); (C) 2 балла: прерывистая плевральная линия (синяя стрелка), множество В-линий (красные стрелки) и консолидация (желтая стрелка); (D) 3 балла: прерывистая плевральная линия (синяя стрелка), большой участок белого легкого (белая стрелка) и субплевральная консолидация (желтая стрелка).

equipment because they can be wrapped in single-use plastic covers, reducing the risk of contamination. If these devices are unavailable, portable ones can be used, although maximum care for sterilization is necessary. The authors realized an easy score system to evaluate lung involvement of COVID-19 patients: for each of the 14 areas evaluated the ultrasound examiner writes the highest score obtained [9]:

- Score 0: If you can see a continuous and regular pleural line with horizontal artifacts, referred to as A-lines (Figure A).
- Score 1: If the pleural line is indented and there are visible vertical areas (linked to local changes) referred to as B-lines. Vertical artifacts, resulting in the so-called sonographic interstitial syndrome (SIS) are indicative of a hyperdense pre-consolidated lung state (Figure B).
- Score 2: If the pleural line is broken and there are consolidated areas due to the loss of aeration, with associated areas of white, and with air still present; this condition is called white lung (Figure C).
- Score 3: If there are largely extended parts of white lung (Figure D) [9].

In recent years, other authors have proposed similar scores. According to Q. Deng et al each zone was scored as follows: a normal lung pattern with normal

lung sliding with A-lines or fewer than two isolated B-lines was scored as 0; the presence of 3 or more well-spaced B-lines presented in a single intercostal space was scored as 1; the presence of crowded B-lines (more than 50% range in a view) with or without consolidation limited to the subpleural space was scored as 2; the presence of confluent B-lines (approaching 100% range in a view) or a tissue pattern with dynamic air bronchogram, defined as lung consolidation, was scored as 3 [15]. The most severe ultrasound finding can be considered representative of the entire zone. In the same way, L. Ji et al. used the following scores in line with previous studies: score 0: well-spaced B-lines < 3; score 1: well-spaced B-lines ≥ 3; score 2: multiple coalescent B-lines; score 3: lung consolidation [16]. The pleural line was quantitatively scored as follows: score 0: normal; score 1: irregular pleural line; score 2: blurred pleural line [16] (table).

According to available evidence, suspicious ultrasound findings, even not specific, for COVID-19 pneumonia are the presence of alterations of pleural line and SIS with patchy, bilateral distribution in symptomatic patients; white lung with patchy, bilateral distribution associated or not with small subpleural consolidations. SIS with homogeneous bilateral distribution without spared areas and regular, bright, vertical artifacts with gravitational distribution, is suggestive of cardiogenic pulmonary oedema. Moreover, large, unilateral consolidations, as well as large pleural effusions, are patterns usually not compatible with COVID-19 pneumonia [17, 18].

Clinical applications

No prospective studies have been published describing the impact of LUS in the management of pregnant women affected by COVID-19. In a small series of patients, LUS has been used in this management. The authors assessed lung involvement of four pregnant patients on admission to hospital and during disease. The advantage of LUS is that it is radiation-free, and therefore can be used as the first diagnostic step before chest X-ray or CT scan [19].

Last year, M.G. Porpora et al. evaluated the role of LUS in the decision-making process, studying the correlation between LUS score and CT score carried out after delivery, which strengthens the reliability of LUS as an alternative diagnostic method to CT in pregnant women [20]. Chest CT was performed after delivery in patients with high LUS score or persistent respiratory symptoms and showed a score up to 4 with an involvement <10% in five cases, a score between 5 and 8 with involvement of 10–25% in three women, while in the patients with a LUS score of 23, CT showed 60–70% lung involvement with a score of 16. Even if the CT findings were more precise than LUS in defining pulmonary impairment, these results suggest a positive correlation between LUS and CT [20].

Table. **Score systems for evaluating ultrasound of the lungs**

Таблица. **Системы балльной оценки ультразвукового исследования легких**

Author, ref. / Автор, № источника	N° of areas explored / Количество исследуемых зон	Score 0 / 0 баллов	Score 1 / 1 балл	Score 2 / 2 балла	Score 3 / 3 балла	Total score / Сумма баллов
Soldati G. [9]	12	Continuous and regular pleural line with horizontal artifacts, referred to as A-lines / Непрерывная и ровная плевральная линия с горизонтальными артефактами – А-линиями	Pleural line is indented with vertical areas referred to as B-lines / Плевральная линия прерывается вертикально расположенными В-линиями	Pleural line is broken with consolidated areas, and areas of white / Плевральная линия прерывается консолидированными участками и участками белого цвета	Largely extended part of white lung / Значительная часть легкого представлена белым цветом	36
Deng Q. [21]	8	Normal lung sliding with A-lines or <2 isolated B-lines / Нормальное движение легких с А-линиями или <2 изолированными В-линиями	≥3 well- spaced B-lines presented in a single intercostal space / ≥3 четко разделенных В-линий, представленных в одном межреберье	Crowded B-lines (> 50% range in a view) with or without consolidation limited to the subpleural space / Множество В-линий (>50% в зоне исследования) с консолидацией, ограниченной субплевральным пространством или без нее	Confluent B-lines or a tissue pattern with dynamic air bronchogram, defined as lung consolidation / Сливающиеся В-линии или рисунок ткани с динамической воздушной бронхограммой – консолидация	24
Ji L. [16]	12	Well-spaced B-lines <3 / Четко отделенные друг от друга В-линии <3	Well-spaced B-lines ≥3 / Четко отделенные друг от друга В-линии ≥3	Multiple coalescent B-lines / Несколько сливающихся В-линий	Lung consolidation / Консолидация	36

CT and LUS images of 39 pregnant patients were retrospectively collected and compared by Q. Deng et al. [21]. Quantitative LUS scores correlated highly with chest CT findings and could effectively evaluate lung lesions in pregnant women. Pearson correlation analysis revealed high correlation on admission (r = 0.793, $p < 0.01$) between LUS and CT. Some authors proposed an approach to manage admission of pregnant women to hospital when COVID-19 is suspected (fever, dry cough, and dyspnea) [22].

Patients should undergo LUS to define subsequent diagnostic/therapeutic steps. In most cases, pregnant women have a normal LUS pattern, while, in advanced pregnancy, a mild, posterior, bilateral, basal, homogenous SIS could be detectable for volume reduction of inferior lung lobes.

If LUS findings show patchy, bilateral SIS with or without small patchy, bilateral, subpleural consolidations, patients must isolate until the results of microbiological tests (both nasal/throat swab and rapid serologic tests). If LUS does not indicate COVID-19 lung involvement, arterial blood gases (ABG) must be evaluated. When PaO2/FiO2 ratio is < 400, patients should be isolated, until microbiological test results (both nasal/throat swab and rapid serologic tests) are obtained. a positive result of these tests requires hospitalization and isolation. If microbiological tests are both negative, a chest X-ray is necessary. In case of both LUS with no signs of COVID-19 pneumonia and normal gas exchanges with PaO2/FiO2 > 400, pregnant women undergo maternal and fetal monitoring until microbiological test results. If both microbiological tests are negative, the patient should be isolated at home, maintaining contact either in the case of worsening symptoms requiring hospital admission or in the case of mild and stable symptoms, waiting for the results of the second Sars-CoV-2 swab test.

In the literature there are other non-systematic pictorial reviews whose authors postulated that LUS should be the first-choice imaging method in pregnant women suspected of having COVID-19 infection [8]. A. Giannini et al. used LUS to evaluate the progression of disease in pregnant women affected by COVID-19 pneumonia and they suggested the additional use of LUS in routine lung ultrasonography aimed at tracking the evolution of the disease [23]. In contrast, M. Sperandeo et al. considered the use of LUS in COVID-19 pneumonia restricted and confusing, because of the nonspecific findings that may be misleading [24].

DISCUSSION

LUS has been demonstrated to be an accurate imaging method to detect pulmonary and pleural conditions and evaluate lung involvement and its evolution in pregnant women affected by COVID-19. During pregnancy, there is a need for rapid, low-cost, safe, and bed-side assessment of the maternal lung in patients with suspected coronavirus disease. Chest CT may be reserved for cases where LUS is insufficient to answer the clinical question. In addition, LUS results are immediately available to the clinician, allowing decisions about the initial empirical treatment and it is also an easily learnable tool.

In developing areas like low- and middle-income countries, ultrasound may be the only useful radiological service. During a pandemic, training is also fundamental for the sustainability, quality, and reliability of this method. LUS can be learned by a variety of medical professionals, not just radiologists, to permit rapid assessment and treatment in a variety of settings [25].

This narrative review demonstrated that LUS can be used in a standardized way to detect lung involvement. Little data is available in the literature on this topic. We recognize that our study is a narrative review and not a systematic review or metaanalysis, lacking important requirements for quality control such as risk of bias, quality assessment, and statistical analysis. However, our goal was to provide an overview of the literature on the new role of LUS in diagnosing pregnant women affected by COVID-19 and to offer a strategy to manage these patients.

CONCLUSION

The pandemic has taught us to reallocate our resources, and to make the best use of our talents. LUS is a promising imaging tool that can be used for pregnant women with suspected COVID-19 pneumonia following an initial fetal assessment. This review can encourage obstetricians to learn LUS to be used during pandemics and to provide more knowledge in this field. Other prospective studies should be explored.

AUTHOR CONTRIBUTIONS

Francesca Moro is responsible for study design, drafting of the manuscript and data interpretations. Giuliana Beneduce researched and analyzed the literature on the review topic and drafted the manuscript. Danilo Buonsenso, Chiara Landolfo, and Floriana Mascilini, participated in writing the text of the manuscript and its interpretation. Giovanni Scambia and Antonia Carla Testa are responsible for the critical revision of the manuscript and for the important intellectual content and 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

Ф. Моро разработала дизайн исследования, участвовала в интерпретации данных и написании рукописи. Дж. Бенедуче проводила поиск и анализ источников по теме обзора и подготовила текст рукописи к публикации. Д. Буонсенсо, К. Ландольфо и Ф. Масцилини участвовали в интерпретации данных и написании текста. Дж. Скамбиа и А.К. Теста разработали общую концепцию статьи, руководили ее написанием и несут ответственность за критический пересмотр рукописи на предмет основного интеллектуального содержания. Все авторы участвовали в обсуждении и редактировании работы. Все авторы одобрили окончательную версию публикации.

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Review / Обзор
https://doi.org/10.47093/2218-7332.2021.12.2.35-43

Effects of COVID-19 on maternal anxiety and depressive disease: a literature review

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Abstract

The coronavirus SARS-CoV-2 (COVID-19) infection is a public health emergency of international concern. Pandemics pose a challenge to psychological resilience and can have an adverse impact on mental health. The impact of the ensuing social isolation and loneliness imposed by quarantine along with the worries about the risks of the infection and its economic fallout would appear likely to affect the mental health of the population. It has been reported that women are more likely to experience anxiety and depression symptoms during COVID-19 than men. COVID-19 pandemic had a profound impact on the level of anxiety and depression of pregnant women according to their basal level and pregnancy characteristics. Antenatal mental disorders may be a risk factor for maternal mental health problems such as an increased likelihood of postnatal depression and adverse obstetric and developmental outcomes. Effective coping strategies are associated with better psychological wellbeing during the COVID-19 pandemic, including reduced anxiety and depression. The increased risk of mental disorders due to COVID-19 requires policies to be developed to address prenatal and postpartum care to promote maternal–child wellbeing outcomes.

Keywords: COVID-19; SARS-CoV-2; pregnancy; maternal anxiety; maternal depression; maternal mental health; maternal mental disorders
MeSH terms:
PREGNANCY COMPLICATIONS, INFECTIOUS – DIAGNOSIS
PREGNANCY COMPLICATIONS, INFECTIOUS – PSYCHOLOGY
COVID-19 – DIAGNOSIS
COVID-19 – COMPLICATIONS
ANXIETY – PREVENTION & CONTROL
ANXIETY – ETIOLOGY
DEPRESSION, POSTPARTUM – PREVENTION & CONTROL
DEPRESSION, POSTPARTUM – ETIOLOGY
For citation: Mappa I., Distefano F. A., Rizzo G. Effects of COVID-19 on maternal anxiety and depressive disease: a literature review. Sechenov Medical Journal. 2021; 12(2): 35–43. https://doi.org/10.47093/2218-7332.2021.12.2.35-43

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Conflict of interests. The authors declare that there is no conflict of interest.
Financial support. The study was not sponsored (own resources).

Received: 01.08.2021
Accepted: 13.08.2021
Date of publication: 29.09.2021

УДК 618.3-06:[616.98:578.834.1]}-06:616.895-084

Влияние COVID-19 на тревожность и депрессивные расстройства у матерей: обзор литературы

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Аннотация

Инфекция, вызванная коронавирусом SARS-CoV-2 (COVID-19), представляет собой чрезвычайную ситуацию в области общественного здравоохранения, имеющую международное значение. Пандемии бросают вызов психологической устойчивости и могут отрицательно сказаться на психическом здоровье. Последствия социальной изоляции и одиночества, вызванные карантином, наряду с опасениями по поводу риска инфекции и ее экономических последствий, вероятно, оказывают влияние на психическое здоровье населения. Сообщается, что женщины чаще, чем мужчины, испытывают симптомы тревоги и депрессии во время пандемии COVID-19. Выраженный эффект пандемия COVID-19 оказала на уровень тревожности и депрессии беременных женщин в зависимости от их базальной тревожности и особенностей течения беременности. Дородовые психические расстройства могут быть фактором риска возникновения проблем с психическим здоровьем матери, таких как повышенная вероятность послеродовой депрессии и акушерских осложнений, а также нарушений развития плода. Эффективные стратегии преодоления связаны с улучшением психологического благополучия во время пандемии COVID-19, включая снижение тревожности и депрессии. Повышенный риск психических расстройств из-за COVID-19 требует разработки программ для обеспечения дородового и послеродового ухода с целью улучшения благополучия матери и ребенка.

Ключевые слова: COVID-19; SARS-CoV-2; беременность; тревожность у матерей; депрессия у матерей; психическое здоровье матери; психическое расстройство матери

Рубрики MeSH:
БЕРЕМЕННОСТИ ОСЛОЖНЕНИЯ ИНФЕКЦИОННЫЕ – ДИАГНОСТИКА
БЕРЕМЕННОСТИ ОСЛОЖНЕНИЯ ИНФЕКЦИОННЫЕ – ПСИХОЛОГИЯ
COVID-19 – ДИАГНОСТИКА
COVID-19 – ОСЛОЖНЕНИЯ
ТРЕВОГИ СОСТОЯНИЕ – ПРОФИЛАКТИКА И КОНТРОЛЬ
ТРЕВОГИ СОСТОЯНИЕ – ЭТИОЛОГИЯ
ДЕПРЕССИЯ ПОСЛЕРОДОВАЯ – ПРОФИЛАКТИКА И КОНТРОЛЬ
ДЕПРЕССИЯ ПОСЛЕРОДОВАЯ – ЭТИОЛОГИЯ

Для цитирования: Маппа И., Дистефано Ф.А., Риццо Д. Влияние COVID-19 на тревожность и депрессивные расстройства у матерей: обзор литературы. Сеченовский вестник. 2021; 12(2): 35–43. https://doi.org/10.47093/2218-7332.2021.12.2.35-43

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Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Финансирование. Исследование не имело спонсорской поддержки (собственные ресурсы).

Поступила: 01.08.2021
Принята: 13.08.2021
Дата печати: 29.09.2021

List of abbreviation

CI – confidence interval
COVID-19 – COrona VIrus Disease 2019
IQR – interquartile range
SARS – severe acute respiratory syndrome
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
STAI – state-trait anxiety inventory

HIGHLIGHTS	КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ
The COVID-19 outbreak has a major psychological impact on pregnant women	Вспышка COVID-19 оказывает серьезное психологическое воздействие на беременных женщин
SARS-CoV-2 induces anxiety in 77% of pregnant women	Инфекция SARS-CoV-2 вызывает повышенную тревожность у 77% беременных женщин
Anxiety is more frequent in pregnancies with a higher level of education	Повышенная тревожность чаще возникает у беременных с более высоким уровнем образования
Anxiety is more frequent in women unfavorable to COVID-19 vaccination	Повышенная тревожность чаще встречается у женщин, не желающих вакцинироваться от COVID-19
One in three pregnant women experience depression during the pandemic	Каждая третья беременная женщина испытывает депрессию во время пандемии

The coronavirus 2019-nCoV (COrona VIrus Disease 2019, COVID-19) infection is a public health emergency of international concern in which a coronavirus has been identified as the cause of an outbreak of respiratory illness. It was first detected in Wuhan, China [1], spreading rapidly to other countries worldwide [2, 3]. On the 11th of March 2020, the World Health Organization (WHO) announced the new Coronavirus pandemic outbreak according to the WHO official website of the World Health Organization[1].

As the pandemic unfolded, public concern about the risks to life and health, inadequate healthcare services, and economic consequences grew. As part of the infection containment strategies, governments around the world imposed unprecedented restrictions on movement, work, and travel for all people in a city, region, or country and these resulted in compromising personal and social liberty. Lockdown and mandatory quarantine are the most commonly used and effective measures that are implemented by governments to contain the transmission of respiratory infectious diseases, including the COVID-19 disease. Within a month of the declaration of the pandemic, 90% of the world's population was subject to some kind of restriction of movement to limit infection spread[2].

In non-pandemic times, quarantine and social isolation are well-known risk factors for psychological and psychiatric disturbances in the general population [4, 5], particularly for children and adolescents, the elderly, and those from lower socio-economic groups, females, as well as people with pre-existing mental health conditions [6].

The impact of the ensuing social isolation and loneliness along with the worries about the risks of the infection and its economic fallout would appear likely to have influenced the mental health of the population. Indeed, increased mental health morbidity including anxiety and depression, in a similar context, has been reported previously with fears arising from the severe acute respiratory syndrome (SARS) outbreak [7].

Pandemics pose a challenge to psychological resilience and can have an adverse impact on mental health [8, 9], and it has been reported that women are more likely to experience anxiety and depressive symptoms during COVID-19 than men [10].

Prenatal and postnatal mental disorders induce disturbances in the physical activity, nutrition, and sleep of pregnant and postpartum women; these disturbances subsequently affect the mood of pregnant and postpartum women and the development of fetuses and children [11].

Anxiety is a common response to any stressful situation. Pregnant women, who experience mental and physical changes during gestation, are more likely to be at risk. Prevalence of anxiety disorder during pregnancy, in developed and developing countries, are 10 and 25%, respectively [12]. Anxiety symptoms during pregnancy have emerged as an independent risk factor for adverse obstetric and developmental outcomes [13]. Antenatal mental disorders may be a risk factor for maternal mental health problems such as an increased likelihood of postnatal depression [14], impaired bonding [15], and physical disorders, such as preeclampsia [16], gestational hypertension [17], and gestational diabetes [18], preterm birth [19, 13] miscarriage [20, 21], low infant birth

[1] https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 Accessed July 27th, 2021.
[2] https://www.pewresearch.org/fact-tank/2020/04/01/more-than-nine-in-ten-people-worldwide-live-in-countries-with-travel-restrictions-amid-covid-19/ Accessed July 27th, 2021.

weight and fetal growth restriction [22, 23], and lower Apgar scores at birth [24].

ANXIETY

A systematic review and meta-analysis that involved 102 studies with 221,974 antenatal and postnatal women from 34 countries found that the pooled prevalence of anxiety among these participants was 15.2% [25].

We hypothesized that the COVID-19 pandemic may have had a profound impact on the level of anxiety of pregnant women that may be different according to their basal level of anxiety and pregnancy characteristics. We therefore performed a study in the days of maximum spread of COVID 19 in Italy (March 9 – March 10, 2020) close to the day of the total lockdown sanctioned by the Italian government (March 9, 2020) [26].

We sent each woman a questionnaire structured into two sections: section A concentrated on 18 items of maternal characteristics and on testing women's knowledge and concerns about perinatal complications; section B containing 40 items validated the scale for scoring anxiety: state-trait anxiety inventory (STAI).

The STAI is a 40-items scale, which uses a 4-point Likert scale for each item. The scale can be used to measure both trait anxiety (how dispositionally anxious a person is across time and situations) and state anxiety (how anxious a person is feeling at a particular moment) as it consists of two separate sub-scales (STAI-T and STAI-S, respectively) each containing 20 items. An abnormal value of STAI was considered when ≥ 40 [27].

The questionnaire was returned filled by 178 women (89%) within 48 h from the shipment and these women were considered for the study.

A fear that COVID-19 could induce fetal structural anomalies was present in 83 women (46.6%; 95% confidence interval [CI] 39.4–53.9), fetal growth restriction in 116 (65.2%; 95% CI 57.9–71.7) and preterm birth in 91 (51.1%; 95th CI 43.8–58.3). The median trait anxiety score (STAI-T) was 37 (interquartile range [IQR] 20–43) and 68 women (38.2%; 95% CI 31.3–45.5) showed a STAI-T score ≥ 40. The psychological impact of COVID-19 outbreaks, measured using the S scale, revealed increased values of STAI-S scale (median 49 IQR 40–56) with a significant increase of 12 points in median values when compared to T scale ($p \leq 0.0001$). Therefore, there is significantly higher prevalence (77.0%; 95% CI 70.1–82.5) of women that surpass the cut-off score of 40 for state of anxiety when STAI-S was applied ($p \leq 0.0001$).

A higher educational status was associated with a significant increase in the prevalence of STAI-S values ≥ 40 ($p = 0.004$) but not of STAI-T values ($p = 0.158$). No significant differences in maternal age, gestational age, parity and employment status were evidenced between women with normal (< 40) or abnormal (≥ 40) STAI-T and S scores.

We also performed a study to estimate the propensity of Italian pregnant women receiving the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine during their gestation evaluating the maternal anxiety induced by the vaccination campaign [28, 29]. A questionnaire was sent on the 27th of December, the first day of the initiation of SARS-CoV-2 vaccinations in Italy, to 200 women, which was returned filled by 161 women (80.5%). The questionnaire was structured in two sections: part-A aimed to acquire 16 items on maternal characteristics and to test women's knowledge and concerns about vaccines; part-B containing the STAI.

To evaluate the maternal concern about perinatal complications induced by SARS-CoV-2 vaccination, the following fears were also considered: fetal structural anomalies, growth anomalies, and preterm birth. A fear that the SARS-CoV-2 vaccination could induce fetal structural anomalies was present in 78 women (48.4%; 95% CI 40.5–56.4), fetal growth restriction in 54 (33.5%; 95% CI 26.3–41.4), and preterm birth in 51 (31.6%; 95% CI 24.5–39.4). The median trait anxiety score (STAI-T) was 36 (IQR 31–45), and 61 women (37.9%; 95% CI 30.3–45.8) showed an STAI-T score ≥ 40. The psychological impact of the SARS-CoV-2 vaccine revealed a significant increase in STAI-S values (median 47 IQR 36–56; $p < 0.0001$) with a positive linear correlation between STAI-T and S scores (Pearson $r = 0.48$; $p < 0.0001$).

Of the women considered, 136 (84.5%) felt vaccination was a breakthrough for resolving the pandemic (vaccine positive), while the remaining 25 (25.5%) considered the vaccine not useful (vaccine negative). Among the former group, 72 women (52.9%) were favorable to receiving the vaccine during pregnancy, a percentage significantly higher ($p = 0.022$) when compared to the vaccine negative group (28%). Further women negative to the SARS-CoV-2 vaccine showed a lower educational level ($p < 0.0001$) and a higher prevalence of unemployment ($p = 0.016$) when compared to the vaccine positive group. No differences were found among the other parameters tested. No differences were found between groups in basal anxiety as expressed by the presence of STAI-T values ≥ 40 (positive 37.5%; 95 CI 29.3–46.2 vs. negative 40%; 95 CI 21.1–61.3: $p = 0.813$), while there was a significant higher prevalence of abnormal STAI-S vales (negative 88.0%; 95% CI 68.7–97.4 vs. positive 63.4%; 95% CI 55.3–72.0) in the group of women negative to a vaccine ($p = 0.018$).

Our data also showed a high level of trait anxiety with abnormal values in 40% of the pregnant women. We evidenced a subgroup of pregnant women who were negative to vaccination that differs from the positive group for the educational and employment status. Of interest was the fact that, in this group despite the trait anxiety being like the group positive to the vaccine,

the anxiety induced by the potential use of the vaccine resulted significantly higher.

According to a systematic review and meta-analysis of 23 studies, with 20,569 participants (16,797 pregnant women and 3,772 postpartum women), during the COVID-19 pandemic and with 3,677 pregnant women before the COVID-19 pandemic, the prevalence rates of anxiety, among pregnant women during the COVID-19 pandemic was 37% (95% CI 25–49%), with a pooled relative risk of anxiety 1.65 (95% CI: 1.25–2.19) relative to those in pregnant women in the same locations during and before the COVID-19 pandemic. Through subgroup analysis, multigravida women had higher prevalence rates of anxiety than primigravida women, and the prevalence of anxiety decreased during pregnancy [30].

Moreover, H. Yan et al. [30] found several results that contradicted the results of some previous studies and highlighted a higher prevalence of anxiety among pregnant women with a university degree or above than amongst pregnant women with low educational levels [31] and a higher prevalence of anxiety among employed pregnant women than among unemployed pregnant women [32]. High educational level indicates high knowledgeability, which may amplify the adverse effects of mental health during the COVID-19 pandemic, and employed pregnant women may face difficult situations such the loss of jobs and earnings due to the COVID-19 pandemic. These difficult situations have a negative influence on mental health.

DEPRESSION

A systematic review and meta-analysis including 101 studies discovered that the pooled prevalence of depression among women in the perinatal period was 11.9% [33]. The prevalence of postpartum depression was evaluated at 12.0% in a systematic review and meta-analysis that encompassed 58 studies with 37,294 postnatal women [34].

Y. Wu et al. showed that the prevalence of depressive symptoms amongst pregnant women increased from 26% to 34.2% at the beginning of the pandemic, with the contemporary increase in anxiety symptoms [35].

In a meta-analysis of eight studies on 7,750 women, despite depression through the Edinburgh Postnatal Depression Scale score increasing among women in pregnancy and the perinatal period during the COVID-19 pandemic, it did not reach a statistically significant level compared to the non-pandemic period [36].

A systematic review and meta-analysis conducted with 20,569 participants showed that the prevalence rates of depression among pregnant women during the COVID-19 pandemic was 31% (95% CI 20–42%). The prevalence of postpartum depression during the COVID-19 pandemic was 22% (95% CI 15–29%). The pooled relative risk of depression in pregnant women was 1.08 (95% CI: 0.80–1.46), relative to those in pregnant women in the same locations during and before the COVID-19 pandemic [30].

Multigravida women had higher prevalence rates of depression than primigravida women during the COVID-19 pandemic, and the prevalence of depression followed a U pattern. Specifically, the prevalence of depression was high in the first and third trimesters and was the lowest in the second trimester.

There is evidence for higher depression scores among pregnant women with longer years of education [37].

U. Akgor et al. [38] observed higher levels of depression in older pregnant women, and especially aged 35 and over. This data is consistent with other studies [39, 40]. However, some studies reported the opposite and concluded that younger pregnant women were more prone to depression during the COVID pandemic [35, 41].

In a survey of 257 participants, the youngest age group (18–25 years) accounts for the largest proportion (10/22, 45.5 %) of people with both depression and anxiety, and this was consistent among depressed people (17/50, 34.0%) [42].

Low socioeconomic status was confirmed as one of several risk factors for depressive symptoms [35].

Pregnant women who worry about their finances were more likely to have higher clinical depression scores (adjusted Odds Ratio: 2.23; 95 % CI = 1.80, 2.77, $p < 0.001$, adjusted model R2 = 0.06). Pregnant women with both high and low incomes were at risk of developing depression if they experienced COVID-19-associated financial stress [43].

Women who reported poor social support and social isolation also have higher depressive symptoms at all-time points. Loneliness was also associated with a greater increase in depressive symptoms although not anxiety symptoms, from prior to during the pandemic [44].

According to psychodynamics, depression is a general state of inhibition, where actions are undermined, however, anxiety is a general state of alertness that motivates people toward to actions. The presence of a factor that affects the whole world, such as a pandemic process, where both being in the hospital and not being able to come to the hospital cause concerns, can explain the positive correlation between these two different and almost opposite feelings.

COPING STRATEGY

Coping is a primary component of an individual's response to stressful events [45]. Several studies have shown that effective coping strategies are associated with better psychological wellbeing during the COVID-19 pandemic, including reduced anxiety and depression [46–50].

The assessment of coping is crucial to understanding the ways in which psychological stress and stressful life events can be buffered partly from being able to control the stressor or relying on support from others (i.e., social support) [45, 51–53]. Sociocultural contexts must be considered in the study of perinatal stress and coping [54]. Coping strategy can also vary depending on race, ethnicity, and socioeconomic status [55, 56].

Research has distinguished between three major types of coping: (1) problem-focused coping, which involves actions aimed at addressing the problem (e.g., planning, seeking instrumental support), (2) emotion-focused coping, which aims to manage negative emotions (e.g., seeking emotional support, cognitive restructuring), and (3) dysfunctional coping, which involves maladaptive strategies that are not helpful in dealing with the stressor (e.g., denial, behavioral disengagement) [57].

J.E. Khoury et al. [58] found that particular COVID-19-related experiences were differentially associated with distinct forms of coping. Specifically, individuals who saw the COVID-19 pandemic as having a greater negative impact engaged in more dysfunctional coping and less emotion-focused coping. In contrast, greater financial difficulties and social isolation were associated with more dysfunctional coping and problem-focused coping, but not emotion-focused coping [58].

IMPLICATIONS FOR CLINICAL PRACTICE

Increased risk of mental disorders due to COVID-19 requires that policies are developed to address prenatal and postpartum care to promote maternal–child wellbeing outcomes. It is important for health professional working with childbearing women to identify any stressors during prenatal care and provide resources to obtain psychological support to manage and/or reduce their impact [59].

Health professional should increase awareness about the transmission of the disease, explaining the precautions that can be taken for prenatal, postpartum, breastfeeding, and neonatal care; and asking patients for psychiatry consultation to increase the psychiatric well-being of pregnant women [38].

H. Bayrampour et al. [60] showed that the higher the risk perception level of pregnant women, the more severe the anxiety level. Therefore, medical teams should make the risk perception level of pregnant women precise by spreading accurate information to them to reduce their anxiety levels. Social support could regulate anxiety directly and negatively or affect it indirectly through risk perception. Thus, during the epidemic, health professionals can take two measures to maintain the mental health of pregnant woman and reduce anxiety: actively mobilize the social support system for pregnant women and reduce the risk perception level of pregnant women in relation COVID-19 [61].

Social support includes subjective and objective support, and its utilization. Previous studies have shown that a high level of social support plays a protective role against anxiety during pregnancy [62, 63]. Social support can play a direct protective role in individuals' negative emotions, by helping with behavior and providing emotional support. In addition, social support can also improve the assessment and coping skills of individuals, reduce the perceived severity of stressful events, and thus play an indirect protective role in mental health [64].

Recent meta-analyses of randomized controlled trials have shown that pre- and post-natal exercise can reduce depression and depressive symptoms [65].

During the COVID-19 pandemic pregnant women have shown a significant decrease in engagement in physical activity compared to their lifestyle habits during pregnancy from before the confinement. Physical exercise has been demonstrated to be effective in the treatment of mild to moderate depression in the non-pregnant population [66]. Physical activity is a relatively costless intervention that can improve maternal wellbeing [67, 68].

Moreover, a self-care daily program can be based on the NEST-S principles: Nutrition, Exercise, Sleep, Time for Self, Support can be helpful[3].

HealthCare providers must have clear evidence-informed guidelines in place for either treating individuals or referring to other professionals, and, in the event of referral, ensuring that patients are assisted [69].

CONCLUSION

There is a greater psychological impact, as well as higher rates of anxiety and depression, in pregnant women during the COVID-19 outbreak, and this highlights the need for intervention. Meeting the mental health needs of pregnant and postpartum women during the COVID-19 pandemic is a growing concern and a serious issue because a large body of robust evidence suggests that prenatal and postnatal mental disorders induce severe adverse influences on mothers, fetuses, and children.

The identification of high-risk women is crucial in order to be able to suggest the possible implementation of early psychological interventions and prevent some pregnancy stress-related complications.

[3] https://www.heretohelp.bc.ca/sites/default/files/coping-with-depression-during-pregnancy-and-following-birth-a-cognitive-behaviour-therapy-based-self-management-guide-for-women.pdf Accessed July 27th, 2021.

AUTHOR CONTRIBUTIONS

Ilenia Mappa developed the general concept of the article, researched and analyzed the literature on the review topic. Flavia Adalgisa Distefano, 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

И. Маппа разработала общую концепцию статьи, исследовала и проанализировала литературу по теме обзора. Ф.А. Дистефано участвовала 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 статьи.

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Review / Обзор
https://doi.org/10.47093/2218-7332.2021.12.2.44-54

Treatment of COVID-19 disease in pregnancy and breastfeeding

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Abstract

The physiological and anatomical clinical characteristics of pregnant women make them susceptible to complications caused by coronavirus disease (COVID-19). Increased coagulation and risk of thromboembolic phenomena are common during pregnancy; they are further enhanced when associated with a thrombogenic pathology such as in COVID-19. The treatment of COVID-19 is controversial and limited, even for non-pregnant patients. During pregnancy, the options are even more restricted due to the teratogenicity of some drugs and anatomical and physiological difficulties, especially in advanced pregnancy in patients with respiratory failure. Therefore, the focus of treatment for pregnant patients should be centered on isolation, monitoring fetal and maternal vital signs, uterine activity, and general maternal–fetal well-being. The prescription of drugs and management orientation should be based on gestational age and maternal clinical conditions. The optimal type of delivery is guided by obstetric indications and COVID-19 disease severity. Breastfeeding should be encouraged with the use of masks and hand hygiene. The treatment of pregnant women with COVID-19 brings important peculiarities that should be considered in order to make better decisions for preserving the health of the mother and fetus.

Keywords: antivirals; corticosteroids; anticoagulation; enoxaparin; oxygen supplementation; labor management
MeSH terms:
PREGNANCY COMPLICATIONS, INFECTIOUS – DIAGNOSIS
PREGNANCY COMPLICATIONS, INFECTIOUS – THERAPY
COVID-19 – DIAGNOSIS
COVID-19 – COMPLICATIONS
COVID-19 – THERAPY
For citation: Rios S.S., Resende C.N., Peixoto A.B., Araujo Júnior E. Treatment of COVID-19 disease in pregnancy and breastfeeding. Sechenov Medical Journal. 2021; 12(2): 44–54. https://doi.org/10.47093/2218-7332.2021.12.2.44-54

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Conflict of interests. The authors declare that there is no conflict of interests.
Financial support. The study was not sponsored (own resources).

Received: 28.03.2021
Accepted: 19.05.2021
Date of publication: 29.09.2021

УДК 618.2-06:[616.98:578.834.1]-085.2

Лечение COVID-19 при беременности и кормлении грудью

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Аннотация

Анатомо-физиологические особенности беременных женщин делают их особенно восприимчивыми к осложнениям коронавирусного заболевания (COVID-19). Повышенная свертываемость крови с риском тромбоэмболических осложнений характерна в период беременности, она еще более усиливается, когда ассоциирована с протромботическими состояниями, такими как COVID-19. Лечение COVID-19 является предметом дискуссии даже для небеременных. Во время беременности медикаментозная терапия ограничена из-за тератогенности некоторых препаратов и анатомо-физиологических особенностей, особенно в поздние сроки беременности у пациенток с дыхательной недостаточностью. Поэтому основное внимание в лечении беременных женщин должно уделяться изоляции, мониторингу жизненно важных показателей плода и матери, сократительной активности матки. Назначение препаратов и общие принципы ведения должны основываться на гестационном возрасте и клиническом состоянии матери. Выбор способа родоразрешения определяется акушерскими показаниями и тяжестью течения COVID-19. Следует сохранять грудное вскармливание при условии использования масок и средств для гигиены рук. Лечение беременных женщин с COVID-19 имеет важные особенности, которые необходимо учитывать для принятия лучшего решения с целью сохранения здоровья матери и плода.

Ключевые слова: противовирусные средства; кортикостероиды; антикоагуляция; эноксапарин; кислородная поддержка; ведение родов

Рубрики MeSH:
БЕРЕМЕННОСТИ ОСЛОЖНЕНИЯ ИНФЕКЦИОННЫЕ – ДИАГНОСТИКА
БЕРЕМЕННОСТИ ОСЛОЖНЕНИЯ ИНФЕКЦИОННЫЕ – ТЕРАПИЯ
COVID-19 – ДИАГНОСТИКА
COVID-19 – ОСЛОЖНЕНИЯ
COVID-19 – ТЕРАПИЯ

Для цитирования: Риос С.С., Резенде Ц.Н., Пейшото А.В., Араухо-мл. Э. Лечение COVID-19 при беременности и кормлении грудью. Сеченовский вестник. 2021; 12(2): 44–54. https://doi.org/10.47093/2218-7332.2021.12.2.44-54

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Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Финансирование. Исследование не имело спонсорской поддержки (собственные ресурсы).

Поступила: 28.03.2021
Принята: 19.05.2021
Дата печати: 29.09.2021

List of abbreviations

COVID-19 – COrona VIrus Disease 2019
ACE2 – angiotensin-converting enzyme 2
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

HIGHLIGHTS	КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ
Due to the serious complications of COVID-19 during pregnancy, greater attention is needed in the care and treatment of the patients during the pandemic period.	В связи с возможностью развития серьезных осложнений COVID-19 во время беременности необходимо уделять большое внимание уходу и лечению пациентов в период пандемии.
Most pregnant women will have few symptoms; however, some of them may have more serious complications than non-pregnant women.	У большинства беременных женщин отмечено легкое течение заболевания; однако у некоторых из них осложнения COVID-19 могут быть более выраженными, чем у небеременных женщин.
Factors associated with adverse outcomes such as the following: diabetes mellitus, obesity, maternal age >40 years and third trimester of the gestational period.	К факторам риска неблагоприятного прогноза относятся: сахарный диабет, ожирение, возраст матери > 40 лет и третий триместр беременности.
The clinical findings of pregnant women with COVID-19 are similar to non-pregnant women. These symptoms are the following: fever, fatigue, myalgia, and dyspnea.	Клинические симптомы COVID-19 аналогичны таковым у небеременных женщин: лихорадка, слабость, миалгия и одышка.
Obstetric complications occur due to cytokine storm and the most frequent are: spontaneous miscarriage, fetal growth restriction, preterm birth, premature rupture of membrane, and stillbirth.	Акушерские осложнения могут развиться как результат цитокинового шторма и наиболее частыми являются: самопроизвольный выкидыш, задержка роста плода, преждевременные роды, преждевременный разрыв плодных оболочек и мертворождение.
Treatment of pregnant women with COVID-19 is focused on early isolation, infection control, oxygen therapy, mechanical ventilation (when indicated), fluid control, laboratory tests, maternal and fetal monitoring, adequate delivery management, and multidisciplinary care team.	Лечение беременных женщин с COVID-19 проводится мультидисциплинарной бригадой и включает: изоляцию на ранних стадиях заболевания, контроль инфекции, кислородную поддержку, механическую вентиляцию (по показаниям), контроль водного баланса, лабораторный контроль, мониторинг состояния матери и плода.
Treatment of the viral phase is controversial in the literature.	Данные о возможности использования противовирусных средств противоречивы.
Corticosteroids for cytokine storm control as well as the use of low molecular weight heparin (enoxaparin) to decrease thromboembolism complications are indicated.	Показано использование кортикостероидов для контроля цитокинового шторма, а также низкомолекулярного гепарина (эноксапарина) для снижения риска развития тромбоэмболических осложнений.
Breastfeeding protects both mother and child and should be encouraged.	Грудное вскармливание защищает как мать, так и ребенка, и его следует сохранять.
Knowledge of the available treatment to pregnant women can help achieve better perinatal outcomes.	Информированность о возможности адекватной терапии для беременных может помочь в достижении лучших перинатальных исходов.

The clinical and physiological characteristics of pregnant women make them vulnerable to coronavirus disease (COVID-19) and its complications [1]. It is believed that pregnant women have no greater risk of developing complications due to COVID-19; however, studies have shown an increased risk of morbidity, respiratory failure, mechanical ventilation, and death among these patients [2–4]. As an increase in maternal deaths has been reported, greater assistance for the maternal–fetal dyad during the COVID-19 pandemic is required [1]. It is known that the typical changes in pregnancy can lead to a greater impact on the respiratory, immune, coagulation and cardiac systems [5]. Thus, pregnant women and newborns require greater attention and care in the prevention, diagnosis, and treatment of COVID-19 [1], and it is important to understand the treatment of pregnant women to reduce the impact of COVID-19 on this population [1]. This review aimed to bridge the knowledge gap on the association between COVID-19 and pregnancy as the available information on it is limited [6].

COVID-19 infects the respiratory mucosa and other target cells by adhering to angiotensin-converting enzyme 2 (ACE2), which is the functional receptor for severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2) and severe acute respiratory syndrome coronavirus [1]. This triggers a major immune response, leading to a cytokine storm secondary to viral aggression and causes complications in pregnancy. The ACE2 are present particularly in the lung and intestinal cells; hence, these are the most commonly affected organs [1]. In the lungs the binding of SARS-CoV-2 to ACE2 causes alveolar damage and pulmonary consolidation. The presence of ACE2 receptors in the vascular endothelium explains the placental changes found in pregnant women affected by SARS-CoV-2 [1].

The disease caused by SARS-CoV-2 is divided into the following stages: the initial phase called viremia, the phase 2 or pulmonary phase, and lastly, the critical or severe phase, in which the disease progresses, especially in those who present with comorbidities [7]. The clinical picture can vary from asymptomatic to mild, and critical [3]. The disease is considered mild when it does not reach the lungs, and severe when patients develop pneumonia and dyspnea, respiratory rate greater than or equal to 30 breaths per minute, saturation less than or equal to 93%, and pulmonary infiltrate >50% in 24–48 hours. Critical patients include those with respiratory failure, septic shock and/or dysfunction, and multiple organ failure [8].

Most pregnant women will have a light course and will recover without the need to anticipate delivery [3]. One study found that 86% of pregnant women had mild illness, 9.3% had severe illness, and 4.7% had critical illness. These percentages are similar to those described for not-pregnant adults with COVID-19 (80% mild, 15% severe, and 5% critical) [9]. However, studies have shown that the risks of worsening and progressing to the critical stages of the disease, as well as the need for mechanical ventilation, are greater among pregnant women than among the general population [3]. The factors associated with a worse prognosis and increased mortality among pregnant women are diabetes, obesity, and age >40 years. Those in the third trimester also have a higher risk of admission to intensive care units, as well as being mechanically ventilated [3]. According to a study by Berry M. et al. [10], pregnant women with advanced pregnancies are at a greater risk. In two reports describing 18 pregnancies with COVID-19, all were infected in the third trimester [11]. Altered tests with leukopenia, anemia, C-protein reaction, procalcitonin, and ferritin were also related to the severity of the disease in pregnant women [10].

The clinical findings among pregnant women with COVID-19 were similar to those of non-pregnant adults, and the main symptoms were cough, fatigue, myalgia, shortness of breath, and fever [1, 3]. Obstetric complications can occur due to a cytokine storm, and the most frequently observed complications are spontaneous abortion, delayed intrauterine growth, fetal distress, premature birth, premature rupture of membranes, and stillbirth [1, 3].

Chest X-ray with abdominal protection and blood tests such as those for complete blood count, ultra-sensitive C-protein reaction, urea, creatinine, electrolytes (including Mg, K, Na, Ca), liver profile, and coagulation should be performed if the patient present with increased respiratory rate, decreased oxygen saturation (SO_2; <96%), increased body temperature; and dyspnea. Fetal auscultation obstetric ultrasound and cardiotocography should also be performed depending on the gestational age of the pregnancy to assess fetal well-being [12].

TREATMENT

The basic guidelines for the treatment of COVID-19 in pregnancy are focused on early isolation, infection control, empirical antibiotic therapy, oxygen therapy, mechanical ventilation in case of respiratory failure, prevention of excess fluids, laboratory tests, fetal and uterine monitoring, individualized approach to the type of delivery, and multidisciplinary care [11].

The first step to be performed by the attending physician is to classify the stage of the patient. The initial phase, also called viremia, usually covers the first 5 days of the disease, in which the patient has mild symptoms of upper airway infection such as sore throat, cough, anosmia, and ageusia with or without fever and myalgia [12, 13]. Most patients will have complete resolution of symptoms at this stage, but some progress to the moderate or pulmonary stage of the disease. In phase 2 or pulmonary disease, which usually occurs from the sixth day of illness onwards, with symptoms such as easy fatigability, cough, chest pain, and myalgia. If nothing is done during the initial and 2nd phase, the patient may progress to a severe condition in which she has organ failure, a drop in SO_2 < 90% sepsis, and septic shock [12].

TREATMENT OF THE INITIAL STAGE OF THE DISEASE

The treatment of patients with COVID-19 in phase 1 is controversial [14]. Many recommend that the patient stays at home and goes to the hospital only during desaturation [15]. However, there is a growing understanding that drugs should be used early to reduce viral aggression in order to reduce the damage caused by the virus, to decrease blood hypercoagulation, and to reduce the immune response [13, 16].

The most commonly used drugs to decrease viral load in non-pregnant women are hydroxychloroquine, ivermectin, and nitazoxanide. These drugs can be prescribed alone or in conjunction with antibiotics such as azithromycin and doxycycline [13], which have proven efficacy against the virus and immunomodulatory effects [17]. Additionally, vitamins and minerals have also been prescribed. The treatment of pregnant women is similar to that of non-pregnant women, and only the use of teratogenic drugs must be avoided.

Chloroquine and hydroxychloroquine have been used for more than 70 years, making it a safe drug

for use in SARS-CoV-2 [18]. The antiviral role of hydroxychloroquine includes blocking sialic acid receptors and restricting of pH mediated spike protein cleavage that occurs at the binding site of the angiotensin-converting enzyme ACE2 [19]. It also acts by altering the acidic environment in lysosomes and endosomes, thus preventing endocytosis and inhibiting cytokine storms [20]. Although studies show a lack of efficacy of hydroxychloroquine in advanced stages of COVID-19 [21], according to Risch, the use of hydroxychloroquine in critically ill patients with COVID-19 is not relevant; it has the greatest benefit in the early stages of the disease. Moreover, there are five studies including two controlled trials that have demonstrated significant efficacy in outpatient treatment of patients with COVID-19 [22]. Considering the systemic crisis caused by COVID-19, the use of hydroxychloroquine seems to be a good choice [20].

Hydroxychloroquine can also be considered a safer therapeutic option for pregnant women infected with SARS-CoV-2 [6, 23]. The clinical data for the use of chloroquine and hydroxychloroquine in pregnant women are reassuring [24]. According to the guidelines, the treatment should be initiated in the viral phase of the disease; therefore, in the first 5 days of symptoms, hydroxychloroquine 400 mg every 12 hours should be given on the first day and then reduced to 200 mg every 12 h for another 4 days [12]. Fesler M.C. and Stricker R.B. [4] have suggested that hydroxychloroquine can even be used prophylactically in the pre-exposure of pregnant women to COVID-19 as this drug is safe during pregnancy and could prevent gestational complications and serious evolution in this high-risk population. The proposal would be to offer hydroxychloroquine 400 mg weekly to this population [4]. However, the half-life of hydroxychloroquine is long, and the exposure period is 210 days for chloroquine and 420 days for hydroxychloroquine after interruption of intake. The most reported side effects are related to the eyes and heart rate. Pregnant women, especially those who are at risk of prematurity, should be monitored through ultrasound. After childbirth, ophthalmological monitoring of the child should be performed [24]. According to Fesler M.C. and Stricker R.B. [4], hydroxychloroquine should be prescribed during pregnancy with the aim of saving lives, in view of the expansion of the pandemic. However, use during this period must be decided based on a risk-benefit analysis [24].

Ivermectin for use in the viral phase has been shown to be safe and effective in treating adults with COVID-19 [25]. In fact, studies have shown a positive interaction between ivermectin and protein viral targets that lead to SARS-CoV-2. Ivermectin decreases mortality and reduces symptoms in patients with COVID-19, so it can be a potential drug for the treatment of COVID-19 [26]. The combination of ivermectin and doxycycline also appears to be effective against COVID-19 [26]. However, ivermectin, when used at doses 10-100 times higher than the current doses used for humans, has been shown to be teratogenic in mammals, although among women who inadvertently used ivermectin, no neonatal deaths, prematurity, or maternal morbidity, although it is still unclear whether it increases the risk of miscarriage and stillbirth. The literature is scarce on the safety of using this drug in pregnancy, so the data are insufficient to ensure that ivermectin is safe during pregnancy [27].

Nitazoxanide has antiviral action against SARS-CoV-2 *in vitro* and suppresses cytokine production by controlling the cytokine storm. In addition, nitazoxanide has bronchodilator action on the airways [28]. Nitazoxanide is a category B drug used during pregnancy [29].

Regarding the use of antibiotics with antiviral actions against COVID-19, Azithromycin and doxycycline are frequently prescribed. Azithromycin has potential in the treatment of patients with COVID-19 due to its antiviral and immunomodulatory actions [30]. It can be used as monotherapy [30], or in combination with nitazoxanide or hydroxychloroquine. The use of both has been shown to be effective if used in the early phase of COVID-19 [31]. In addition, studies have shown that the combination of hydroxychloroquine and azithromycin may be a treatment option in pregnancy, and cases that have been successfully treated in the literature have been described [32]. The use of azithromycin in pregnancy is not associated with an increase in malformation above the 1–3% baseline; therefore, macrolides are generally safe during pregnancy [33]. In a national multicenter study, the use of macrolides during pregnancy was not associated with an increased risk of major congenital malformations [34]. The authors recommend the use of azithromycin 500 mg for 5 days for non-pregnant women [13]; for pregnant women, the guidance is to use azithromycin 500 mg on the initial day followed by 250 mg for another 4 days [32]. Breastfed newborns exposed to macrolides showed mild symptoms such as diarrhea, insomnia, loss of appetite, drowsiness, and skin rash [35].

Doxycycline is considered a class D drug in the Food and Drug Administration (FDA) pregnancy classification along with tetracyclines, although a systematic review has shown the safety profile of this drug in children and pregnant women, in contrast to tetracyclines [36]. Wormser G.P. et al. believes [37] that doxycycline can be prescribed selectively for pregnant women and nursing mothers in situations where other safer antibiotics are not available, but it should be used for the shortest possible period.

Regarding vitamins and minerals, zinc deficiency is also strongly associated with conditions that increase the risk of developing severe COVID-19, which includes aging, immune deficiency, obesity, diabetes, and atherosclerosis. Therefore, zinc may have a protective effect as a preventive and adjuvant therapy against COVID-19 by reducing inflammation, improving mucociliary clearance, preventing lung injury, and modulating antiviral and antibacterial immunity [38]. Zinc sulfate 15 mg daily from

the 16th week of gestation until delivery [39]. Vitamin D studies have shown that low levels of vitamin D increase the risk of hospitalization and deaths caused by COVID-19 [40]. Moreover, the use of vitamin D in pregnancy can reduce the risk of pre-eclampsia, postpartum hemorrhage, gestational diabetes, and low birth weight [41]. The use of high doses of vitamin D (2,400 UI day) during pregnancy was associated with a lower risk of tooth enamel damage [42]. Popular belief suggests that vitamin C reduces the viral effects of the common cold; however, studies regarding this are controversial [43]; and with respect to COVID-19, the authors suggest the use of intravenous vitamin C to reduce the risk of virus-induced cytokine storms [44].

If pregnant woman develop fever, it should be controlled twice a day, and if necessary, paracetamol 500–1000 mg every 6–8 hours should be used [12]. Women with mild symptoms can be isolated at home and followed over the phone [12].

TREATMENT OF PULMONARY PHASE AND CRITICALLY ILL PREGNANT PATIENTS

For moderate and severe cases, the treatment of the disease does not differ between pregnant and non-pregnant patients. It is performed with the use of corticosteroids, anticoagulants, antibiotics, and other drugs depending on the conditions of the patient and the severity of the disease. Oxygen is prescribed in cases of oxygen desaturation, and if clinical conditions deteriorate, and the patient progresses to the critical stage of the disease, mechanical ventilation is indicated. According to López M. et al. hospitalization for critical patients is recommended to monitor vital signs such as blood pressure, respiratory rate, SO_2, and heart rate [12]. The main drugs used in this phase are corticosteroids, anticoagulants, antibiotics, and antivirals.

Corticosteroids are the central and most important drugs in the treatment of patients with COVID-19. At the beginning of the pandemic, there were many questions regarding the use of corticosteroids in patients with COVID-19. It was believed that the use of corticosteroids could be associated with an increase in disease morbidity and mortality as it was thought to delay the elimination of the virus [12, 45]. However, a recovery study published in June 2020 broke this paradigm and showed that corticosteroids helped in the treatment of patients on mechanical ventilation or using oxygen [46]. Moreover, other studies have confirmed that in decompensated patients, in desaturation and with a high inflammatory response, corticosteroid use increases survival [47]. Recent research has shown that, although the recommendations of some studies indicate the use of corticosteroids only for patients in advanced stages of the disease, good results have been obtained with the use of corticosteroids starting at the beginning of phase 2 or from day 6 of symptoms at home without the need for hospitalization [13, 48].

Corticosteroids can be used routinely in pregnant COVID-19 patients for both fetal lung maturation and treatment of COVID-19 [49]. According to López, the use of corticosteroids for fetal lung maturation in patients with COVID-19 is safe [12]. These findings reiterate the safety of corticosteroids for use in pregnant women with COVID-19 and acute respiratory distress syndrome [50]. Corticosteroids are also indicated in pregnant women who require oxygen therapy or mechanical ventilation. Thus, pregnant women with $SO_2 < 94\%$ can use corticosteroids for both fetal lung maturation and treatment of COVID-19; in the first 2 days 4 doses of dexamethasone should be administered and then methylprednisolone should be administered for the remaining 8 days of treatment [51]. Methylprednisolone has been used in critically ill patients and has shown benefits in the management of COVID-19 [12], although dexamethasone is the only drug approved for use in pregnant women who require mechanical ventilation or supplemental oxygen [49]. Data on dexamethasone in breastfed babies are limited, and methylprednisolone may be indicated [51].

The gestation period is known to be prothrombotic. Pregnant women are in a state of hypercoagulability with an elevated risk for deep venous thrombosis and the development of disseminated intravascular coagulation, which could be life threatening [52]. Considering that COVID-19 is also a thrombotic disease, pregnant women affected by SARS-CoV-2 infection have a higher risk of developing thromboembolic complications [53]. Severe disease can complicate with disseminated intravascular coagulation, which is associated with high mortality. It is a systematic response to the virus and tissues damaged by the infection [54].

Studies have shown that thromboembolism as well as coagulopathies are in fact increased in pregnant women affected by COVID-19; therefore, these women must be closely monitored for the greatest risk of deterioration [53]. Moreover, the risk of thromboembolism and pulmonary embolism in pregnant women is highest during the puerperium period; hence, prophylaxis should be considered in this period [55]. The D-dimer, a blood clotting marker, grows progressively during pregnancy and peaks on the first day after delivery. Then, it decreases rapidly within 3 days, then linearly thereafter, and becomes normal in the 42 days after delivery. If the D-dimer does not start to decrease in the postpartum period, thromboembolism is considered [52]. The D-dimer is a product of fibrin degradation which is elevated during thrombus formation and breakdown in COVID-19 patients. As COVID-19 infection progresses, the clotting system is activated to stop viral infection [54]. The levels of D-dimer and fibrinogen increase during all pregnancies, with 98% of patients showing an increase at 36 weeks [56].

Although COVID-19 is a thromboembolic disease, there is no consensus on the use of anticoagulants, whether therapeutic or prophylactic, as well as

the precise moment when they should be used. Studies have found that the use of prophylactic anticoagulation reduces mortality in patients with COVID-19 when admitted to the hospital [57]. With regard to COVID-19 and gestation, the prophylactic use of enoxaparin has been oriented especially to those who are at greater risk, such as obese women [58]. On the other hand, other studies have found that the therapeutic use of enoxaparin in COVID-19 has led to a 2.3-fold increase in mortality, so some studies say that anticoagulation may not be effective in this syndrome. Moreover, some authors agree that most patients who died did so due to hypoxia secondary to acute renal failure, shock, and multiple organ failure. Although thrombosis may have contributed to mortality, it did not appear to be specifically related to it [59]. Anticoagulation therapy with enoxaparin appears to have a better prognosis in critically ill patients, especially those with markedly high D-dimer levels [60].

Researchers advocating the use of anticoagulation have used enoxaparin for the treatment of hypercoagulable states in patients with COVID-19 [57]. Low-molecular-weight enoxaparin has been used for >20 years in pregnant women and is the anticoagulant of choice to be used in pregnancy in patients at risk for thrombosis [61]. The best-known indications are those for the prophylaxis of thromboembolism, prevention of abortion in thrombophilia patients, and prevention of arterial thrombosis in patients with heart valve disease. Enoxaparin does not cross the placenta; hence, it is safe for the fetus [61]. The mechanism of action of enoxaparin involves the action of anti-factor Xa in maternal blood, inhibition of tissue factor by placental trophoblasts, and anti-inflammatory action. The main side effects associated with the use of enoxaparin are localized mild allergies (2%) and increased bleeding (2%); the severity is dose dependent [61].

Assessments for detecting coagulation changes as well as the use of low-molecular-weight heparin should be considered and discussed between the attending physician and the patient [2]. The prophylactic dose of subcutaneous enoxaparin is 30–40 mg/day. The dose of subcutaneous heparin is 5,000 μL for every 8 hours [59]. Thromboprophylaxis should be performed considering the severity of the disease, the outpatient or hospital situation with associated morbidities, and contraindications to the use of anticoagulants [49]. The use of low molecular weight enoxaparin prophylactic doses during hospitalization for up to 2 weeks after independence of D-dimer levels is recommended [12]. There is no contraindication for aspirin use during pregnancy [49].

Remdesivir decreases viral load by inhibiting SARS-CoV-2 replication in patients affected by the virus, reducing inflammation, mild symptoms, and lung damage associated with COVID-19. It has been used in a compassionate manner [62]. Remdesivir inhibits COVID-19 *in vitro* [18]. Remdesivir, lopinavir, and ritonavir can be used during pregnancy and lactation, but data on non-pregnant women showed no benefit [49]. However, according to López M. et al. [12], tocilizumab, a monoclonal antibody with inhibitory action on IL-6, or remdesivir (an RNA polymerase inhibitor with *in vitro* action against SARS-CoV-2) have shown good efficacy in critically ill patients, but there is concern about the use of these drugs during pregnancy. The role of immunomodulatory monoclonal antibodies (tocilizumab), immunomodulators (tacrolimus), interferon, inhaled nitric oxide and convalescent plasma during pregnancy and lactation require further evaluation [49].

In case of a suspicion of alveolar infiltrate or increase in procalcitonin (indicates bacterial superinfection), intravenous ceftriaxone 1–2 g/day and teicoplanin 400 mg every 12 hours in 3 doses followed by 400 mg/day should be given [12]. Even for drugs that are not contraindicated during pregnancy, the patient must be asked to sign the informed consent for compassionate use [12].

In pregnant women with SO_2 < 94% saturation, oxygen support with a nasal cannula of 1-6 L/min should be offered in order to achieve SO_2 between 94% and 96% [50]. If the cannula is not sufficient, switch to a Venturi mask, and if necessary, indicate a positive pressure mask [12]. Another option would be high flow with a 60 L/min nasal cannula for patients who do not improve with nasal flow, in cases where intubation would be indicated. It is similar to a conventional cannula in that it offers oxygen flow as high as 60 L/min and the air is humidified and heated. However, patients should be stable, aware, and have a normal cough reflex [50]. The identification of severe cases allows the use of O_2 support and an indication for an intensive care unit. Careful monitoring is recommended as many patients have sudden deterioration [12]. The assistance in this stage must be provided by an anesthesiologist, clinician, or intensivist, as intubation [12] may be necessary. The patient should be in prone position if possible. Pregnant women with refractory hypoxemia can be in prone position as long as physiological changes and gestational risks are considered, taking into account the pregnant physiology and anatomy [50, 63].

Mortality among non-pregnant women who require mechanical ventilation is 88%. However, Lucarelli E. et al. [64] reported three cases of pregnant women who were intubated due to respiratory failure and pneumonia due to COVID-19. After several days, they were extubated and were able to continue monitoring their pregnancies with no proven adverse effects. Pregnant patients on mechanical ventilation should use neuromuscular-blocking agents for a minimum time [49].

Obstetric management in intubated patients can be as follows: before 23–24 weeks of gestation, fetal monitoring is not recommended for pregnant women with respiratory failure caused by COVID-19, as an emergency cesarean would bring more risks to the mother than fetal benefits [50]. After this gestational age, evaluation of each case is recommended as delivery under general anesthesia presents significant risks for the mother and the health

team. At 24–28 weeks, monitoring depends on fetal weight and neonatal conditions [50]. Over 28 weeks of pregnancy the maternal-fetal monitoring must be continuous. If maternal conditions deteriorate, the delivery is indicated, probably by cesarean section [50].

In pregnant women, due to the risk of pulmonary edema from inflammation, fluids must be controlled especially in those with desaturation. If saturation deteriorates in a patient with a positive fluid balance, use of furosemide is indicated [50].

LABOR MANAGEMENT

Pregnant women should be isolated for 2 weeks or, after negative RT-PCR (reverse transcription polymerase chain reaction), taking measures to avoid lying in bed due to the risk of thromboembolism caused by COVID-19, and by pregnancy, daily consultation by telehealth [12]. Perform obstetric examinations and in-person consultation only if indispensable cardiotocography is carried out to assess the fetus, depending on maternal conditions and gestational age [12].

At the beginning of the pandemic, the indication for cesarean delivery was common due to the lack of knowledge of vertical transmission [65]. However, studies have shown that cesarean sections should be indicated according to the usual obstetric conditions, as the risk of vertical transmission is not an indication for cesarean section [12]. Moreover, maternal infection with SARS-CoV-2 is not an indication for cesarean section. The timing and type of delivery should be based on obstetric indications, clinical and fetal conditions such as gestational age, obstetric history, maternal comorbidities, and disease severity [1]. With regard to maternal indication, in a patient with respiratory failure, childbirth may worsen the pulmonary situation, and maternal hypoxia may increase the risk of fetal impairment. In this case, indicate a cesarean section between and 32–34 weeks in severely critically ill patients, when the risk of prematurity can be assumed by the service. Before 32 weeks, balance maternal–fetal risks, especially in intubated patients or those who need them [12], and perform continuous monitoring by cardiotocography and, if fetal distress is suggested, indicate delivery immediately by the most appropriate method that conditions permit [12].

Minimize the frequency of maternal exams, do it every 2–4 hours, and with the least number of professionals. Monitor SO_2 respiratory rate and temperature every hour [12]. Do not indicate delivery for a stable patient with COVID-19. The ideal is to schedule when a patient is negative [12], and seek to establish a safer delivery for the mother, baby, and health team [65]. Women should be instructed on the most appropriate type of delivery for each case, respecting the correct indications to reduce unplanned cesarean sections and the psychological impact of childbirth during the pandemic. One study showed that 68.9% of women had a cesarean delivery and COVID-19 was the main indication for it. COVID-19 is also associated with premature birth, although neonatal outcomes are generally favorable [65].

At delivery, opioids and remifentanil are used with caution because of the risk of respiratory depression. Nitrous oxide can be used for labor analgesia [49]. Neuraxial analgesia is indicated, as it can also be used for cesarean section in cases of conversion [12]. Histopathological examination of the placenta should be required [1]. Prophylactic enoxaparin should be taken daily 40–80 kg or 60 mg if greater than 80 kg due to the risk of thromboembolism in the puerperium and COVID-19 [60]. Discharge is the same as any patient with COVID-19, and after discharge, the puerperal woman was followed up via telehealth. If there is a need for evaluation during the contagious period, all precautions should be taken [12].

All patients, and even asymptomatic patients, should be tested before elective procedures, and the correct protective equipment, such as an N95 mask, one or two gloves, a long-sleeved lab coat, and eye protection, should always be worn [12]. The room should have negative pressure. Pregnant women must wear surgical masks during delivery. After delivery, leave the patient in the same room as before and, if possible, she should be assisted by the same team of health professionals. Offer contact with the newborn. All materials must be considered contaminated [12].

The transmission of COVID-19 from person to person occurs through respiratory droplets after contact with an infected person (<2 m or direct contact with an infected surface) [12]. One study showed that there was no vertical transmission in 206 newborns [65]. Vertical transmission being possible has not yet been conclusively proven [3].

BREASTFEEDING

Breastfeeding protects the mother and child, and the benefits are unquestionable and should be encouraged. The decision to continue breastfeeding during COVID-19 should be made considering the clinical peculiarities of COVID-19 and the protective effects of breastfeeding [66]. As COVID-19 is not transmitted by breast milk, the benefits of breastfeeding outweigh the risks and can even protect the mother and newborn. For breastfeeding to be safe, infection control protocols must be strictly adhered to [66]. The mother must wear an N95 or surgical mask and perform hand hygiene when in contact with her newborn, especially during breastfeeding [12]. The mother should undergo hand disinfection and respiratory hygiene [1]. Neonates should be tested and isolated to avoid contact with contaminated droplets [12]. The mother and baby should be together and maintain skin-to-skin contact during the COVID-19 period. If the mother is very sick and unable to breastfeed, she can express the milk, and a healthy person should breastfeed the newborn [66]. Another option, if feasible, is to discharge the asymptomatic newborn to be cared for by a relative who does not have the disease, but if

he is symptomatic and needs to stay in the hospital due to prematurity, for example, he must remain isolated in the intensive care unit [12]. Newborns should be monitored for suspicious symptoms of COVID-19 [1].

CONCLUSION

As the risks of COVID-19 complications are higher in pregnant patients, a knowledge of the behavior that can help in better decision-making to preserve the health of the maternal–fetal dyad is encouraged. The patient must remain in isolation and be monitored and treated according to the stage of the disease, taking into account the obstetric conditions, the anatomy and physiology of the gestational period, and the severity of the disease. The type of delivery should consider this information. The health team must be preserved from unnecessary exposure to viral contamination, and breastfeeding must be guided by encouraging early mother–child contact as long as hygiene rules and the use of masks are respected. Knowledge of the treatment available today for pregnant patients with COVID-19 will help leading to better evolution and maternal–fetal outcomes.

AUTHOR CONTRIBUTIONS

Salete da Silva Rios researched and analyzed the literature on the review topic. Juliana Rios Chen, Ceres Nunes de Resende, Ana Carolina Rios Chen and Alberto Borges Peixoto, participated in writing the text of the manuscript and its interpretation. Edward Araujo Júnior 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

С.С. Риос провел поиск и анализ литературы по теме обзора. Ю.Р. Чен, Ц.Н. Резенде, А.К.Р. Чен и А.В. Пейшото участвовали в написании текста рукописи и его интерпретации. Э. Араухо-мл. разработал общую концепцию статьи и руководил ее написанием. Все авторы участвовали в обсуждении и редактировании работы. Все авторы утвердили окончательную версию публикации.

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Review / Обзор
https://doi.org/10.47093/2218-7332.2021.12.2.55-61

Professional ethics of recommendations: implications for COVID-19 vaccination of women who are pregnant or planning to become pregnant

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Abstract

There has been changing guidance from national and international professional associations, national and international non-governmental organizations, and health officials in national governments for obstetrician-gynecologists about COVID-19 vaccination of pregnant women and women who are planning to become pregnant. in this paper, we provide an ethical framework that provides the needed guidance to decision making about recommending COVID-19 vaccination to these patients. the unique feature of this ethical framework is that it is based on professional ethics in obstetrics and gynecology. We begin with an account of three key components of professional ethics in obstetrics and gynecology and how they are pertinent to the ethics of making recommendations that should be understood in obstetric and gynecologic practice generally. We then identify the implications of this overview for the specific topic of the ethics of recommending COVID-19 vaccination.

Keywords: COVID-19; COVID-19 vaccination; ethical principle of beneficence; ethical principle of respect for autonomy; medically reasonable; professional ethics in obstetrics and gynecology
MeSH terms:
PREGNANCY COMPLICATIONS, INFECTIOUS – PREVENTION & CONTROL
COVID-19 – COMPLICATIONS
COVID-19 – PREVENTION & CONTROL
COVID-19 – VACCINES – THERAPEUTIC USE
VACCINATION – METHODS
VACCINATION – ETHICS
For citation: Chervenak F.A., McCullough L.B., Grünebaum A. Professional ethics of recommendations: implications for COVID-19 vaccination of women who are pregnant or planning to become pregnant. Sechenov Medical Journal. 2021; 12(2): 55–61. https://doi.org/10.47093/2218-7332.2021.12.2.55-61

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Conflict of interests. The authors declare that there is no conflict of interest.
Financial support. Supported by Departmental funds.

Received: 04.08.2021
Accepted: 09.08.2021
Date of publication: 29.09.2021

УДК: 618.3-06:[616.98:578.834.1]-084

Профессиональная этика рекомендаций: значение вакцинации против COVID-19 беременных или планирующих беременность женщин

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Аннотация

Внесены изменения в руководства национальных и международных профессиональных ассоциаций, национальных и международных неправительственных организаций, а также органов управления здравоохранения в национальных правительствах для акушеров-гинекологов в отношении вакцинации против COVID-19 беременных женщин и женщин, планирующих беременность. В этом документе представлены этические принципы, которые обеспечивают необходимое руководство для принятия решений о рекомендации вакцинации COVID-19 этой группе пациентов. Уникальная особенность этих этических принципов состоит в том, что они основаны на профессиональной этике в акушерстве и гинекологии. Обзор начинается с описания трех ключевых компонентов профессиональной этики в акушерстве и гинекологии и того, как они соотносятся с этикой рекомендаций, которые следует принимать в акушерской и гинекологической практике в целом. Затем определяется значение этого обзора для конкретной темы – рекомендации по вакцинации COVID-19.

Ключевые слова: COVID-19; вакцинация от COVID-19; этический принцип милосердия; этический принцип уважения автономии; медицинское обоснование; профессиональная этика в акушерстве и гинекологии

Рубрики MeSH:
БЕРЕМЕННОСТИ ОСЛОЖНЕНИЯ ИНФЕКЦИОННЫЕ – ПРОФИЛАКТИКА И КОНТРОЛЬ
COVID-19 – ОСЛОЖНЕНИЯ
COVID-19 – ПРОФИЛАКТИКА И КОНТРОЛЬ
COVID-19 ВАКЦИНЫ – ТЕРАПЕВТИЧЕСКОЕ ПРИМЕНЕНИЕ
ВАКЦИНАЦИЯ – МЕТОДЫ
ВАКЦИНАЦИЯ – ЭТИКА

Для цитирования: Червенак Ф.А., Маккалоу Л.Б., Грюнебаум А. Профессиональная этика рекомендаций: значение вакцинации против COVID-19 беременных или планирующих беременность женщин. Сеченовский вестник. 2021; 12(2): 55–61. https://doi.org/10.47093/2218-7332.2021.12.2.55-61

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Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Финансирование. Исследование поддерживается ведомственными фондами.

Поступила: 04.08.2021
Принята: 09.08.2021
Дата печати: 29.09.2021

HIGHLIGHTS	КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ
Professional ethics in obstetrics and gynecology should guide obstetrician-gynecologists in counselling pregnant patients about COVID-19 vaccination.	Профессиональная этика в акушерстве и гинекологии должна служить ориентиром для акушеров-гинекологов при консультировании беременных по поводу вакцинации против COVID-19.
Obstetrician-gynecologists should recommend COVID-19 vaccination to their pregnant patients and patients who are planning to become pregnant.	Акушеры-гинекологи должны рекомендовать вакцинацию от COVID-19 беременным пациенткам и пациенткам, которые планируют беременность.

Making recommendations about clinical management to pregnant patients is routine in obstetric practice. Obstetricians make a range of recommendations to patients, about, for example, coming in for prenatal visits, diet and exercise, and refraining from the use of tobacco products and consuming alcohol beverages. Such recommendations promote both maternal and fetal health. Obstetricians also make recommendations to protect maternal health, e.g., cesarean delivery to manage pre-eclampsia, and to protect fetal and neonatal health, cesarean delivery for severe fetal distress. Obstetricians recommend the flu vaccine each year.

In this context, it should be of considerable concern to obstetrician-gynecologists that currently there is conflicting guidance from national and international professional associations, national and international non-governmental organizations, and health officials in national governments about COVID-19 vaccination of pregnant women and women who are planning to become pregnant. the purpose of this paper is to provide an ethical framework that provides clear guidance to decision making about recommending COVID-19 vaccination to these patients. This ethical framework is based on professional ethics in obstetrics and gynecology [1]. We therefore start with an overview of three key components of professional ethics in obstetrics and gynecology and how they are pertinent to the ethics of making recommendations that should be understood in obstetric and gynecologic practice generally. We then identify the implications of this overview for the specific topic of the ethics of recommending COVID-19 vaccination.

THREE COMPONENTS OF PROFESSIONAL ETHICS IN OBSTETRICS AND GYNECOLOGY

Ethical principles

The three components of the proposed ethical framework are two ethical principles – beneficence and respect for autonomy – and the clinical ethical concept of medical reasonableness. Ethical principles and clinical ethical concepts are designed to provide clear, practical guidance to clinical judgment and clinical management [1].

The ethical principle of beneficence

The ethical principle of beneficence is the older of the two ethical principles. One of the first occurrences of the word “beneficence” in the global history of medical ethics occurs in the first book entitled, “Medical Ethics”, by the English physician-ethicist, Thomas Percival (1740–1804), and published in 1803. Percival invokes the principle of beneficence when he sets out an ethical framework for the responsible use of “drugs and wines” – fortified wines then being thought to aid in the treatment of digestive disorders and to calm nerves – in the formulary of the Manchester Royal Infirmary in England. Their use should be guided by “beneficence”, by which Percival meant an evidence-based evaluation of their efficacy [2, 3].

Percival’s account contains a compressed version of the ethical principle, which is not surprising given that he is perhaps the first explicit invocation of the principle. the ethical principle of beneficence was fully formulated in the last third of the previous century. It creates the ethical obligation of the physician to identify and provide clinical management that in evidence-based clinical management is predicted to result in net clinical benefit for the patient, a greater balance of clinical goods over clinical harms. the clinical goods include the management as well as the prevention of disease and disability and the prevention of death (though not at all costs). the clinical harms include especially pain, distress, and suffering, as well as preventable death. With Percival, we emphasize that the evidence base for beneficence-based clinical judgment does not include the physician’s idiosyncratic views or unanalyzed “personal experience”. the latter is usually distorted by unrecognized biases, which evidence-based reasoning is designed to critically appraise and mitigate [1].

The reliability of beneficence-based clinical judgment is a function of its evidence base. the stronger the evidence base, the more reliable are the clinical judgments based on it. Conversely, the weaker the evidence base, the less reliable are the clinical judgments based on it.

The beneficence-based concept of medical reasonableness

When a form of clinical judgment is supported in beneficence-based clinical judgment it is known in professional ethics in medicine as “medically reasonable”. Forms of clinical management that are not supported in beneficence-based clinical judgment are not medically reasonable and should therefore not be included in the clinical management of the patient’s

condition (pregnancy is a condition, not a disease or disability), disease, or disability [1].

The ethical principle of respect for autonomy

The ethical principle of respect for autonomy also has its origins in eighteenth-century British medical ethics, in the work of Percival's predecessor, the Scottish physician-ethicist John Gregory (1724–1773). in his lectures on medical ethics to his students, published in 1772 [4, 5] Gregory supports the ethical obligation of physicians to be honest with gravely ill patients about the clinical gravity and implications of end-stage disease and injury. He also states that patients have the "right to speak" when their own health or life is at stake. Physicians have the ethical obligation to listen and to evaluate the patient's views and preferences. When these are what we would now call medically reasonable, the physician should endorse them. When the patient's views and preferences are not medically reasonable the physician should withhold endorsement – and be prepared for the adverse outcomes that might follow and provide clinical management of them without comment or, especially, complaint.

Like the ethical principle of beneficence, the ethical principle of respect for autonomy was fully formulated in the last third of the twentieth century. This principle integrates the beneficence-based concept of medical reasonableness with respect for the patient's right "to speak" or, as we would now say, the patient's right to self-determination. the ethical principle of respect for autonomy creates the ethical obligation of the physician to empower each patient to make informed and voluntary decisions about the clinical management of her condition, disease, or diagnosis. the physician empowers the patient to make informed decisions by providing her with information on her condition or diagnosis and about the medically reasonable alternatives for the clinical management of her condition or diagnosis, as well as the clinical benefits and risks of each such alternative. the physician empowers the patient to make voluntary decisions by making a reasonable effort to ensure that the patient's decision-making process is free of both internal controlling influences and external controlling influences. Psychosocial support should be provided, as needed, with the goal of achieving voluntary decision making [1].

Offering and recommending clinical management

Sometimes more than one medically reasonable alternative is supported in beneficence-based clinical judgment. For example, trial of labor after a previous cesarean delivery by a low transverse incision is supported in beneficence-based clinical judgment as medically reasonable and so is planned cesarean delivery [6]. When there are two or more medically reasonable alternatives, the ethical principle of respect for autonomy creates the ethical obligation to offer both and to support the patient to understand and evaluate each alternative based on her values and beliefs. Inasmuch as the physician is not able to determine which alternative better supports the patient's values and beliefs, the physician should not make a recommendation. Instead, shared decision making – in the sense of offering but not recommending the medically reasonable alternatives in the context of the patient's values and beliefs – should guide the physician's role in the patient's decision-making process [1].

Sometimes there is only one medically reasonable form of clinical management, for example, cesarean delivery to manage well-documented, intrapartum complete placenta previa. This form of clinical management dramatically reduces the risk of maternal mortality and essentially eliminates the risk of stillbirth and neonatal mortality. These clinical realities mean that there is no support in beneficence-based clinical judgment for vaginal delivery. Cesarean delivery should therefore be unhesitatingly recommended, and if necessary, strongly support the patient's decision making. Shared decision making, in the meaning described above, is not the appropriate model for decision making because it conveys the false impression that not accepting the recommendation of the only medically reasonable alternative, i.e., not being vaccinated against COVOD-19, is acceptable in professional ethics in obstetrics and gynecology [1].

Some take the view that making recommendations is not compatible with the ethical principle of respect for autonomy and do so in the name of championing the rights of patients, especially women who are patients [7]. This is, to say the least, ironic, since this view, to be plausible, must assume that female and pregnant patients are systematically at risk of being controlled by their physicians. This view infantilizes female and pregnant patients. Worse still, it combines the influencing of a patient's decision making (which recommendations are undoubtedly meant to do) with asserting a controlling influence. This is a conceptual error and conceptual errors are not permitted in ethical reasoning, just as they are not permitted in scientific and clinical reasoning. This view is also inconsistent with evidence-based reasoning: patients report that their physicians' recommendations are the most important consideration in their decision making about clinical management [8]. the claim that making recommendations is not compatible with the ethical principle of respect for autonomy therefore fails and should be discarded.

Offering vs. recommending COVID-19 vaccination

There is a crucial difference between shared decision making and making recommendations. Shared decision making starts with the patient's values and beliefs about COVID-19 vaccination, which becomes the controlling factor of the decision-making process. This means that

the physician has the autonomy-based ethical obligation not to challenge but always to support the decision of the patient, including refusing the COVID-19 vaccination. Making recommendations about COVID-19 vaccination starts with the clinical reality that there is only one medically reasonable alternative, which becomes the controlling factor of the physician's clinical judgment and therefore in the decision-making process. This means that the physician has the ethical obligation to respectfully challenge the decision of a pregnant patient or patient planning to become pregnant to refuse COVID-19 vaccination.

The form that this respectful challenge should take is guided by the ethical principle of respect for autonomy: to empower the patient to reconsider her refusal in the context of the preventable clinical risks that implementing her refusal creates. in the United States, when patients refuse recommended clinical management, the physician has the legal obligation of informed refusal. the physician should inform the patient about the risks that refusal creates and document this disclosure in the patient's record. Doing so reduces the physician's professional liability should those risks occur [1]. There is an ethical dimension to informed refusal that applies in all settings globally: in a respectful manner the physician should point out refusing the COVID-19 vaccination means that the patient will have to rely on other measures such as masking and maintaining the prescribed distance from others, and these measures are not as effective as full immunization. the goal is to empower the patient to understand that these risks exist and that they could happen to her. She should be asked what she would think if those risks did indeed happen to her. in virtually all cases, the patient will express concern. She should be asked why to elicit her values and beliefs about protecting her life and health and that of her fetus. the physician can then point out the common ground that exists between the physician and the patient: the value of protecting both the life and health of the patient. the physician can then explain that this common ground motivates the recommendation of COVID-19 vaccination. the physician should repeat the recommendation as *the only way* to implement her values and beliefs.

This process of eliciting the patient's values about protecting her life and health, making common ground explicit, and re-iterating the recommendation as the way to implement the patient's values and beliefs is known as respectful persuasion [1], an important but underappreciated clinical tool for implementing the ethical principle of respect for patient autonomy. the justification for using this tool is evidence that patients consider the physician's recommendation as very important in their decision making [8]. Making recommendations coupled with respectful persuasion should both be understood as autonomy-enhancing.

Recommending COVID-19 vaccination to pregnant women and women planning to become pregnant

The ethical principle of beneficence should guide the physician's assessment of the benefits and risks of COVID-19 vaccination for pregnant women and women planning to become pregnant [9]. This assessment begins with the risk of not being vaccinated. COVID-19 is a more serious disease for infected pregnant patients than it is for non-pregnant patients. Pregnant women and recently pregnant women are at an increased risk for severe illness and other pregnancy complications from COVID-19 when compared to non-pregnant women [10–14]. Severe illness means that a person with COVID-19 may more likely need to be hospitalized, be admitted to an intensive care unit, or be on a ventilator.

In addition, pregnant women with COVID-19 are also at increased risk for preterm birth (delivering the baby earlier than 37 weeks) and might be at increased risk for other poor pregnancy outcomes.

Having certain underlying medical conditions, and other factors, including age, can further increase a pregnant or recently pregnant (for at least 42 days following the end of pregnancy) woman's risk for developing severe COVID-19 illness.

After pregnancy, changes that occur in the body during pregnancy that increase the risk for severe illness from respiratory viral infections like COVID-19 can continue. For example, increased risk for developing blood clots during pregnancy can continue after pregnancy and increase the risk for severe illness, as in recently pregnant people with H1N1 influenza.

This risk can be reduced by wearing an appropriate mask and maintaining social distance, but these are not as effective as vaccination. This is especially the case in a country with a low vaccination rate, currently reported to be 25.84% in Russia[1]. the recently completed placebo-controlled randomized trial of the GAM-COVID-Vac showed 91.6% efficacy with a good safety profile [15–17]. These results are like those reported for the mRNA vaccines [9]. Fully vaccinated patients may continue to use masks and maintain social distance, but the need to do so will diminish. the resulting increase in personal freedom is an important psychosocial benefit that should not be discounted. the risks of the vaccine are rare and, in most cases, clinically manageable. the public health implications of a vaccine with 91.6% efficacy are significant. This significance increases in countries like Russia with low current vaccination rates.

CONCLUSION

Beneficence-based clinical judgment is clear on two points. First, not being vaccinated against COVID-19 is not a medically reasonable alternative for pregnant

[1] Our World in Data. Coronavirus (COVID-19) Vaccinations. https://ourworldindata.org/covid-vaccinations?country=RUS Accessed Aug 4th, 2021.

women or for women planning to become pregnant. Second, the vaccine currently available in Russia is highly effective with a good safety profile. This conclusion can be made with confidence even in the absence of a randomized clinical trial with pregnant women and women planning to become pregnant in an intervention arm. This beneficence-based clinical judgment is the same that the authors and their colleagues at Northwell Health reached concerning vaccines with emergency approval from the U.S. Food and Drug Administration, even in the absence of such a randomized clinical trial [9]. There we argued that this beneficence-based clinical judgment supports COVID-19 vaccination as the only medically reasonable alternative for preventing COVID-19 in pregnant patients and in patients planning to become pregnant. There we showed that in ethical reasoning this beneficence-based clinical judgment supports recommending COVID-19 vaccination to these patients is a matter of professional responsibility. Here we draw the same conclusion from the same beneficence-based clinical judgment. Obstetrician-gynecologists and other physicians in Russia, and in every other country, should recommend COVID-19 vaccination to their patients who are pregnant and to their patients who are planning to become pregnant.

AUTHOR CONTRIBUTIONS

All authors participated in the research for this paper and its design. All authors participated in preparing successive drafts of the paper and therefore have read and approved the submitted text.

ВКЛАД АВТОРОВ

Все авторы участвовали в организации и проведении исследования для написания этой статьи. Все авторы участвовали в последовательной подготовке текста статьи, прочитали и одобрили представленный текст.

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