

SYSTEMATIC REVIEW

Received: March 17th 2020Accepted: April 7th 2020Published: April 17th 2020MATERNAL AND NEONATAL CONSEQUENCES OF CORONAVIRUS COVID-19
INFECTION DURING PREGNANCY: A SCOPING REVIEW

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Authors declare that there is no conflict of interest.

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a new pathology, declared a public health emergency by the World Health Organization, which can have negative consequences for pregnant women and their newborns. The aim of this study was to explore the available knowledge on the consequences of developing COVI-19 in pregnant women and their neonates.

Methods: Scoping Review, in which the search for articles was conducted using DeCS (“pregnancy”, “coronavirus”, “health”) and MeSH (“pregnan*”, “pregnant women”, “coronavirus”), linking the terms with the Boolean AND operator. Databases used were Web of Science, Scopus, BVS, Scielo and CUIDEN. In addition, the PRISMA methodology was applied.

Results: Ten studies were identified that assessed maternal and neonatal health after maternal COVID-19 infection. Pregnant women seem to had no serious symptoms. Neonates appeared to be affected to a greater extent. A death was reported in a premature newborn whose mother had COVID-19 pneumonia. There did not appear to be vertical transmission from mother to child. Nevertheless, this information was not conclusive.

Conclusions: COVID-19 appears to be more benign with pregnant women than with their neonates.

Key words: SARS-CoV-2, COVID-19, Pregnancy, Neonate, New-born.

RESUMEN

Consecuencias maternas y neonatales de la infección por coronavirus Covid-19 durante el embarazo: una scoping review

Fundamentos: La enfermedad por coronavirus 2019 (COVID-19) es una nueva patología, declarada emergencia de salud pública por la Organización Mundial de la Salud, que puede tener consecuencias negativas en las embarazadas y sus recién nacidos. El objetivo fue explorar el conocimiento disponible sobre las consecuencias de desarrollar COVID-19 en las embarazadas y en los recién nacidos durante el embarazo.

Métodos: Se realizó una *Scoping Review*, en la que se usó la búsqueda de artículos en los directorios DeCS (“embarazo”, “coronavirus”, “salud”) y MeSH (“pregnan*”, “pregnant women”, “coronavirus”), uniendo los términos con el operador booleano AND. Se buscó en las bases de datos Web of Science, Scopus, BVS, Scielo y CUIDEN. Además, se aplicó la metodología PRISMA.

Resultados: Se identificaron 10 estudios en los que se evaluó la salud materna y neonatal tras infección materna por COVID-19. Las embarazadas parecían no presentar síntomas graves. Los neonatos se veían afectados en mayor medida. Se informó de un fallecimiento de un recién nacido prematuro cuya madre tuvo neumonía por COVID-19. No pareció haber transmisión vertical de madre a hijo, aunque esta información no era concluyente.

Conclusiones: El COVID-19 parece ser más benigno con las embarazadas que con sus recién nacidos.

Palabras clave: SARS-CoV-2, COVID-19, Embarazo, Neonato, Recién nacido.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a new pathology with a rapid increase of infections and deaths since it was first identified in Wuhan (China) in December 2019⁽¹⁾. Available data on its effects on pregnant women and offspring are still sparse. Nevertheless, information regarding its detrimental consequences on the respiratory tract may help discover how it may affect pregnant women and their developing fetuses⁽¹⁾.

Coronavirus is a virus that causes infections in humans and animals. More specifically, it is a zoonotic pathology, that is, it can be transmitted from animals to humans⁽²⁾. They can cause several diseases from a common cold to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS-CoV)⁽²⁾. As a result of COVID-19 disease, the World Health Organization (WHO) stated in late January 2020 that we were (and are) facing a pandemic and an international public health emergency⁽³⁾.

During pregnancy, a variety of environmental circumstances can affect maternal and newborn health^(4,5,6). Taking this into consideration, it is known how the environment a pregnant woman is exposed to can create a permanent imprint on fetal physiology, which will last a lifetime. Thus, as stated from the Developmental Origin of Health and Disease (DOHaD) theory promulgated by epidemiologist David Barker, fetal programming that occurs during prenatal development will determine the health and illness of that individual throughout his extrauterine life⁽⁷⁾. Exposure to viruses has been described among the prenatal events that may affect the health of the developing fetus⁽⁸⁾.

Due to the special care we must give to pregnant women and their newborns⁽⁹⁾, and the information provided before, the aim of this study

was to explore the available knowledge on the consequences of developing COVID-19 in pregnant women and newborns during pregnancy.

MATERIAL AND METHODS

In order to perform an initial mapping of the literature, the methodology referring to a scoping review was used^(10,11). The characteristics of a scoping review are that it is systematic and rigorous. In addition, it allows the possibility of generating hypotheses, as well as proposing which areas of study are partially developed⁽¹²⁾.

Thus, the search for articles was carried out using the DeCS (“*pregnancy*”, “*coronavirus*”, “*health*”) and MeSH (“*pregnan**”, “*pregnant women*”, “*coronavirus*”) directories, linking the terms with the Boolean operator AND. The inclusion criteria were: articles in Spanish or English language, published in the last 2 years (due to the novelty of the subject), that included the full text, including pregnant women, and that addressed the maternal and/or neonatal infections consequences of coronavirus infection during pregnancy. In addition, other sources of information were used such as the Spanish Society of Gynecology and Obstetrics (SEGO), the Royal College of Obstetricians and Gynaecologists (UK), The Royal College of Midwives (UK), Royal College of Paediatrics and Child Care (UK) and the WHO final report on the China-WHO joint mission on COVID-19. Exclusion criteria were opinion articles and animal studies.

The databases in which the search was performed were Web of Science, Scopus, BVS, Scielo and CUIDEN. In addition, Google Scholar was used to identify potential articles not indexed in the databases used. The search was carried out between February-March 2020. **Figure 1** shows the PRISMA flow diagram⁽¹³⁾, reflecting the search and selection process for

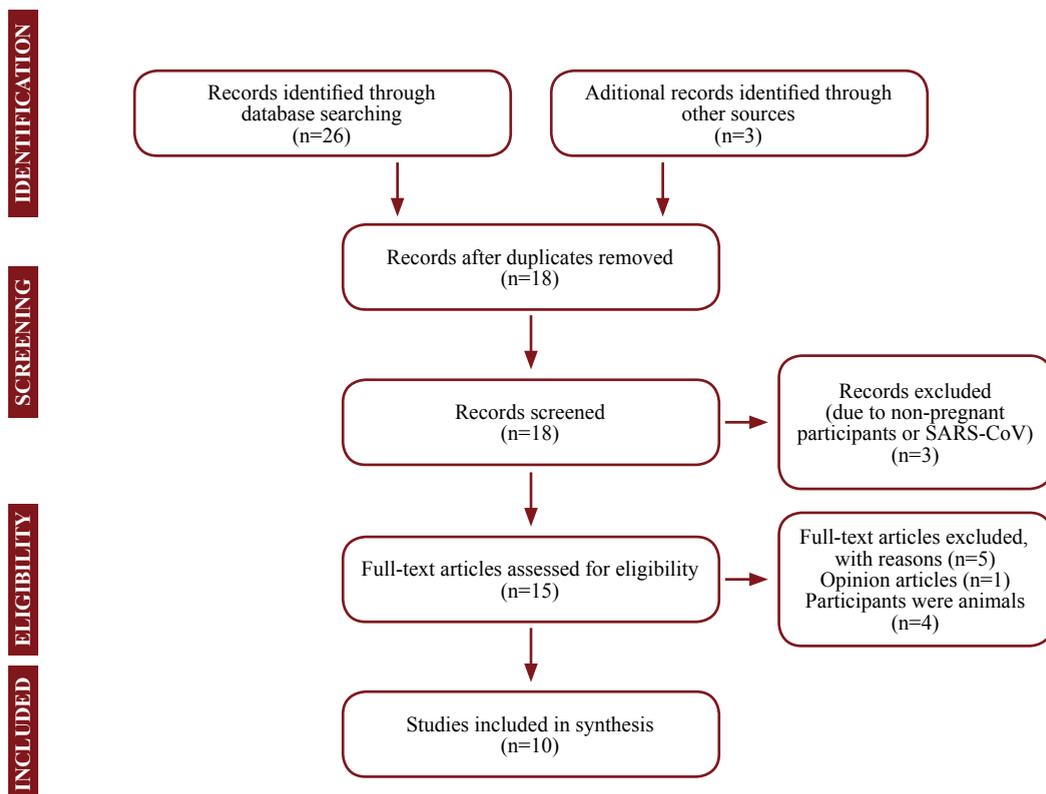
articles according to the inclusion criteria. Finally, 10 studies were selected for further analysis.

RESULTS

The novelty of this topic helped that 10 studies met the inclusion criteria and were included in this scoping review^(14,15,16,17,18,19,20,21,22,23). **Table 1** shows the main results of the included empirical studies (n=5)^(14,15,16,17,18). All empirical studies (n=5) were observational, either single case or case series. The total sample of the 5 empirical studies was 64 pregnant women and 65 neonates (one pregnancy was twin). The 100%

(n=5) of empirical studies were conducted in China^(14,15,16,17,18). A study on recommendations for obstetricians based on the SARS-CoV coronavirus and on the Middle East Respiratory Syndrome (MERS) was included⁽¹⁹⁾. In addition, a consensus of experts from China for perinatal and neonatal management in the prevention and control of COVID-19 was added in the review⁽²⁰⁾. Furthermore, among the documents included in this exploratory review were three reports of recommendations for health professionals prepared by the Spanish Society of Gynecology and Obstetrics (SEGO), the Royal College of Obstetricians and Gynaecologists (UK), The Royal College of Midwives (UK), Royal College

Figure 1
PRISMA flow diagram reflecting the search and selection process.



Source: Modified from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement)⁽¹³⁾.

Table 1
Maternal and neonatal outcomes of the empirical studies included in the scoping review.

First author and publication year	Country	Maternal mean age (years)	Study design	Mean weeks of gestation	Maternal disease (Yes/No)	Maternal death (Yes/No)	Neonatal disease (Yes/No)	Placental infection (Yes/No)	Neonatal death (Yes/No)	Type of delivery	Maternal outcomes
Chen (2020a) ⁽¹⁴⁾	China	29.7	Observational 3 cases	36	Yes	No	Yes	No	No	Vaginal delivery and C-section	COVID-19 positive
Chen (2020b) ⁽¹⁵⁾	China	29	Observational 9 cases	37	Yes	No	No	No	No	Elective C-section	COVID-19 positive
Li (2020) ⁽¹⁶⁾	China	30	Unique case	35	Yes	No	No	No	No	Elective C-section	COVID-19 positive
Liu (2020) ⁽¹⁷⁾	China	Not provided	Observational 41 cases	22-40	Yes	No	No	No	No	Vaginal delivery and C-section	COVID-19 positive
Zhu (2020) ⁽¹⁸⁾	China	30	Observational 10 cases	38	Yes	No	Yes	No	Yes	Vaginal delivery and C-section	COVID-19 positive

of Paediatrics and Child Care (UK) and the China-WHO joint mission on COVID-19^(21,22,23).

Maternal and placental infection by COVID-19.

In all 5 empirical studies, pregnant women tested positive for COVID-19 infection^(14,15,16,17,18).

Although the predominant symptom of pregnant women was fever^(14,15,16,17,18), in some cases, it did not appear until after delivery or caesarean section^(14,15,16,17,18). In a case, the pregnant woman debuted with cholecystitis⁽¹⁸⁾. The vast majority of pregnant women did not have severe pneumonia, nor did they require intensive care. In addition, none died^(14,15,16,17,18), being discharged without excessive complications a few days after admission. According to the reviewed studies, only one pregnant woman had to be transferred to a critical care area, but was also discharged with no complications⁽¹⁴⁾.

COVID-19 coronavirus was not detected in the analyzed placentas^(14,16). Nevertheless, a placenta showed chorionic hemangioma morphology⁽¹⁴⁾ and a different one had a large area of necrosis⁽¹⁴⁾. No placenta showed changes related to chorioamnionitis⁽¹⁴⁾. Amniotic fluid, umbilical cord blood, breast milk, and oropharyngeal swab samples from newborns were negative in 6 cases in one study⁽¹⁵⁾. Samples of amniotic fluid, umbilical cord blood, placenta blood, and breast milk were also negative in a single case study of a positive pregnant woman to SARS-CoV-2⁽¹⁶⁾.

Technical consensus reports for professionals and the China-WHO joint mission found that pregnant women were not more likely to become infected with COVID-19 than non-pregnant women^(19,21,23). The majority of pregnant women only showed mild to moderate symptoms similar to a cold or flu. Only those with some underlying disease, such as diabetes, chronic lung disease, or an immunosuppressed state, were more susceptible to severe symptoms⁽²²⁾.

Neonatal consequences of maternal infection to COVID-19. Neonates from mothers who tested positive for COVID-19 were sampled for the SARS-CoV-2 coronavirus, with three infants having a negative test to SARS-Co-2 oropharyngeal samples in one study⁽¹⁴⁾, and nine neonates having a negative test to SARS-Co-2 oropharyngeal samples in another study⁽¹⁵⁾. A neonate from an unique case study also had a negative test to SARS-Co-2 oropharyngeal samples⁽¹⁶⁾. No symptoms of dyspnea or suffocation were found in the neonates^(14,15,16). Fetal heart rate was only reported in a unique case study with 110 beats per minute⁽¹⁶⁾. This neonate was born by caesarean section and no complications were reported. In one of the studies that carried out a clinical analysis of 10 newborns born to mothers with a positive result for COVID-19, it was found that 40% (n=4) of term births and 60% (n=6) of premature births⁽¹⁸⁾. Additionally, in this same study, two infants were reported to be small for gestational age (SGA) and one was large for gestational age (LGA)⁽¹⁸⁾. Of these infants, a total of 6 had dyspnea, in addition to two who had fever and thrombocytopenia, along with tachycardia, vomiting, and pneumothorax in one case⁽¹⁸⁾. To date of one of the studies included in this review⁽¹⁸⁾, a total of 5 infants has been discharged from hospital, four remained hospitalized and stable, and one had died due to complications. The Chinese consensus group in relation to neonatal management reported two cases of neonates that were positive for SARS-CoV-2, having the worst prognosis those who also were premature⁽²⁰⁾.

Vertical intrauterine transmission of COVID-19 from the pregnant woman to the developing fetus. Vertical transmission refers to microorganisms moving from the mother to the fetus before and after birth, through the cord blood, the placenta, the birth canal or through breastfeeding⁽¹⁸⁾. All empirical studies in this review reported an absence of vertical transmission of

the coronavirus from the pregnant mother to the developing fetus^(14,15,16,17,18). However, it should be noted that there was a neonate from one of the studies who was not tested and it is therefore unknown whether or not he was infected with COVID-19 in the perinatal period⁽¹⁸⁾. Furthermore, as mentioned, maternal infection with COVID-19 had negative consequences in some of the neonates. The Royal College of Obstetricians and Gynaecologists (UK), The Royal College of Midwives (UK) and Royal College of Paediatrics and Child Care (UK)⁽²²⁾ declared in their consensus document for professionals that there was no evidence of vertical transmission (during pregnancy) from mothers to the offspring. Moreover, the group of experts from China, the recommendations of the American Gynaecology Association and the Spanish Society of Gynecology and Obstetrics (SEGO) stated that it is impossible to rule out the circumstance of vertical transmission^(19,20,21).

DISCUSSION

The aim of this study was to know the current state regarding the possible negative consequences of maternal COVID-19 infection on the own health of the pregnant woman and the newborn. In addition, it sought to provide clarity on the vertical transmission of COVID-19 from mother to fetus. Studies of COVID-19 during pregnancy are attracting interest, although empirical research has only been conducted in China. This review constitutes the first study in Spain that addressed the health of pregnant women and newborns in relation to COVID-19. The predominant symptom in pregnant women in this review was fever, which did not always appear before birth^(14,15,16). It should be noted the absence of seriousness of COVID-19 in pregnant women^(14,15,16,17,18,19,21,23). This contradicts what was previously reported regarding SARS-CoV in Hong Kong in 2003 and in respect to a study stating that SARS was much more severe in pregnant women than among non-pregnant

women⁽¹⁹⁾. Some cases required admission to an intensive care unit. During the SARS in 2003, the death of some pregnant women was reported as a consequence of the coronavirus that infected them at that time⁽¹⁹⁾.

Regarding the neonatal consequences of COVID-19, only one baby was reported to have died possibly due to her/his 2,200 g birth weight and prematurity⁽¹⁸⁾. In respect to the rest of the neonates, apparently no lasting complications were observed^(14,15,16,17,18). It is important to note that almost all newborns screened for COVID-19 tested negative, except in one case where the test was not performed. It is unknown whether that neonate was the deceased baby⁽¹⁸⁾. Coronavirus SARS-Cov-2 was not found in any of the analyzed amniotic fluid, breast milk, or cord blood samples^(14,15,16,17,18).

To date and using the information available, there is insufficient evidence to verify that COVID-19 is transmitted vertically from mother to baby^(14,15,16,17,18,21).

International professional associations, being aware of the public health problem we are facing, have developed some recommendations for professionals dedicated to the health of pregnant women^(19,20,21,22,23). These recommendations include the management of those pregnant women during pregnancy, childbirth and postpartum at risk or suffering from an infection by COVID-19^(19,21,22). In addition, they include a list of recommendations regarding newborns care⁽²⁰⁾. Pregnant women and their neonates health must be a priority^(24,25,26).

In conclusion, there is no evidence of greater susceptibility to COVID-19 infection in pregnant women than in non-pregnant women⁽¹⁹⁾. Furthermore, there is no evidence to support the vertical transmission of SARS-CoV-2 from pregnant women to the fetus^(14,15,16,21,22). This is supported by the absence of SARS-CoV-2 in

breast milk, amniotic fluid and umbilical cord blood samples from newborns of mothers with COVID-19^(14,15,16). According to the studies included in this review, neonatal infection is quite infrequent. Only one single newborn deceased, possibly due to prematurity and low birth weight⁽¹⁸⁾.

This study may have certain limitations. Studies published in Chinese language were not included in the search. Furthermore, pregnant women with a positive result for SARS-CoV-2 and not those with symptoms but without a diagnosis of COVID-19 were included.

Finally, I would like to thank all those people who are trying to respond to this global pandemic.

REFERENCES

1. Yang H, Wang C, Poon LC. Novel coronavirus infection and pregnancy. *Ultrasound Obstet Gynecol.* 2020; 55:435-437.
2. Ministerio de Sanidad. Informe técnico. Enfermedad por coronavirus, COVID-19 [internet]. [cited 2020 March 30]. Available from https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/20200306_ITCoronavirus.V2.pdf.
3. World Health Organization. Responding to community spread of COVID-19. Interim guidance. 2020, 1-6.
4. Caparros-Gonzalez RA, García-García I, Mariñas-Lirola JC, Peralta-Ramírez MI. Protocolo del estudio de cohortes GESTASTRESS sobre los efectos del estrés durante el embarazo mediante la medida del cortisol en cabello de la mujer y del recién nacido. *Rev Esp Salud Publica.* 2018;92. e201804027.
5. Gutiérrez Oyarce A, Ferrero A, Estarlich M, Esplugues A, Iñíguez C, Ballester F. Exposición ambiental a dióxido de nitrógeno y salud respiratoria a los 2 años en la Cohorte INMA-Valencia. *Gac Sanit.* 2019;32:507-12.
6. Caparros-Gonzalez RA, Romero-Gonzalez B, Gonzalez-Perez R, Lucena-Prieto L, Perez-García M, Cruz-Quintana F, Peralta-Ramírez MI. Maternal and neonatal hair cortisol levels are associated with infant neurodevelopment at six months of age. *Journal of Clinical Medicine.* 2019;8(11):e2015.
7. Barker DJ. Fetal origins of coronary heart disease. *BMJ.* 1995 Jul 15;311(6998):171-174.
8. O'Leary DR, Kuhn S, Kniss KL, Hinkley AF, Rasmussen SA, Pape WJ, Kightlinger LK, Beecham BD, Miller TK, Neitzel DF, Michaels SR. Birth outcomes following West Nile Virus infection of pregnant women in the United States: 2003-2004. *Pediatrics.* 2006;117(3):e537-45.
9. Vázquez-Lara JM, Gómez-Salgado J, Fernández-Carrasco FJ, Brieba del Río P, Vázquez-Lara M, Rodríguez-Díaz L. Asistencia al parto inminente extrahospitalario. Actuaciones durante este proceso y cuidados a la madre y al recién nacido. *Rev Esp Sal Publica.* 2018;92. e201809063.
10. Munn Z, Peters MD, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Medical Research Methodology.* 2018;18(1):143.
11. Manchado Garabito R, Tamames Gómez S, López González M, Mohedano Macías L, Veiga de Cabo J. Revisiones sistemáticas exploratorias. *Med Segur Trab.* 2009; 55:12-19.
12. Medina Hernández NS, Duarte Climents G, Lorigo Muñoz R, Miranda Barrero E, Sánchez Gómez MB, Gómez Salgado J. ¿Por qué las embarazadas no se vacunan de la gripe?: una scoping review. *Rev Esp Sal Publica.* 2020; 93. e201904018.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6: e1000097.

14. Chen S, Huang B, Luo DJ, Li X, Yang F, Zhao Y, Nie X, Huang BX. Pregnant women with new coronavirus infection: a clinical characteristics and placental pathological analysis of three cases. *Chinese J Pathol.* 2020a;49:E005.
15. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, Li J, Zhao D, Xu D, Gong Q, Liao J. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *The Lancet.* 2020b; 395:809-815.
16. Li Y, Zhao R, Zheng S, Chen X, Wang J, Sheng X, Zhou J, Cai H, Fang Q, Yu F, Fan J. Early Release-Lack of Vertical Transmission of Severe Acute Respiratory Syndrome Coronavirus 2, China. *Emerg Infect Dis.* 2020.
17. Liu H, Liu F, Li J, Zhang T, Wang D, Lan W. Clinical and CT Imaging Features of the COVID-19 Pneumonia: Focus on Pregnant Women and Children. *The Lancet.* 2020
18. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, Xia S, Zhou W. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr.* 2020;9:51-60.
19. Rasmussen SA, Smulian JC, Lednický JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and Pregnancy: What obstetricians need to know. *Am J Obstet Gynecol.* 2020; 1-35.
20. Wang L, Shi Y, Xiao T, Fu J, Feng X, Mu D, Feng Q, Hei M, Hu X, Li Z, Lu G. Chinese expert consensus on the perinatal and neonatal management for the prevention and control of the 2019 novel coronavirus infection. *Ann Transl Med.* 2020;8:1-8.
21. Sociedad Española de Ginecología y Obstetricia (SEGO). Recomendaciones para la prevención de la infección y el control de la enfermedad por coronavirus 2019 (COVID-19) en la paciente obstétrica. [internet]. [cited 2020 March 31]. Available from http://www.rhaprofesional.com/wp-content/uploads/2020/03/SEGO_España.pdf.
22. Royal College of Obstetricians and Gynecologists, The Royal College of Midwives, Royal College of Paediatrics and Child Care. Coronavirus (COVID-19) Infection in Pregnancy. Information for healthcare professionals. [internet]. [cited 2020 March 31]. Available from http://www.rhaprofesional.com/wpcontent/uploads/2020/03/Royal_College_of_Obstetricians_and_Gynaecologists_ReinoUnido.pdf.
23. Joint Mission World Health Organization-China. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). [internet]. [cited 2020 March 31]. Available from <https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>.
24. Schwartz DA, Graham AL. Potential Maternal and Infant Outcomes from (Wuhan) Coronavirus 2019-nCoV Infecting Pregnant Women: Lessons from SARS, MERS, and Other Human Coronavirus Infections. *Viruses.* 2020;12(2):194.
25. Caparros-Gonzalez RA, Perra O, Alderdice F, Lynn F, Lobel M, García-García I, Peralta-Ramírez MI. Psychometric validation of the Prenatal Distress Questionnaire (PDQ) in pregnant women in Spain. *Women Health.* 2019;59:937-52.
26. Caparros-Gonzalez RA, Romero-Gonzalez B, Quesada-Soto JM, Gonzalez-Perez R, Marinas-Lirola JC, Peralta-Ramírez MI. Maternal hair cortisol levels affect neonatal development among women conceiving with assisted reproductive technology. *J Reprod Infant Psychol.* 2019;37:480-9.