Neonatal outcomes of pregnant women diagnosed with SARS-CoV-2: an integrative review

Desfechos neonatais de gestantes com diagnóstico de SARS-CoV-2: uma revisão integrativa

Resultados neonatales de mujeres embarazadas diagnosticadas con SARS-CoV-2: una revisión integradora

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Abstract
The present study analyzed the neonatal outcomes reported in pregnant women with COVID-19. An integrative review was carried out after formulating the guiding question. That done, the research strategy, selection of criteria and data extraction were carried out. The searches were performed in the databases "PubMed", "Web of Science", "LILACS" and "ScienceDirect" using the following search terms: 2019-nCoV, covid-19, SARS-CoV-2, pregnant, pregnancy, birth, fetal, neonatal, outcomes, complications and adverse. The studies involved 226 pregnant women diagnosed with COVID-19 and 174 healthy pregnant women. Among the 226 pregnant women with COVID-19, there was 01 intrauterine fetal death and 16 remained pregnant until the end of the respective studies. Thus, 209 pregnant women with COVID-19 evolved for childbirth, resulting in 212 live births. Of these, 127 (59.9%) were born by cesarean delivery, 38 (17.9%) were born at <37 weeks of gestational age [3 (1.4%) <28 weeks] and 16 (7.5) were born at weight <2500 g. Neonatal results included 8 (3.8%) with a positive SARS-CoV-2 test, 12 (5.7%) with fetal distress, neonatal asphyxia, vomiting or skin rashes, 2 (0.9%) with intravascular coagulation disseminated, 1 (0.5%) alteration of cardiac enzymes, 1 (0.5%) multiple organ failure and 1 (0.5%) neonatal death. Various complications have been identified in pregnant women with COVID-19, therefore, a greater care must be given to this population group due to a greater risk of neonatal complications.

Keywords: Covid-19; SARS-CoV-2; Pregnant; Neonatal results.

Resumo

O presente estudo analisou os desfechos neonatais relatados em mulheres grávidas com COVID-19. Uma revisão integrativa foi realizada após a formulação da questão norteadora. Feito isso, procedeu-se a estratégia de pesquisa, a seleção dos critérios e a extração dos dados. As buscas foram realizadas nas bases de dados "PubMed", "Web of Science", "LILACS" e "ScienceDirect" utilizando os seguintes termos de busca: 2019-nCoV, covid-19, SARS-CoV-2, gravidez, gestação, nascimento, fetal, neonatal, resultados, complicações e adversos. Os estudos envolveram 226 gestantes com diagnóstico de COVID-19 e 174 gestantes saudáveis. Entre as 226 gestantes com COVID-19, houve 01 óbito fetal intrauterino e 16 permaneceram grávidas até o final dos respectivos estudos. Assim, 209 gestantes com COVID-19 evoluíram para o parto, resultando em 212 nascidos vivos. Destas, 127 (59,9%) nasceram de parto cesáreo, 38 (17,9%) nasceram com <37 semanas de idade gestacional [3 (1,4%) <28 semanas] e 16 (7,5) nasceram com peso <2500 g. Os resultados neonatais incluíram 8 (3,8%) com um teste SARS-CoV-2 positivo, 12 (5,7%) com sofrimento fetal, asfixia neonatal, vômitos ou erupções cutâneas, 2 (0,9%) com coagulação intravascular disseminada, 1 (0,5%) alteração de enzimas cardíacas, 1 (0,5%) falência de múltiplos órgãos e 1 (0,5%) óbito neonatal. Complicações variadas foram identificadas em gestantes com COVID-19, logo, um maior cuidado deve ser prestado a esse grupo populacional devido à um maior risco de complicações neonatais.

Palavras-chave: Covid-19; SARS-CoV-2; Gestação; Resultados neonatais.

Resumen

El presente estudio analizó los resultados neonatales informados en mujeres embarazadas con COVID-19. Se realizó una revisión integradora luego de formular la pregunta orientadora. Hecho esto, se llevó a cabo la estrategia de investigación, selección de criterios y extracción de datos. Las búsquedas se realizaron en las bases de datos "PubMed", "Web of Science", "LILACS" y "ScienceDirect" utilizando los siguientes términos de búsqueda: 2019-nCoV, covid-19, SARS-CoV-2, embarazo, embarazada, parto, fetal, neonatal, resultados, complicaciones y adversas. Los estudios involucraron a 226 mujeres embarazadas diagnosticadas con COVID-19 y 174 mujeres embarazadas sanas. Entre las 226 mujeres embarazadas con COVID-19, hubo 01 muerte fetal intrauterina y 16 permanecieron embarazadas hasta el final de los estudios respectivos. Por lo tanto, 209 mujeres embarazadas con COVID-19 evolucionaron para el parto, lo que resultó en 212 nacidos vivos. De estos, 127 (59,9%) nacieron por cesárea, 38 (17,9%) nacieron con <37 semanas de edad gestacional [3 (1,4%) <28 semanas] y 16 (7,5) nacieron en peso <2500 g. Los resultados neonatales incluyeron 8 (3,8%) con una prueba de SARS-CoV-2 positiva, 12 (5,7%) con sufrimiento fetal, asfixia neonatal, vómitos o erupciones cutáneas, 2 (0,9%) con coagulación intravascular diseminada, 1 (0,5%) alteración de las enzimas cardíacas, 1 (0,5%) insuficiencia multiorgánica y 1 (0,5%) muerte neonatal. Se han identificado diversas complicaciones en gestantes con COVID-19, por lo que se debe brindar una mayor atención a este grupo de población debido a un mayor riesgo de complicaciones neonatales.

Palabras clave: Covid-19; SARS-CoV-2; Embarazada; Resultados neonatales.

1. Introduction

Coronavirus 2019 (COVID-19), responsible for the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Ludvigsson, 2020) and the current pandemic, is one of seven species of coronavirus that infect humans and is among the three that are potentially fatal (Zhou et al., 2020; Lu et al., 2020). The outbreak was considered to have started in Wuhan, China, and the World Health Organization declared the pandemic and a Public Health Emergency of International Importance on January 30, 2020 (Li et al., 2020; Baloch et al., 2020). As of May 29, 2020, 5.701.337 cases of COVID-19 and 357.688 deaths were recorded (Baloch et al., 2020).

Injuries caused by this disease, through imbalance in the immune system, hydroelectrolytic disorders and systemic inflammatory response, can promote tissue damage and impairment of the lung and other organs, as has been observed in the evolution of severe cases to acute renal failure, acute myocardial injury and/or acute myocardial infarction (Bansal, 2020; Lippi & Plebani, 2020). In Wuhan, 94% of fatal patients died from multiple organ failure (Du et al., 2020).

There is still a scarcity of studies on this infection in pregnant women but those already performed have found changes similar to those in non-pregnant adults: immune disorders, systemic inflammation and pulmonary involvement (Wang et al., 2020; Chen et al., 2020). Therefore, the aim of this study is to review neonatal outcomes reported for pregnant women with COVID-19.

2. Methodology

This integrative review was carried out following the formulation of the guiding question, the research strategy, the selection of criteria and data extraction (Whittemore & Knafl, 2005). The guiding question was developed according to the PICO model (Population, Intervention, Comparison, Result) (Schardt et al., 2007), which improves the formulation of the guiding question and the location of relevant studies.

2.1 Search strategy and selection of studies

The searches were performed March 17 – September 28, 2020, in the databases "PubMed", "Web of Science", "LILACS" and "ScienceDirect" using the following search terms: 2019-nCoV, covid-19, SARS-CoV-2, pregnancy, pregnant, born, fetal, neonatal, perinatal outcomes, complication and adverse. No language filters were used and all results were analyzed for title, abstract and full text.

The studies included and reviewed reported obstetric complications and neonatal outcomes for pregnant women with COVID-19 diagnosed using real-time quantitative polymerase chain reaction (qRT-PCR), polymerase chain reaction (PCR) or clinical diagnosis using computed tomography and clinical findings compatible with COVID-19. Studies with undescribed neonatal outcomes were excluded, as well as duplicate studies and those with pregnant women with congenital diseases.

2.2 Data extraction

Data were independently extracted by three researchers: type of study, sample size, average sample age, gestational age (weeks (w) and days (d)), severity of COVID-19 disease, prevalence/incidence of comorbidities and adverse neonatal outcomes. Any disagreement, such as study type, duplicity, case of genetic disease, was resolved by consensus.

3. Results

3.1 Selection of studies

The search in the databases resulted in 427 articles. After exclusion due to duplication, selection by title, by summary, availability and selection by full text, 14 articles with 226 pregnant women with COVID-19 and 174 healthy pregnant women were included in this review. Until the writing of this article was completed (May 28, 2020), new searches, new searches were carried out in the databases for possible new studies to include; no new studies were published and included.

Maternal data and neonatal outcomes from the included studies (were extracted and are available in Table 1. The published studies are of varied methodologies, promoting heterogeneity. Of the 14 studies included, 3 were case reports, 2 were case control studies, 2 were prospective studies and 7 were retrospective studies. Data on the severity of COVID-19 was not discussed in all articles, but some categorized it into mild, moderate, severe or critical symptoms.

Table 1 - General characteristics of the studies included of pregnant women with COVID-19 including neonatal outcomes.

Study reference	Type of study	Sample MA GA N(pregnant women)	Comorbidity N(%)	Delivery Adverse neonatal outcome N(% of neonates)
Lieu et al., 2020.	Case control	N case group N=16 confirmed N= 18 suspected 26 – 37 years-old 38w N control group N= 121 25 – 35 years-old 32 – 39w7d	case group: confirmed group: gestational diabetes mellitus 3(18.7%) premature rupture of membranes 1(6.2%) gestational hypertension 3(18.7%) hypothyroidism 2(12.5%) preeclampsia 1(6.2%) sinus tachycardia 1(6.2%) suspected group: preeclampsia 1(5.6%) placenta previa 1(5.6%) control group: comorbities not informed	case group: N= 36 (100%) cesarean section 32 (88.9%) 2 sets of twins, 1 in the confirmed group and 1 in the suspected group confirmed group: N= 17 (100%) prematurity 4(23.5%) low birth weight 3(17.6%) intrauterine fetal distress 2(11.8%) suspected group (18 neonates (100%): N=19 (100%) prematurity 4(21.1%) low birth weight 2(10.5%); intrauterine fetal distress 1(5.3%) control group: N= 121 (100%) cesarean section 50(41.3%) prematurity 7(5.8%) low birth weight 3(2.5%) intrauterine fetal distress 6(4.9%)
Chen et al., 2020.	Retrospective	N=9 26 – 40 years-old 36w – 39w4d	gestational hypertension 1(11.1%) preeclampsia 1(11.1%) influenza virus 1(11.1%)	N=9 (100%) cesarean section 9(100%) prematurity 4(44.4%) low birth weight 4(44.4%) serum elevation of myocardial enzymes 1(11.1%)
Wang et al., 2020.	Case report	N=1 34 years-old 40w	hypothyroidism 1(100%) history of chromosomal alteration 1(100%); severe COVID-19	N=1 (100%) cesarean section 1(100%) positive test for SARS-CoV-2 1(100%)
Zeng et al., 2020.	Retrospective	N=3 age not informed 31w2d – 40w4d	no comorbidity informed	N=3 (100%) cesarean sections 3(100%) prematurity 1(33.3%) low birth weight 1(33.3%) neonatal asphyxia 1(33.3%) positive test for SARS-CoV-2 3(100%)
Hu et al., 2020.	Retrospective	N=7 30 – 34 years-old 37w – 41w2d	liver dysfunction 1(14.3%)	N=7 (100%) vaginal delivery 7(100%) positive test for SARS-CoV-2 1(14.3%)

Ferrazzi et al., 2020.	Retrospective	N=42 21 - 44 30> 37w 7= 34-37w; 4≤ 34w	gestational diabetes 6(85.7%).	N= 42 (100%) cesarean section 18(42.8%) prematurity 11(26.2%) positive test for SARS-CoV-2 3(7.1%)
Zhu et al., 2020.	Prospective	N=9 25 – 35 years-old 31 – 39w	no comorbidity informed	N= 10 cesarean sections 6(60%) low weight at birth 6(60%) pediatric critical illness score 6(60%) disseminated intravascular coagulation 2(20%) multiple organ failure 1(10%) death neonatal 1(10%) respiratory distress, vomiting or skin rashes 7(90%) 1 case of twin pregnancy
London et al., 2020.	Retrospective	Symptomatic group: N=46 25 – 33 years-old 43 in the third trimester – not detailed + 1 fetal death at 17w + 1 at 25w + 1 at 26w Asymptomatic group: N=22 24 – 34 years-old All in the third trimester of pregnancy – not detailed	Symptomatic group: preeclampsia 2(6.1%) other comorbidity (in the N total) 15(32.6%) – not described Asymptomatic group: preeclampsia 1(4.5%) other comorbidity (in the N total) 4(18.2%) – not described	Symptomatic group: 12 pregnancies were ongoing at study end 01 fetal death at 17weeks N=33 (100%) cesarean section 16(48.5%) prematurity 12(36.4%) Asymptomatic group: N=22 (100%) cesarean section 6(27.3%)
Peng et al., 2020	Case report	N=1 25 years-old 35w3d	no comorbidity	N= 1 (100%) cesarean section 1(100%) prematurity 1(100%) intrauterine fetal distress 1(100%)
Liao et al., 2020	Case control	N case group=10 27-36 years-old 36w2d - 40w2d N control group=53 21 – 37 years old 31w1d – 42w	Case group no comorbidity informed mild respiratory symptoms 10(100%) Control group no comorbidity informed	N= 63 (100%) vaginal delivery 63(100%) Case group: N= 10 (100%) premature 1(10%) Control group: N= 53 (100%) prematurity 5(9.4%) neonatal asphyxia 4(7.5%)
Yu et al., 2020.	Retrospective	N=7 29 – 34 years-old 37 – 41w	hypothyroidism 1(14.3%) polycystic ovary syndrome 1(14.3%)	N= 7 (100%) cesarean section 7(100%)

Liu W et al., 2020.	Prospective	N=19 27 – 34 years-old 38w6d (average reported)	no comorbidity informed	N= 19 (100%) cesarean sections 18(94.7%)
Liu D et al., 2020.	Retrospective	N=15 23 – 40 years-old 12 – 38w	thalassemia and gestational diabetes mellitus 1(6.7%) replacement of mitral and tricuspid valves 1(6.7%) placenta previa 1(6.7%).	4 pregnancies were ongoing at study end N= 11 (100%) cesarean section 10(90.9%)
Xiong et al., 2020.	Case report	N=1 25 years-old 38w4d	no comorbidity	N= 1(100%) vaginal delivery 1(100%)

MA= maternal age at time of study; GA: gestational age at time of study (w= week; d=day); N= number of participants;
Source: Authors.

The 226 pregnant women with COVID-19 included 18 from one study (Li et al., 2020) with suspected infection based on signs, symptoms and changes in chest CT scan characteristic of COVID-19 and negative laboratory tests. According to the authors of that study (Li et al., 2020), cases of false negatives may be common for cases of COVID-19 infection due to due to virulence, advanced disease sampling and inappropriate swabbing sites.

3.2 Characteristics and comorbidities of pregnant women with COVID-19

Among maternal characteristics at time of study, the age of the pregnant women ranged from 21 to 44 years-old and the gestational age ranged from 12 to 42 weeks. Three pregnant women with COVID-19 had twin pregnancies (Li et al., 2020; Zhu et al., 2020). In addition, of the 226 pregnant women, 01 had an intrauterine fetal death at 17 weeks of gestation and 16 were still pregnant at the end of the study. Therefore, 209 pregnant women and their neonatal outcomes were described.

The presence or absence of comorbidity of 185 pregnant women was reported. Of these, 51 (27.6%) had pre-existing comorbidities or diseases during pregnancy (gestational diabetes mellitus, pre-eclampsia, placenta previa, influenza virus). Severe symptoms were reported in only one study of a 34-year-old woman, 40 weeks of gestation, and a clinical history of hypothyroidism and obstetric chromosomal alteration (Wang et al., 2020). The other studies followed with reports of mild, moderate or unreported respiratory symptoms (Li et al., 2020; Chen et al., 2020; Zeng et al., 2020; Hu et al., 2020; Ferrazzi et al., 2020; Zhu et al., 2020; London et al., 2020; Peng et al., 2020; Liao et al., 2020; Yu et al., 2020; Liu et al., 2020; Liu et al., 2020; Xiong et al., 2020). Among pregnant women without COVID-19, there was no report of pre-existing comorbidity or gestational disease.

3.3 Neonatal outcomes

Neonatal outcomes were reported for 212 infants born to 209 women with COVID-19 (confirmed and suspected), including 3 sets of twins in two studies (Li et al., 2020; Zhu et al., 2020). Of these 127 (59.9%) were delivered by cesarean section and 85 (40.1%) vaginally. Thirty-eight (17.9%) were born <37 gestational weeks [3 (1.4%) were born extremely premature at <28 gestational weeks], and 16 (7.5%) were born with low birth weight (<2500 g).

Neonatal complications were reported in 10, included fetal distress, neonatal asphyxia, vomiting or skin rashes (n=12 [5.7%]), alteration of cardiac enzymes (n=1 [0.5%]), positive test for SARS-CoV-2 (n=8 [3.8%]), disseminated intravascular

coagulation (n=2 [0.9%]), multiple organ failure (n=1 [0.5%]) and death (n=1 [0.5%]). No maternal or fetal complications or adverse neonatal outcomes were reported in 4 studies (Yu et al., 2020; Liu et al., 2020; Liu et al., 2020; Xiong et al., 2020).

Newborns with a positive test for SARS-CoV-2 were reported in 04 studies [13-16] and all survived until the end of the respective study. One case was related in a case report (34-year-old pregnant woman, 40 gestational weeks, hypothyroidism, chromosomal alteration in a previous pregnancy and severity of COVID-19), where a newborn was diagnosed with SARS-CoV-2 through a test performed after birth and evolved without complications until hospital discharge (Wang et al., 2020).

The remaining (n = 7) newborns positive for SARS-CoV-2 have been reported in three other studies (Zeng et al, 2020; Hu et al., 2020; Ferrazzi et al., 2020). Of these, 06 were born by cesarean section (Zeng et al, 2020; Ferrazzi et al., 2020) and 01 were born by vaginal delivery (Hu et al., 2020), 06 were born at term (Hu et al., 2020; Ferrazzi et al., 2020) and 01 was premature (31 weeks (w) and 2 days (d)), had low birth weight (1580g), had asphyxia and received mechanical ventilation (Zeng et al, 2020). According to the authors, two of these cases were positive after the newborn had contact (be breastfed) (Ferrazzi et al., 2020).

It is important to consider that, except for the case reported in the previous paragraph, the other records of disseminated intravascular coagulation, organ dysfunction, neonatal death, alteration of cardiac enzymes, fetal distress, neonatal asphyxia, vomiting or skin rashes were not in newborns diagnosed with COVID-19 (liu et al., 2020; Chen et al., 2020; Zeeng et al., 2020; Zhu et al., 2020; Peng et al., 2020; Liao et al., 2020).

Three studies analyzed neonatal outcomes according to the presence or absence of symptoms of COVID-19 (London et al., 2020), with or without the diagnosis of COVID-19 [20] or with laboratory or suspected diagnosis (Liu et al., 2020). In the comparison between symptomatic and asymptomatic pregnant women, the prevalence of outcomes was among symptomatic women with 16 (48.5%) cases of cesarean birth *vs* 6 (27.3%), 12 (36.4%) cases of prematurity *vs* 0. The one fetal death occurred in a symptomatic woman (London et al., 2020).

In a study of 10 pregnant women with COVID-19 and mild respiratory symptoms and 53 pregnant women without COVID-19, all infants were born by vaginal delivery and the proportion born prematurely was similar (10.0% of the cases and 9.4% of the controls). Four (7.5%) infants in the control group had neonatal asphyxia (Liao et al., 2020). Another study compared outcomes among pregnant women who had laboratory confirmed COVID-19, women with suspected COVID-19 clinically diagnosed, and women without COVID-19 (Liu et al., 2020). Adverse outcomes were reported with similar frequency in the neonates born to women with confirmed and suspected COVID-19, including prematurity (23.5% *vs* 21.1%), low birth weight (17.6% *vs* 10.5%), and intrauterine fetal distress (11.8% *vs* 5.3%). However, the proportions of neonates born preterm and with low birth weight were higher than among infants born to non-infected women.

4. Discussion

In this review, 8 (3.8%) of 212 live newborns from women diagnosed with COVID-19 tested positive for COVID-19. Two had unprotected contact with their mothers while the remaining six had been kept isolated. Other adverse neonatal outcomes were reported including prematurity, low birth weight, multiple organ failure and death.

There is a need for more information about COVID-19 during pregnancy, but studies have shown changes similar to those reported in non-pregnant women (Chen et al., 2020; Zhao et al., 2020): immune disorders, hyperinflammation ("called cytokine storm") and damage endothelial (Guzik et al., 2020; Bairey Merz et al., 2020; Monteil et al., 2020). Laboratory data record changes in the count of white blood cells, lymphocytes, neutrophils and platelets, in addition to a significant increase in the serum concentration of inflammatory biomarkers, such as ferritin, C-reactive protein (CRP), interleukin (IL)-6, IL-8, IL-10). Markers of impairment of other organs related to the severity of the disease, such as kidneys, heart and liver, were

identified through changes in the serum level of creatinine, albumin, blood urea nitrogen, creatinine kinase, myoglobin, aspartate aminotransferase (AST) and ALT (alanine aminotransferase) (Henry et al., 2020).

In other inflammatory diseases that arise during pregnancy, there is a significant increase in adverse neonatal outcomes, such as prematurity, low birth weight and restricted intrauterine growth (Skrablin et al., 2007). These adverse outcomes, in turn, are associated with a higher risk of neonatal complications, a longer hospital stay, a higher risk of sequelae and mortality (Leung et al., 2018; Cardoso-Demartini et al., 2011; Maggi et al., 2014). In this study, 08 cases of neonates with COVID-19 were reported, in addition to serious complications (neonatal asphyxia, multiple organ failure and death).

As shown in Table 1, although not all studies reported details, information about the presence of comorbidity was described for 185 pregnant women and 51 (27.6%) had it. In a study of 46 pregnant women with COVID-19 (Lokken et al., 2020), disease severity and worse neonatal outcomes were associated with the presence of pre-existing comorbidity combined with overweight or obesity. It is important to consider the presence of comorbidity as a risk factor for pregnant women with COVID-19, since it can cause a sum of changes and complications that directly affect fetal development and the progress of pregnancy, and is already associated to worse neonatal outcomes (Guedes et al., 2020).

5. Final Considerations

This review identified the main neonatal outcomes of pregnant women diagnosed with COVID. This disease is not yet fully understood and, therefore, poses numerous challenges for the health system. The published data, until then, are of varied methodologies and results, as well as the outcomes found. Various complications have been identified in pregnant women with COVID-19, therefore, a greater care must be given to this population group due to a greater risk of neonatal complications.

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