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Combities associated with maternal mortality in Covid-19

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ABSTRACT
The present work deals with actions to promote public health in the federal service, analyzing issues of administrative law and raising the hypothesis whether such actions constitute public policies in relation to this sector. For this, it uses doctrines, information from public agencies, other studies already carried out and legislation. The research is of the exploratory type with documentary and bibliographic source. This study concludes considering that these practices offered by the Federal Public Administration to the federal public servant, are not characterized as public policies, since they are presented in a timely and differentiated manner in the different federative units of the Integrated Subsystem of Attention to the Health of the Server (SIASS).it possible to transform fun into learning.

Keywords: Pregnant Women, postpartum period, maternal mortality, COVID-19, comorbidities.

1 INTRODUCTION

In December 2019, a new virus emerged and put Chinese authorities on alert by increasing the number of hospitalizations for pneumonia in China's Wuhan province. It was a disease of unknown etiology, which rapidly spread, and reached pandemic status on March 11, 2020, with the main symptoms of fever, unproductive cough, dyspnea, and fatigue (ORTEGA et al., 2020).

In this scenario, it was discovered to be a new coronavirus, of the genus betacoronavirus, family coronaviridae. This agent has a zoonotic character, therefore the constant interaction between humans and animals, allied to the recombination of their genomes, which enable the emergence of new coronaviruses that arise with the potential to cause diseases in humans (NA et al., 2020).

The virus spreads from droplets, produced during coughing and sneezing. SARS-CoV-2 enters the cell through the ECA-2 receptor of the host cell. It is present in several tissues of the human body and has high expression in pulmonary epithelial cells, mainly alveolar epithelial cells, being then a reservoir for replication and invasion of the virus (ORTEGA et al., 2020).

Much has been reported about the social, economic, and cultural impacts, in addition to the overload of the health system in an alarming way, in which inputs, such as mechanical ventilators and hospital beds, have become scarce. It is important to point out the spread of misinformation about treatment and vaccination, which culminated in the high rate of deaths (BARCELLOS; XAVIER; 2022).

According to the World Health Organization, maternal mortality (MM) is the death of a woman in the period of gestation or in the period of 42 days after its termination, which does not depend on the duration or location, triggered by reasons or measures related to pregnancy, whose accidental or incidental causes are not included. It constitutes a public health challenge, particularly in developing countries, where the gap in access to health services is highlighted (CÁ et al., 2022).

The physiological changes that occur during pregnancy result in an increased risk of susceptibility, morbidity, and mortality due to viral infections. The pregnant woman has a decrease of 20 to 30% in her pulmonary functional residual capacity, due to the relaxation of the rib ligaments, upward movement of the diaphragm due to uterine enlargement, increase in the subcostal angle and transverse diameter of the chest wall. Allied to this, increased progesterone stimulates the respiratory center, leading to hyperventilation. Thus, the pregnant woman is more prone to hypoxia, an unfavorable situation for women during the disease (ZHAO et al., 2020).

It is understood that the expression of the ACE 2 receptor is increased during pregnancy, which may provide greater susceptibility to the entry of SARS-CoV-2, in addition to regulating blood pressure, favoring infection. Other changes such as decreased thymus and CD4+ and CD8+ T cell production may favor the virus (MCCARTNEY et al., 2020).

Chronic diseases, when associated, are called comorbidities, and in pregnancy, this coexistence of diseases amplifies maternal-fetal exposure, since the immune and physiological system are altered. Regardless of the comorbidity that the woman presents, when infected by COVID-19, the risk of developing a respiratory distress aggravating the disease is greater, so that there is a need for hospitalization (CUNHA et al., 2022).

The presence of comorbidities is associated with MM because they accentuate the vulnerabilities to which these pregnant women are exposed, since the cytokine storm, characteristic of Covid-19, can trigger a greater inflammatory response and changes in the immune response (HANNA; HANNA, SHARMA, 2020).

Despite the high number of comorbidities present in the literature, knowing the most frequent ones can help direct care from the health team to pregnant women with Covid-19. Thus, the aim of this study was to summarize evidence regarding comorbidities associated with maternal mortality from Covid-19.

2 METHOD

This is an integrative literature review, which is characterized by the gathering of data from studies of various methodologies. IR comprises a rigorous, principled method that adds knowledge to evidence-based practice. It seeks to answer a current question, or already studied, from the careful analysis and precise synthesis of the information from the sources studied (STILLWELL et al., 2010).

We used the steps that comprise the IR process, which are: formulation of the guiding question, search or sampling in the literature, data collection, critical analysis of the included studies, discussion of the results and presentation of the integrative review (MELNYK et al., 2010).

To delimit the guiding question, the PVO strategy was used: P (person): pregnant and postpartum women, V (variable): comorbidities and O (Outcome/outcome): maternal mortality due to COVID-19. Then, the guiding question of this study was composed: "What is the evidence of comorbidities associated with maternal mortality from COVID-19?".

The database search took place in October 2022 by two researchers. Through the Portal de Periódicos da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), with a proxy licensed from the Federal University of Mato Grosso do Sul, the databases EMBASE, SCOPUS (Elsevier), PUBMED (Central – PMC), Web of Science - (Main Collection), CINAHL - (Cumulative Index to Nursing and Allied Health Literature) and VHL - (Virtual Health Library) were accessed.

The following descriptors were used: Pregnant Women, Postpartum Period, Comorbidity, Maternal Mortality (DeCS); Pregnant Women, Postpartum Period, Comorbidity, Maternal Mortality (MeSH); pregnant woman, puerperium, comorbidity, maternal mortality (EMTREE). The crossing strategies are presented in Chart 1.

Table 1: Cross-checks performed in the databases.

Database	Intersection
EMBASE	('pregnant woman'/exp OR 'puerperium'/exp) AND 'comorbidity'/exp AND 'maternal mortality'/exp
SCOPUS	(ALL (“pregnant woman”) OR ALL (puerperium) AND ALL (comorbidity) AND ALL (“maternal mortality”)) AND (LIMIT-TO (DOCTYPE, “ar”))
PUBMED	((("Pregnant Women"[Mesh]) OR "Postpartum Period"[Mesh]) AND "Comorbidity"[Mesh]) AND "Maternal Mortality"[Mesh]
Web of Science	(((ALL= (Pregnant Women)) OR ALL= (Postpartum Period)) AND ALL=(Comorbidity)) AND ALL=(Maternal Mortality)
CINAHL	(Pregnant women or pregnant woman or pregnancy or pregnant or expecting mother) AND (comorbidity or comorbidities) AND (maternal mortality or maternal deaths or pregnancy related deaths)
	(Postpartum period or postnatal care or postpartum or puerperium or postnatal) AND (comorbidity or comorbidities) AND (maternal mortality or maternal deaths or pregnancy related deaths)
BVS	(Pregnant Women) OR (Postpartum Period) AND (Comorbidity) AND (Maternal Mortality)
	(Pregnant Women) OR (Postpartum Period) AND (Comorbidity) AND (Maternal Mortality)

Source: The Authors, 2023.

The following were included: a) full articles available in full in the databases; b) articles that addressed comorbidities associated with maternal mortality from COVID-19; c) studies in any language and without time frame. The following were excluded: a) duplicate articles will be considered only once; b) publications arising from letters to the editor, reviews, editorials, expert opinions and reviews.

The articles were retrieved and anchored in the Rayyan QCRI software, the duplicates were excluded, and two researchers screened the articles independently, reading the titles and abstracts, in cases of doubt the consensus was reached by a third researcher.

For data collection, the Microsoft Office Excel software was used, where information was extracted from the articles selected as a final sample, through the variables of interest: identification of the publication and the scientific journal, methodological aspects of the study, evidence on the comorbidities associated with maternal mortality from COVID-19, limitations and conclusions.

To analyze the level of evidence, the reference of the Joanna Briggs Institute Collaborating Center (JBI) presented in Chart 2 was used:

Table 2: Level of evidence according to the Joanna Briggs Institute.

Level of evidence	**Description**
Tier I	Evidence obtained from a systematic review of randomized controlled trials.
Tier II	Evidence obtained from a randomized controlled trial.
Level III.1	Evidence obtained from well-designed controlled clinical trials without randomization.
Level III.2	Evidence obtained from well-designed cohort or case-control studies.
Level III.3	Evidence obtained from multiple time series, with or without intervention, and dramatic results in uncontrolled experiments.
Level IV	Opinions of respected authorities, based on clinical criteria and experience, descriptive studies or reports of expert committees.

Source: The Authors, 2023.

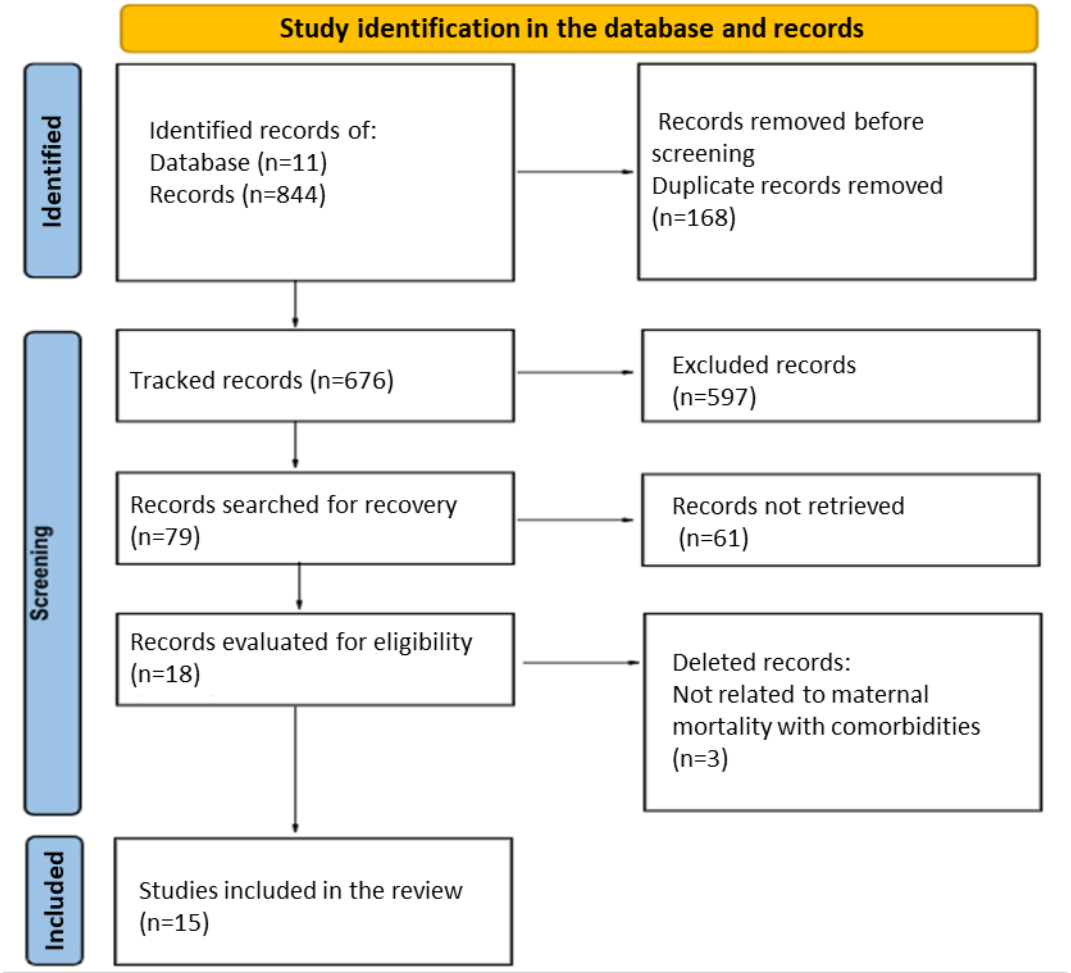
The results were synthesized in a synoptic chart descriptively, for better interpretation and grouped for analysis by comorbidities found in the studies.

3 FINDINGS

The search for articles in the databases resulted in a total of 844 articles. A total of 168 duplicates were excluded, leaving 676 articles for screening in the Rayyan. After reading titles and abstracts, 18 articles were selected for analysis in this study. The articles were read in full, and 3 articles

were excluded, which do not contemplate the question of this study. The final sample corresponds to 15 articles (Figure 1).

Figure 1: Flowchart of the study collection process.



Source: The Authors, 2023.

The articles produced in Brazil stood out, and corresponded to approximately 53% of the total. There was a significant variation in the absolute number of maternal mortalities, depending on the type of study, with records ranging from 1 to 1858 cases of maternal death, analyzed in the researches.

Regarding the types of studies found in the present literature review, there was a predominance of studies from observational studies (n=14; 93.3%), and only one study was classified as a case study (6.7%). Among the studies analyzed, eight were classified as level of evidence III.2 (53.3%), six as level III.3 (40%) and one as level IV (6.7%). It is noteworthy that all the comorbidities mentioned in each study are shown in Chart 3.

Table 3: Identification of included studies by title, author, country, maternal mortality, level of evidence/study type, and comorbidities, 2023.

1st Author and year	Country	Maternal Mortality (N)	Level of Evidence/Type of Study	Comorbidities*
Takemoto, 2020	Brazil	124	Level III.2 Cross-sectional study with data analysis from the acute respiratory distress syndrome (ARDS) Surveillance System of the Ministry of Health.	CVD, diabetes, obesity, asthma.
Serra, 2021	Brazil	295	Level III.2 Retrospective study of data from the Influenza Epidemiological Surveillance Information System of the Brazilian Ministry of Health	Diabetes, CVD, CKD, obesity, asthma, immunodepression.
Rodríguez, 2021	Mexico	304	Level III.2 Descriptive study based on data available in SISVER – National System of Epidemiological Surveillance of Viral Respiratory Diseases and the Weekly Reports of Epidemiological Surveillance of Maternal Deaths of 2020 and 2021	Obesity, diabetes, hypertension, asthma, CKD, immunodepression.
Leal, 2021	Brazil	362	Level III.2 Population-based study based on data from the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe) of the Ministry of Health	Hypertension, diabetes, obesity, asthma or other chronic lung diseases, immunosuppression, hematological diseases, CKD, neurological disease or depression, chronic liver disease, tuberculosis, smoking.
Bachani, 2020	India	3	Level III.3 Retrospective single-center study that extracted data from medical records of a tertiary hospital for pregnant women with COVID-19 in India.	1st Case: Anemia, thrombocytopenia and hypothyroidism. 2nd Case: Hypertension, CKD, hypothyroidism, Intrahepatic Cholestasis of Pregnancy. 3rd Case: Emergency hysterectomy.
Aminimoghaddam, 2020	Iran	15	Level III.3 Retrospective study that extracted data from medical records of Firoozgar General Hospital, a referral hospital for Covid in Iran.	Diabetes, hypertension, CVD.
Moghadam, 2021	Iran	1	Level IV Case study of a 27-year-old woman who died of Covid at Lolagar Health Center in Iran	Diabetes.
Basu, 2021	South Africa	6	Level III.3 Retrospective study of all maternal deaths from April to September 2020 in Ekurhuleni Health District. COVID records and maternity case records were used.	Hypertension, HIV, diabetes.
Lokken, 2021	USA	3	Level III.3	Obesity, hypertension, autoimmune disease, congenital heart disease.

			This is a retrospective multicenter cohort study with analysis of medical records from 35 hospitals in the state of Washington, USA.	
Takemoto, 2022	Brazil	20	Level III.3 Descriptive analysis study based on secondary data compiled through media articles and epidemiological/surveillance reports	Asthma, Obesity, Mitral Stenosis, preeclampsia, CKD, gestational hypertension, pyelonephritis, CVD.
Filho, 2022	Brazil	15	Level III.3 This is a quantitative, cross-sectional study that extracted SIVEP-Influenza notifications.	Heart disease, diabetes, asthma.
Torres-Torres, 2021	Mexico	176	Level III.2 An ongoing prospective cohort study that extracted data from 475 hospitals from the Mexican National Coronavirus Registry.	Obesity, diabetes, hypertension, asthma, kidney disease, smoking, immunosuppression, CVD.
Siqueira, 2022	Brazil	1858	Level III.2 Population-based cohort study based on data reported in SIVEP-Influenza.	Obesity, CVD, diabetes, asthma, immunosuppression, lung disease, CKD, hematologic disease, neurological disease, liver disease.
Scheler, 2021	Brazil	148	Level III.2 cross-sectional study with data from SIVEP - INFLUENZA.	CVD, diabetes, obesity, respiratory disease (including asthma)
Godoi, 2021	Brazil	15	Level III.2 quantitative and retrospective research that analyzed the SIVEP-influenza Database, including COVID-19 data and made available by DATASUS.	CVD, diabetes, asthma

*Comorbidities were organized by absolute quantity, from the most present to the least. Legend: MM - Maternal death, CVD - Cardiovascular Disease, CKD - Chronic Kidney Disease, HIV - Human Immunodeficiency Virus.
Source: The Authors, 2023.

4 DISCUSSIONS

In this integrative review, five comorbidities were found that stood out, the same were repeated in almost all the studies analyzed as the most present quantitatively: obesity, diabetes mellitus (DM), cardiovascular diseases (CVD), hypertension and asthma. Due to the divergence of methodologies, some authors approached hypertension within the CVD group and others in a segmented way.

Among the 15 articles analyzed in this study, eight of them, published by Takemoto (2020), Serra (2021), Rodríguez (2021), Leal (2021), Lokken (2021), Takemoto (2022), Siqueira (2022) and Scheler (2021), reported the presence of obesity as a comorbidity in maternal mortality due to COVID-19. These findings proved that obesity emerged as a significant comorbidity in this population group, fatal to aggravate the clinical outcome.

The impact of obesity on the individual with Covid-19 is associated with reduced oxygen saturation due to impaired ventilation in the base region of the lungs. Changes in the secretion of cytokines, adipokines, and interferon reduce the immune response. The care of individuals with this condition should be greater, since just over 68% need ventilation in a critical state (EJAZ et al., 2020).

It was found that about 80% of the articles investigated mentioned the presence of Diabetes Mellitus (DM) as a comorbidity in maternal mortality in the occurrence of COVID-19. The identification of diabetes mellitus as a comorbidity underscores the need for preventive and control interventions for diabetes mellitus, with the intention of reducing the risk of serious complications associated with COVID-19 in pregnant women.

A systematic review reinforces the evidence that DM is associated with death from Covid-19 in the general population with a two-fold higher probability (KUMAR et al., 2020). DM can lead to increased risk of severe pneumonia, enzyme levels of tissue injury, hypercoagulability, and uncontrolled inflammatory response. In addition, individuals with DM are susceptible to inflammatory changes that aggravate Covid-19, evidenced by the increase in inflammatory biomarkers (GUO et al., 2020).

SARS-CoV-2 infection triggers the innate immune response and activation of standard recognition receptors, with secretion of the antiviral cytokine INF-γ, pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) (VABRET et al., 2020). The presence of IL-1 induces the production of nitric oxide, which inhibits anaerobic glycolysis of myocytes and causes reduced myocardial contractility. This cytokine also leads to the production of TNF-α. IL-6 has the function of replacing IL-1 in order to cause the same effects. High concentrations of IL-6 are linked to heart failure and death. The presence of elevated TNF-α concentrations impairs the Keap1/Nrf2 response, resulting in cardiomyocyte death from severe oxidative stress. It is possible that low levels of TNF-α may have a protective effect (LIU; LIU; WANG, 2021).

The analysis of this review revealed that approximately 60% of the articles investigated mentioned the presence of cardiovascular diseases (CVD) as a comorbidity in maternal mortality due to COVID-19, while 53.33% of the articles mentioned hypertension as an associated comorbidity.

It is noteworthy that high systolic blood pressure (SBP > 140 mmHg), when associated with elevated pulse pressure (≥ 60 mmHg), can be used as a predictor of mortality related to vascular remodeling and vascular stiffness (GALLO; CALVEZ; Savoy, 2022).

Hypertension may be linked to immune activation and oxidative stress, producing reactive oxygen species, increased activity of NADPH oxidases, cell migration and adhesion to the endothelial surface (PATRICK; VAN BEUSECUM; Kirabo, 2021). The cytokine storm results in endothelitis and has as a consequence the induction of vascular permeability, secretion of adhesion molecules, TNF-α, angiopoietin-2, negative regulation of eNOS, decreases the production of prostacyclin, induces platelet capture and dysregulation of the coagulation cascade, thrombin activation and fibrin production (BIKDELI et al., 2020).

The presence of intravascular thrombosis can cause further damage to the endothelium and lead to a constant cycle between inflammation and endothelial dysfunction. Microthromboses in the coronary and pulmonary circulation can lead to myocardial damage and contribute to severe hypoxia and respiratory distress (LINDNER et al., 2020).

Ten studies analyzed in this review reported asthma as a comorbidity and provide relevant insights into the comorbidities associated with MM and COVID-19-related deaths.

It is observed that the relationship between Covid-19 mortality in individuals with asthma is not significant. The situations in which comorbidity is present, in severe cases or death, other comorbidities existed and were more expressive for these outcomes than asthma (ADIR et al., 2021). It is noteworthy that individuals with non-allergic asthma had a higher risk of positivity for SARS-CoV-2 and severe clinical outcomes than those with allergic asthma (YANG et al., 2020).

It is suggested that the presence of asthma may have a protective effect against SARS-CoV-2 infection. Th2 inflammation reduces the production of pro-inflammatory cytokines and plays a role in late hyperinflammation. This effect on cytokines would reduce cytokine storm and other consequences (BEURNIER et al., 2020).

Two other comorbidities less present are autoimmune diseases and chronic kidney disease (CKD). Approximately 33.33% of the articles investigated in this review mentioned the presence of autoimmune diseases as a comorbidity for maternal mortality due to COVID-19, while 40% of the articles mentioned CKD as comorbidities that are also associated with this type of mortality.

The hyperinflammatory state generated by cytokines can lead to activation of components that result in autoimmune reactions. Despite little understanding about the association of Covid-19 and autoimmunity, reports of some diseases are present in the literature: Guillain-Barré syndrome, immune

thrombocytopenic purpura, autoimmune hemolytic anemia, Kawasaki disease and autoimmune thyroid disease (YAZDANPANAH; REZAEI, 2022).

The presence of CKD prior to Covid-19 is greater than the onset of this condition after infection. Individuals with this association may enter a hyperinflammatory and hypercoagulable state that are risk factors for acute kidney injury, severe disease, and death (PECLY et al., 2021). A multivariate regression infers that poor renal function is an independent factor for mortality, being twice as high in the general spectrum and almost five times in the in-hospital spectrum (URIBARRI et al., 2020).

It is observed that the inferences presented in this study and related to comorbidities associated with Covid-19 and maternal death, tend to support evidence from the literature that points to hospitalization in intensive care for Covid-19 as higher in cohorts with higher rates of comorbidity (KHALIL et al., 2020).

This study presents as limitations the non-use of gray literature and the heterogeneity of studies found in relation to the method and populations analyzed.

5 CONCLUSIONS

In the scientific literature, a broad spectrum of comorbidities has been associated with maternal mortality due to COVID-19. Among these comorbidities, six stand out as the most relevant, these being obesity, diabetes mellitus, cardiovascular diseases, arterial hypertension, autoimmune diseases, and chronic kidney disease. All these comorbidities are intrinsically related to the characteristics of the pathophysiological process triggered by SARS-CoV-2. Surprisingly, although asthma is frequently observed, the literature does not suggest a direct association with maternal mortality when confronted with other comorbidities.

By recognizing the comorbidities mentioned here as possible risk factors and including them in care strategies, the health team will be better prepared to face the challenges presented by maternal mortality due to COVID-19.

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