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ASSOCIATION BETWEEN SARS-COV-2 AND Helicobacterpylori INFECTION FOR HYPEREMESIS PREGNANCY: CONTRIBUTION OF THE NERVOUS, IMMUNOLOGICAL AND ENDOCRINE SYSTEMS IN A BIDIRECTIONAL AXIS

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ABSTRACT

Nausea and vomiting are symptoms commonly presented in the first trimester of pregnancy. However, when there is an exacerbation of these symptoms, it progresses to hyperemesis gravidarum (HG). Recent studies indicate an association between infection of the gastric mucosa by *Helicobacter pylori* and the occurrence of hyperemesis gravidarum. This infection has a high prevalence in pregnant women, as pregnancy itself brings risk factors for the infection to occur. In addition, with the advent of the pandemic, it became evident that pregnancy is also a risk factor for SARS-COV-2 infection, consequently estimating the susceptibility to hyperemesis gravidarum resulting from the vulnerability of the gastric mucosa and other maternal-fetal implications. To correlate the infection promoted by SARS-COV-2 and *Helicobacter pylori* to hyperemesis gravidarum, emphasizing the contribution of the nervous, immune and endocrine systems in a bidirectional axis. This is an integrative literature review. By taking hold of clear norms and scientific rigor, the following steps will be taken to prepare the study: identification of the theme and selection of the hypothesis; establishment of criteria for inclusion and exclusion of studies; literature search; definition of the information to be extracted from the selected studies; categorization of studies; evaluation of studies included in the integrative review; interpretation of results and synthesis of knowledge. With this research, it is expected that a better screening of patients with GH will be carried out, in order to avoid gestational complications resulting from the condition, such as prematurity and stillbirth. In addition, to increase the visibility of the association of HG with *Helicobacter pylori* infection by linking it, hordially, with SARS-COV-2 infection. With this, it is expected with the present work, an expansion of the literature regarding the mechanisms of gastric protection and its relevance in pregnancy, except for its vulnerability to infections and subsequent maternal-fetal implications.

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INTRODUCTION

Nausea and vomiting are symptoms commonly presented in the first trimester of pregnancy, affecting approximately 80% of patients. However, when there is an exacerbation of these symptoms, it progresses to hyperemesis gravidarum (HG), which is also known as incoercible vomiting or pernicious vomiting and affects 0.3 to 1% of the population (VAZ, 2019). It is considered HG when symptoms occur between the 4th and 10th week of gestation, with a significant improvement until the 20th week. However, in isolated cases, symptoms may persist until the end of pregnancy. The clinical condition is disabling in most cases due to intermittent discomfort, dehydration, hydroelectrolyte and acid-base imbalance, nutritional deficiency that can lead to a loss of 5% of pre-gestational body weight, resulting in hospitalization for intravenous hydration and parenteral nutrition (ALFENAS et al., 2017). Recent studies indicate the association between infection of the gastric mucosa by Helicobacter pylori and the occurrence of hyperemesis gravidarum (TEIXEIRA; SOUZA; ROCHA, 2017). This infection has a high prevalence in pregnant women, as pregnancy itself brings risk factors for the infection to occur, as well as hormonal and immunological fluctuations that guarantee maternal tolerance related to the fetus, which can trigger latent infection during pregnancy (AFSAR et al., 2020). When not treated properly, HG can result in complications during delivery such as premature placental abruption, preeclampsia, stillbirth, low gestational age and in rarer but extremely severe cases, hypercoagulation, central tip myelinosis, Wernicke's encephalopathy and esophageal trauma, such as Mallory-Weiss disease due to prolonged vomiting (ALFENAS et al., 2017). In this context, it can be inferred that the gastric mucosa needs protective factors to maintain its physical integrity, specifically in gestational conditions, thus avoiding ulcerative lesions and opportunistic infections. These occur when there is an imbalance of offensive factors, including infection by Helicobacter pylori, which can be sensitized by some viral

pathogens. (SOUZA et al., 2016). Nowadays, according to ZHANG et al (2021) through infection caused by the SARS-COV-2 virus, it was observed that the distribution of the virus entry receptor can be highly associated with the pathogenesis of the infection, with this, it was discovered that ACE II (SARS-COV-2 intracellular receptor) and the viral nucleocapsid were mainly in the cytoplasm of gastrointestinal epithelial cells. However, the virus can be inactivated by stomach acid, decreasing the likelihood of infection in a healthy stomach. On the other hand, in patients with non-integral gastric mucosa, as in intestinal metaplasia (IM), they usually develop Helicobacter pylori infection. In addition to the increase in enterocytes, IM is accompanied by the loss of parietal cells. This results in increased gastric pH, making it difficult for the virus to inactivate. Therefore, it is speculated that patients with a history of infection by Helicobacter pylori and MI may be susceptible to SARS-COV-2 (ZHANG et al, 2021) estimating, consequently, the susceptibility to hyperemesis gravidarum and other maternal and fetal implications.

METHODOLOGY

This is an sistematic literature review. By taking hold of clear norms and scientific rigor, the following steps will be taken to prepare the study: identification of the theme and selection of the hypothesis; establishment of criteria for inclusion and exclusion of studies; literature search; definition of the information to be extracted from the selected studies; categorization of studies; evaluation of studies included in the integrative review; interpretation of results and synthesis of knowledge. The question that guided this literature review was: SARS-COV-2 and Helicobacter pylori co-infection is associated with a higher risk of hyperemesis in pregnancy?

The data collection to compose this study was carried out between February and April 2022 and the search was conducted in the Virtual Health Library (BVS), in which the following databases were searched: Latin American and Caribbean Literature in Ciê Health

Table 1. List of articles reviewed using the study methodology and their respective year of publication

TITLE	MAGAZINE	REFERENCE	YEAR
Hematological Parameters to Predict the Severity of Hyperemesis Gravidarum and Ketonuria.	Revista Brasileira Ginecologia e Obstetrícia	ASLAN, M. M. et al. Hematological Parameters to Predict the Severity of Hyperemesis Gravidarum and Ketonuria. Rev Bras Ginecol Obstet. 2022.	2022
Association Between Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis.	JAMA Netw Open	BARAL, Ranu et al. Association Between Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021.	2021
Helicobacter pylori cagA virulence gene and severe esogastroduodenal diseases: is there an association?	Arq Gastroenteroly	OLIVEIRA, A. K. S.et al. Helicobacter pylori cagA virulence gene and severe esogastroduodenal diseases: is there an association? Arq Gastroenterol. v. 58 no 4 out/dez, 2021.	2021
Anti-diarrheal therapeutic potential of diminazene aceturate stimulation of the ACE II/Ang-(1–7)/Mas receptor axis in mice: A trial study.	Biochemical Pharmacology	SOUZA, Luan KM et al. Anti-diarrheal therapeutic potential of diminazene aceturate stimulation of the ACE II/Ang-(1–7)/Mas receptor axis in mice: A trial study. Biochemical Pharmacology, v. 186, p. 114500, 2021.	2021
General aspects of COVID-19 and its consequences	Institutional repository – Federal University of São Paulo (USP)	SILVA, Wagner Zaki Ribeiro da. General aspects of COVID-19 and its consequences. Institutional repository – Federal University of São Paulo (USP) 2021.	2021
Susceptibility factors of stomach for SARS-CoV-2 and treatment implication of mucosal protective agent in COVID-19.	Frontiers in Medicine	ZHANG, Min et al. Susceptibility factors of stomach for SARS-CoV-2 and treatment implication of mucosal protective agent in COVID-19. Frontiers in Medicine, p. 1046, 2021	2021
Helicobacter pylori infection and micronutrient deficiency in pregnant women: a systematic review and meta-analysis.	BMJ Open Gastro	AFSAR MNA, et al. Helicobacter pylori infection and micronutrient deficiency in pregnant women: a systematic review and meta-analysis. BMJ Open Gastro 2020.	2020
Pathophysiology of thrombosis associated with SARS-CoV-2 infection.	Jornal Vascular Brasileiro	CASELLA, Ivan Benaduce. Pathophysiology of thrombosis associated with SARS-CoV-2 infection. Jornal Vascular Brasileiro, v. 19, 2020.	2020
COVID19 pandemic: Pathophysiology and manifestations from the gastrointestinal.	World Journal of WJG Gastroenterology	GALANOPOULOS M.; et al. COVID19 pandemic: Pathophysiology and manifestations from the gastrointestinal trac.World Journal of W J G Gastroenterology August 21, 2020 Vol 26 Issue 31, p. 45794588, 2020.	2020
SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor	Cell	HOFFMANN, Markus et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell, v. 181, n. 2, p. 271-280. e8, 2020	2020
COVID19: gastrointestinal symptoms and potential sources of SARS-CoV-2 transmission	Anaesthesiology Intensive Therapy	KOTFIS K.; ZYDECKA K S. COVID19: gastrointestinal symptoms and potential sources of SARSCoV2 transmission. Anaesthesiology Intensive Therapy; Warsaw Vol. 52, Ed. 2, (2020), p. 171172, 2020.	2020
Women's Position on COVID-19 and Pregnancy International Journal for Innovation Education and Research	Brazilian Archives of Cardiology	MARQUES-SANTOS, Celi et al. Women's Position on COVID-19 and Pregnancy International Journal for Innovation Education and Research Vol.10 No.0 (2022), pg. 9 Cardiopathies–Department of Women's Cardiology of the Brazilian Society of Cardiology–2020. Brazilian Archives of Cardiology, v. 115, p. 975-986, 2020.	2020
Is pregnancy a risk factor of COVID- 19?	Journal of Obstetrics & Gynecology and Reproductive Biology	PHOSWA, Wendy N.; KHALIQ, Olive P. Is pregnancy a risk factor of COVID- 19?. European Journal of Obstetrics & Gynecology and Reproductive Biology, v. 252, p. 605-609, 2020	2020
ACE2: the key molecule for understanding the pathophysiology of severe and critical conditions of COVID-19: demon or angel?	Viruses	XIAO, Li; SAKAGAMI, Hiroshi; MIWA, Nobuhiko. ACE2: the key molecule for understanding the pathophysiology of severe and critical conditions of COVID-19: demon or angel?. Viruses, v. 12, n. 5, p. 491, 2020.	2020
Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target.	Intensive care medicine	ZHANG, Haibo et al. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: International Journal for Innovation Education and Research Vol.10 No.0 (2022), pg. 10 molecular mechanisms and potential therapeutic target. Intensive care medicine, v. 46, n. 4, p. 586-590, 2020	2020
Effect of allantoin on gastric ulcer: study of mechanism of gastroprotection	Sistema de bibliotecas-Universidade Federal de Goiás	SILVA, D. M. Effect of allantoin on gastric ulcer: study of the gastroprotective mechanism. 2019. 119 f. Thesis (Doctorate in Biological Sciences) - Federal University of Goiás, Goiânia, 2019.	2019

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Nausea and vomiting in pregnancy	Female	VAZ, Jorge Oliveira. Nausea and vomiting in pregnancy. Female, p. 52-54, 2019.	2019
The risk of Helicobacter pylori infection for adverse pregnancy outcomes: A systematic review and meta-analysis	Wiley Online Library	ZHAN, Yongle et al. The risk of Helicobacter pylori infection for adverse pregnancy outcomes: A systematic review and meta-analysis. Helicobacter, Wiley Online Library v. 24, n. 2, p. e12562, 2019.	2019
Roles of cyclooxygenase, prostaglandin E2 and EP receptors in mucosal protection and ulcer healing in the gastrointestinal tract.	Current pharmaceutical design	TAKEUCHI, Koji; AMAGASE, Kikuko. Roles of cyclooxygenase, prostaglandin E2 and EP receptors in mucosal protection and ulcer healing in the gastrointestinal tract. Current pharmaceutical design, v. 24, n. 18, p. 2002-2011, 2018	2018
The impacts of H. pylori virulence factors on the development of gastroduodenal diseases.	Journal of Biomedical Science	WEI-LUN, C; YI-CHUN, Y; BOR-SHYANG, S. The impacts of H. pylori virulence factors on the development of gastroduodenal diseases. Chang et al. Journal of Biomedical Science, 2018.	2018
Hiperemese gravídica associada a fatores psicossociais: revisão sistemática.	Interdisciplinary Journal of Experimental Studies	ALFENAS, Ana Raquel Barbosa et al. Hiperemese gravídica associada a fatores psicossociais: revisão sistemática. Revista Interdisciplinar de Estudos Experimentais-Animais e Humanos Interdisciplinary Journal of Experimental Studies, v. 9, n. 1, 2017.	2017
Nausea and vomiting of pregnancy – What's new?	Auton Neurosciences	BUSTOS M, VENKATARAMANAN R, CARITIS S. Nausea and vomiting of pregnancy – What's new? Auton Neurosci. 2017;202:62-72.	2017
Immune evasion strategies and persistence of Helicobacter pylori.	Curr Top Microbiology Immunology	MEJIAS-LUQUE, R AND GERHARD, M. Immune evasion strategies and persistence of Helicobacter pylori. Curr Top Microbiol Immunol. 2017;400:53–71.	2017
Association between helicobacter pylori infection and hyperemesis gravidarum.	Int J Reprod Contracept Obstet Gynecology	ELMAHDY, M; A. ELMARSAFAWY, A; ELKAFASH, D. Association between helicobacter pylori infection and hyperemesis gravidarum. Int J Reprod Contracept Obstet Gynecol. 2016 Sept;5(9):3175-3180	2016
Micronutrient deficiencies in pregnancy worldwide: health effects and prevention	Nature Reviews Endocrinology	GERNAND, Alison D. et al. Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. Nature Reviews Endocrinology, v. 12, n. 5, p. 274-289, 2016.	2016
Helicobacter pylori infection: an overview of bacterial virulence factors and pathogenesis	Biomedicine J.	KAO, C. Y, SHEU, B. S, WU, J.J. Helicobacter pylori infection: an overview of bacterial virulence factors and pathogenesis. Biom J. 2016;39(1):14–23.	2016
Diminazene aceturate, an angiotensin-converting enzyme II activator, prevents gastric mucosal damage in mice: Role of the angiotensin-(1–7)/Mas receptor axis.	Biochemical pharmacology	SOUZA, Luan Kelves M. et al. Diminazene aceturate, an angiotensin-converting enzyme II activator, prevents gastric mucosal damage in mice: Role of the angiotensin-(1–7)/Mas receptor axis. Biochemical pharmacology, v. 112, p. 50-59, 2016.	2016
Helicobacter pylori: infection, laboratory diagnosis and treatment.	Academic Journey	TEIXEIRA, Thamirys Freitas; DE SOUZA, Iure Kalinine Ferraz; ROCHA, Roberta Dias Rodrigues. Helicobacter pylori: infection, laboratory diagnosis and treatment. Academic Journey, vol. 6, no. 12, p. 481-504, 2016.	2016
Helicobacter pylori infection and gastrointestinal symptoms on Chilean pregnant women	Association Medical Bras	POVEDA, G.F. et al. Helicobacter pylori infection and gastrointestinal symptoms on Chilean pregnant women. Rev Assoc Med Bras 2014;60:306–10	2014
Respiratory physiology in pregnancy	Clinics in chest medicine	HEGEWALD, Matthew J.; CRAPO, Robert O. Respiratory physiology in pregnancy. Clinics in chest medicine, v. 32, n. 1, p. 1-13, 2011.	2011
Mucin dynamics and enteric pathogens.	Nature Reviews Microbiology	MCGUCKIN, Michael A. et al. Mucin dynamics and enteric pathogens. Nature Reviews Microbiology, v. 9, n. 4, p. 265-278, 2011	2011
Angiotensin II-generating enzymes, angiotensin- converting enzyme (ACE) and mast cell chymase (CMA1), in gastric inflammation may be regulated by H. pylori and associated cytokines	Pathology	CARL-MCGRATH, Stacy et al. Angiotensin II-generating enzymes, angiotensin- converting enzyme (ACE) and mast cell chymase (CMA1), in gastric inflammation may be regulated by H. pylori and associated cytokines. Pathology, v. 41, n. 5, p. 419-427, 2009.	2009
Host-bacterial interactions in helicobacter pylori infection.	Gastroenterology	AMIEVA, M.R. AND EL-OMAR, E. M. Host-bacterial interactions in helicobacter pylori infection. Gastroenterology. 2008;134(1):306–23.	2008

Source: own authorship.

Sciences (LILACS), National Library of Medicine (NLM-PubMed) and Scientific Electronic Library OnLine (SCIELO) and in interactive clinical decision support UpToDate. To search for indexed articles, the following descriptors were used: hyperemesis gravidarum, Helicobacter pylori and SARS-COV-2. To systematize the research, the Boolean operator "AND" was applied, found in the databases a sum of 82 articles. Inclusion criteria were articles published in the time frame from 2016 to 2022; written in Portuguese, Spanish or English and made available in full in the database. The exclusion criteria were duplicate articles, reviews, conference proceedings, opinion articles, literature reviews, reflection, editorials, theses, dissertations and articles that did not directly address the topic of this study. After surveying the publications, the abstracts were read and analyzed according to the pre-established inclusion and exclusion criteria. Thus, 33 works were selected. For data analysis, an instrument was developed with the following variables: authors, study type, sample, study location and year of publication, main results and conclusions.

RESULTS

Gastric Mucosa Protection Mechanisms: Regarding the approach, the gastric mucosa has several mechanisms that maintain its integrity, namely protecting it against the colonization of pathogenic agents and mucosal lesions (Table 2). The stomach is a source of secreted products, as it has the capacity to secrete hydrochloric acid, concluding an environment with an acidic pH, which provides a favorable area for the absorption of calcium, vitamin B12 and iron, in addition to favoring the digestion of food without digesting or deteriorate and disfavor the entry of pathogens (SILVA et al., 2019). The main mechanism behind these abilities is attributed to the presence of a semipermeable barrier at the most extreme line of the luminal surface: mucus, which together with bicarbonate, are part of the pre-epithelial protective factors and therefore constitute the first line of action. mucosal defense. When the mucus-bicarbonate barrier is overloaded, other protective mechanisms take effect, including epithelial repair and the maintenance and distribution of mucosal blood flow (SILVA et al., 2019).

Table 2. Factors intrinsic to gastric protection mechanisms

Intrinsic protection components	Forms of action	Defense factors	References
Hydrochloric Acid (HCL)	• Environment, favorable to the absorption of iron, calcium and vitamin B12; • Digestion of food without deterioration of the gastric mucosa; • Makes the environment unfavorable for pathogens to enter.	**Acid Ph**	SILVA et al. , 2019.
Mucus-bicarbonate barrier	• Forms a semipermeable barrier as the first line of mucosal defense; • Forms a sterile protection layer, with antimicrobial action, preventing direct contact with pathogens in the gastric mucosa; • It has mucins in its composition that limit the entry of pathogens, in order to act as false substrates for microbial adhesins.	**Pre-epithelial protective factors**	SILVA et al. , 2019; MCGUCKIN et al., 2011.
Prostaglandins and prostacyclins	• Stimulate the secretion of mucus and bicarbonate; • They trigger inflammatory reactions, with prostaglandin E2 (PGE2) being the most effective in this regard; • Regulate of hydrochloric acid, mucus, bicarbonate, local blood flow; • Responsible for maintaining the integrity of the gastric mucosa.	**Mechanism of cytoprotection and chemotaxis**	TAKEUCHI; AMAGASE, 2018.
Angiotensin II Converting Enzyme (ACE II)	• It fulfills the function of converting angiotensins I and II into angiotensins 1-9 and 1-7 that have vasodilator and anti-inflammatory effects that oppose the deleterious effects of angiotensin II; • Physiological effects on injured vasculature, promoting restoration after injury; • Reducible character in the expression and release of pro-inflammatory with IL-1ÿ and TNF-ÿ cytokines that are known to impair gastric defense.	**Anti-inflammatory and restorative action**	SOUZA et al., 2021.

Source: own authorship.

Another relevant feature of the mucus barrier is its property of acting as a sterile protection layer, avoiding the direct contact of pathogens with the epithelium, through the antimicrobial action of the mucus, since the mucins that constitute mucus limit the arrival of pathogens by steric hindrance and by acting as false substrates for microbial adhesins (MCGUCKIN et al., 2011). It is reasonable to say that the antimicrobial role of mucus is supported by the fact that in experimental studies with deficiencies in mucus secretion or in mucins from surface cells, they have become the opportune area for the increase of some pathologies during infection (MCGUCKIN et al., 2011). Prostaglandins and prostacyclins are present along the gastrointestinal tract (GIT) stimulating mucus and bicarbonate secretion, as well as playing a central role in mucosal defense mechanisms, with PGE2 (prostaglandin E2) being the most effective in these actions.

They are involved in several cytoprotective mechanisms such as the regulation of acid secretion hydrochloric acid, mucus, bicarbonate, local blood flow, in addition to being responsible for maintaining the integrity of the gastric mucosa (TAKEUCHI; AMAGASE, 2018). Given this scenario, another intrinsic factor in the protection mechanism of the gastric mucosa is due to the association with Angiotensin-Converting Enzyme II (ACE II), where its expression in the normal intestinal mucosa is a defensive factor and its deregulation can cause gastrointestinal symptoms and injuries. (SOUZA et al., 2021). The ACE II protein has the function of converting angiotensins I and II into angiotensins, respectively, into angiotensins (Ang) 1-9 and 1-7, these have vasodilator and anti-inflammatory effects that oppose the inflammatory and hypertensive effects of angiotensin II (XIAO L; MIWA, N, 2020). Recent studies have identified Ang-(1-7) as the main product of this conversion, with emphasis on the presentation of intense physiological effects, mainly on the vasculature, since the injured gastric mucosa produces an abundant amount of Ang-(1-7).). Thus, Ang-(1-7) can protect and help restore the mucosa after injury (SOUZA et al., 2021). Accordingly, other studies also confirmed that Ang-(1-7) has a reducible character in the expression and release of pro-inflammatory such as IL-1ÿ and TNF-ÿ cytokines, which are known to impair gastric defense, thus suggesting, that the anti-inflammatory properties of Ang-(1-7) may contribute to the protection of the effects of this Ang I metabolite in the stomach (SOUZA et al., 2021).

Virulence of Helicobacter pylori: Helicobacter pylori is the most common cause of chronic bacterial infection in humans. However, about 85% of those infected have mild asymptomatic gastritis, 15% may develop peptic ulcers, and about 1% progress to gastric cancer (WEI-LUN, C; YI-CHUN, Y; BOR-SHYANG, S. ; 2018). Thus, it is worth studying the factors that determine or condition the emergence of different clinical manifestations among individuals. The clinical presentation of this disease is part of a process of interaction between bacterial virulence (such as CagA, VacA, BabA), genetics of the for example, interleukins (IL) IL-1β, IL-10 and tumor necrosis factor alpha (TNF alpha) and environmental factors (AMIEVA, M.R. AND EL-OMAR, E. M, 2008; WEI-LUN CHANG, YI-CHUN YEH AND BOR-SHYANG SHEU, 2018; (KAO, C.Y, SHEU, B.S, WU, J.J. 2016; WEI-LUN, C; YI-CHUN, Y; BOR-SHYANG, S; 2018). The transmission of this bacterium is related to precarious socioeconomic conditions, such as low coverage of basic sanitation, garbage collection and treated water, justifying the higher prevalence of the disease in developing countries (OLIVEIRA, A. K. S et al. 2121).

Virulence designates the mechanisms by which the microorganism is able to exert its pathogenicity. Thus, we have factors related to colonization, immune escape and disease induction that condition the onset of symptoms of greater or lesser severity. For the colonization process, the virulence factors are urease, flagella, chemotaxis system and adhesins, among others under study. These factors are related to the ability of the bacteria to adhere and attach to the gastric mucosa (WEI-LUN, C; YI-CHUN, Y; BOR-SHYANG, S; 2018). After adhering to the surface, an immunological cascade is initiated by the host aimed at the destruction of Helicobacter pylori. This cascade is mediated by host immunomodulators, such as inflammatory interleukins and tumor necrosis factor, which aim at the destruction of the infectious agent. For this reason, there is a range of factors that help the pathogen to escape immune clearance and remain attached to the host, such as LPS protein, flagella, CagA, T4SS and vacA, among others already identified. These factors act in different ways to reduce the host's immune response, such as molecular mimicry, anti-inflammatory response, suppression of phagocytosis, blockade of T cell response, induction of dendritic cell tolerance, among others (MEJIAS-LUQUE et al. al, 2018). Other proteins expressed by Helicobacter pylori, in turn, are related to the development of specific gastric diseases. Although most patients are asymptomatic or oligosymptomatic, the expression of proteins such as CagA&T4SS,

VacA, BabA and HtrA (related to gastric adenocardinoma, MALT tumor and peptic ulcer), DupA (duodenal ulcer) and IceA and OipA (gastric ulcer) condition the appearance of more serious diseases in the population, defining greater morbidity and mortality (WEI-LUN, C; YI-CHUN, Y; BOR- SHYANG, S, 2018). Despite not being completely elucidated, the role of the inflammatory process triggered by these proteins has already been established in some works. With regard to GH, the CagA protein and its cytotoxin is an important virulence factor, being associated with a greater inflammatory response in the patient. The exaggerated immune response, especially at the expense of interleukin 6 (IL 6) and tumor necrosis factor alpha (TNF alpha), leads to hepatic and metabolic changes that may be associated with nausea and vomiting during pregnancy (ASLAN M. M. et. al. 2022).

Sars-Cov-2 Infection and gastric protection: The clinical manifestations of SARS-COV-2 infection are multiple, as are the pathophysiological processes that provide them. From this perspective, at the level of gastrointestinal involvement, the pathophysiological mechanism of the virus that causes COVID 19 is to access the intracellular environment through the interaction of its surface glycoprotein S (SPIKE) with human glycoprotein ACE II, which acts as a cell membrane receptor for the pathogen. (HOFFMANN et al., 2020). Evidence from previous SARS studies indicates the tropism of coronaviruses for cells in the gastrointestinal tract. Upon analysis of the unicellular transcriptome of healthy human lung and gastrointestinal tract, it was revealed that ACE II is not only strongly expressed in type 2 pneumocytes (AT2), but also in epithelial cells of the upper esophagus, enterocytes, ileum and colon. (KOTFIS and ZYDECKA, 2020). From a histological point of view, the epithelium of the digestive tract shows plasmacytic and lymphocytic infiltration with interstitial edema, mainly in the stomach, duodenum and rectum and much more irregular lymphocytic infiltration in the esophagus. Thus, SARS-COV-2 can cause digestive symptoms by direct viral invasion into cells target and/or immune-mediated tissue and target organ injury (GALANOPOULOS et al., 2020). However, once SARS-COV-2 binds to the cellular ACE II receptor, it causes the destruction of cells rich in ACE II receptors, which ultimately leads to a reduction in circulating ACE II activity. 2020) and increased permeability of the intestinal barrier to foreign pathogens after infection by the virus, causing both acute intestinal symptoms and later chronic lesions (SILVA, 2021).

Bidirectionality from sars-cov-2 and h. pylori infection for hyperemesis gravids: During pregnancy, immune cells trigger an attenuation of Th1 cell-mediated immunity, due to a physiological shift to a dominant Th2 environment, which contributes to maternal susceptibility to intracellular and extracellular pathogens, in addition to viral infections, in order to increase also general maternal morbidity and mortality (HEGEWALD MJ, 2011). The infection caused by Helicobacter pylori, a pathogen that inhabits the GIT is also responsible for nausea, vomiting and nutritional deficiencies in the population. On the other hand, pregnancy is considered an important risk factor for infection by this pathogen. Thus, several authors associate the bacterium with more severe episodes of nausea and vomiting, as well as the occurrence of hyperemesis during pregnancy (AFSAR, et al. 2020). In addition, with the advent of the pandemic, it became evident that pregnancy is also a risk factor for SARS-COV-2 infection (MARQUES-SANTOS et al, 2020) and this is due to the large contingent of membrane receptors ACE II found in the maternal placenta, specifically in the villous cytotrophoblast and syncytiotrophoblasts. Thus, there is a high expression of ACE II in these placental regions and an increased possibility of the mother to contract SARS-COV-2 is estimated, due to the increase in the numbers of viral receptors (PHOSWA W, 2020). It is known the role of ACE II in the conversion of 1-7 and its anti-inflammatory properties that oppose the inflammatory and hypertensive effects of angiotensin II (BARAL, 2021). ACE II cleaves several regulatory peptides that are secreted as a necessary part of the response to gastric mucosal damage, alleviating or inhibiting the extent of gastric lesions (MCGRATH et al, 2009). The infection caused by SARS-COV-2 causes apoptosis of cells rich in ACE II receptors, causing a reduction in enzymatic activity (BARAL, 2021). The increase in angiotensin II activity, synthesized by the ACE I pathway and mediating most of its deleterious effects through type 1 receptors (AT1R) (CARL-MCGRATH et al, 2009), promotes inflammatory expression in epithelial cells throughout the gastrointestinal tract (GIT), and depending on this situation, the increased permeability of the intestinal barrier in many cases as a result of a previous infection by SARS-COV-2, alters the gastric physiology in an abundant way, which leaves the mucosa prone to infections (SILVA, 2021). In non-pregnant patients, after primary Helicobacter pylori infection, they may present symptoms of acute gastritis, such as nausea, vomiting and poor digestion (DE MORAIS et al, 2021). On the other hand, in pregnant patients, the appearance of chorionic gonadotropin (HCG) and the increase in progesterone and estrogen have direct or indirect potential to cause nausea. The condition is more common in pregnant women who have high levels of HCG, such as in multiple pregnancy, female fetuses, intestinal trophoblastic disease and fetuses with of Down syndrome (VAZ, 2019).

There is an upregulation of angiotensives in the literature that present problems of severity and severity by problems and problems of solving problems and ulcers induced by Helicobacter infection (MCGRATH and also by Helicobacter, 2009). As a result, there is a reduction in the enzymatic activity of ACE II, through cell destruction by SARS-COV-2 (ZHANG et al, 2020). With the increase in the process of causes or causes of debts and claimants, among them, the destruction by Helicopter (2021). Thus, the alteration of gastric and chronic mucosal physiology can reactivate the pH of the juice, a primary or latent infection, an inflammatory response of the chronic mucosa. With this, gastrointestinal symptoms such as frequent nausea and vomiting, which can be expressed in patients, specifically in pregnant women, due to their natural propensity. This mechanism can ultimately evolve into the framework of HG (AFSAR et al., 2020). Helicobacter pylori infection is very likely in pregnant women. This implication in several maternal-fetal nutrients, drugs, the increase in gastric pH causing the infection, which causes absorption deficiency and, associated with hyperemesis gravidarum, can result in maternal malnutrition, especially due to the loss of water-soluble vitamins (AFSAR, 2020). Furthermore, it includes a role in the pathogenesis of several gestational disorders, including iron deficiency anemia, fetal malformations and fetal growth restriction (ALFENAS et al, 2017). It has been shown that inflammatory processes and infections of different bodies, even in the mouth, predispose the relative risk of childbirth (VAZ). Thus, both infections (SARS-COV-2 and Helicobacter pylori) are predisposing to a poor prognosis in pregnancy. HG is an important cause of pregnancy in pregnant women, which in most cases, changes in pregnancy and prenatal nutrition, the possibility of evolution of placenta, baby “SGA” prematurity (ALFENAS et al. 2017).

CONCLUSION

Adequate nutrition during pregnancy, maintaining the balance of nutrients, is an important factor for the preservation and maintenance of maternal well-being, as well as for the optimal growth and development of the fetus (AFSAR et al., 2020).In addition to the conditions mentioned above, the prevalence of acute and chronic diseases caused by Helicobacter pylori is also responsible for nutrient deficiency during pregnancy. development (AFSAR et al., 2020). The pathogen in question contributes to the gastric alteration of the pregnant woman, inducing a chronic inflammatory response of the mucosa and this will eventually result in a higher gastric pH, which may affect the absorption of nutrients (ZHAN et al., 2019). This project is relevant because, to date, there are no studies in the literature that have raised or proven this hypothesis, which in a way shows the innovative potential of the present work. As a result, there is still little evidence of the relationship between Helicobacter pylori infection and the occurrence of hyperemesis gravidarum, specifically because of the large number of individuals who were infected with SARS-COV-2, in which, in this scenario, the protective barrier was compromised. by ACE II in the GIT, increasing the propensity of latent infection.

Therefore, hyperemesis gravidarum can make the condition disabling for the pregnant woman, interfering with her daily activities, in addition to the nutrient deficit. And, as a consequence for the fetus, there is a greater risk of prematurity or low birth weight, among other health problems.

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