



## SARS COV-2 INFECTION IN THE DEVELOPMENT OF PREECLAMPSIA

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### Abstract

**Introduction:** Multiple endocrine neoplasms are a set of syndromes that are inherited in an autosomal dominant manner and are characterized by producing endocrine proliferative lesions, thus leading to hyperfunction of these glands. The characteristics of these lesions can be benign, malignant, or mixed. **Methodology:** During this review, a search was carried out in different indexed journals and others, using keywords such as Multiple endocrine neoplasia, pheochromocytoma, Hyperparathyroidism, in order to obtain original and review articles whose publication had been carried out before 2020. were initially obtained articles but then applying our inclusion and exclusion criteria, we were left with 8 of which we collected the most applicable and relevant information possible. **Results:** There is a clear association between covid 19 and pre-eclampsia, based on the incidence of pre-eclampsia associated with SARS-CoV-2 infection **Conclusion:** In Colombia there is no official report that relates these two pathologies, so the departmental and national statistical analysis is developed with little scientific evidence and unofficial data, which from our point of view would be a point for improvement by the INS, providing a detailed and updated characterization of the relationship between COVID19 and pre-eclampsia

**Keywords:** Preeclampsia, Covid 19, Sars cov 2g.

### INTRODUCTION

Coronaviruses belong to the Coronaviridae family and the Orthocoronavirinae subfamily, they are positive-stranded, single-stranded, enveloped RNA viruses with a lipid membrane derived from host cells. Currently there are four genera of coronaviruses ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ), human coronaviruses (HCoV) are classified into  $\alpha$ -CoV (HCoV-229E and NL63) and  $\beta$ -CoV (MERS-CoV, SARS-CoV, etc) (1). SARS-CoV-2 is a  $\beta$ -CoV, causing severe acute respiratory syndrome (SARS), which has caused the global pandemic of coronavirus disease 2019 (COVID-19) (2). The SARS-CoV-2 virus contains structural and non-structural proteins; Among the latter we find two mainly that are pp1a and pp1ab that play an important role in the pathogenesis of COVID-19. For their part, the four structural proteins include the spike glycoprotein (S), the membrane (M), the envelope (E) and the nucleocapsid proteins (N). Protein S is responsible for binding to host ECA2 receptors and directly invading cells of the upper and lower respiratory tree through its receptor-binding domain. This is also facilitated by TMPRSS2, to initiate the viral infection (3). The small intestine, kidneys, heart, thyroid and adipose tissue have been shown to express the highest levels of ECA2, this indicates that in addition to lung injury, SARS-CoV-2 can invade and affect these tissues. ACE2 has also been shown to be widely expressed in human placenta, placental villi, syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle of primary and secondary villi (4). ACE2, over expressed in pregnant women, allows the entry of the virus into target cells and the formation of the virus-ACE2 complex that could lead to the inactivation of ACE2. This enzyme exhibits high catalytic efficiency to generate angiotensin 1-7 (Ang 1-7) which has a vasodilator,

antithrombotic and anti-inflammatory action and at the same time inactivates the vasoconstrictor effect of angiotensin II. Plasma levels of Ang 1-7 are significantly increased in third trimester pregnant women compared to non-pregnant women. This would contribute to systemic vasodilation and decrease in blood pressure. (5). In pre-eclampsia, a pregnancy-specific hypertensive disorder that affects 3.5% of all pregnancies, there is a loss of balance between vasodilator and vasoconstrictor substances, with an over-exaggerated response of Ang II. Preeclampsia has also been associated with reduced levels of maternal plasma Ang 1-7. Because SARS-CoV-2 not only binds to ECA2, but also causes down regulation, COVID-19 infection during pregnancy can potentiate RAAS abnormalities, that is, increased Ang II relative to a decreased Ang 1-7, which are present in pre-eclampsia (6). COVID-19 and preeclampsia share additional common mechanisms, including endothelial cell dysfunction and coagulation abnormalities (4, 12). Therefore, the objective is to describe the role of SARS-CoV-2 infection in the development of pre-eclampsia (7).

### RESULTS

Preeclampsia is one of the main pathologies of pregnancy, which occurs from week 20 of gestation and is characterized by proteinuria and arterial hypertension and in turn can be accompanied by thrombocytopenia, impaired liver function, acute kidney injury, edema and brain, visual or pulmonary alterations. Depending on the onset of hypertension, preeclampsia can be classified into two main types: early-onset (EOPE) where the clinical signs appear before 34 weeks' gestation, and late-onset (pre-eclampsia at term) where the signs Clinical events occur after 34 weeks' gestation (8). The pathogenesis of preeclampsia remains unclear. However, some researchers have recently identified vascular angiogenic

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biomarkers such as vascular endothelial growth factor (VEGF), placental growth factor (PlGF), and antiangiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt-1) that have been related to its development (9). Other authors such as Gathiram et al similarly establish that the renin-angiotensin-aldosterone system (RAAS) plays an important role in the development of hypertensive disorders of pregnancy and there is a direct relationship between EOPE and increased sensitivity to angiotensin II (Ang II) circulating (10). On the other hand, it is believed that, in early-onset pre-eclampsia, it is initiated by defective spiral arterial remodeling leading to reduced placental blood flow causing increased placental oxidative stress. This results in increased release of various placental factors / proteins, such as sFlt-1, sEng, PlGF, and VEGF into the maternal circulation, leading to endothelial dysfunction and a maternal inflammatory response, leading to increased in maternal blood pressure and proteinuria (11). As mentioned above, the placenta expresses the receptors for ACE2 and COVID-19 infection can produce abnormalities in the RAAS, therefore, in this way a preeclamptic state can develop (12). Therefore, Bloise et al analyzed the expression pattern of genes specific for the cellular entry of SARS-CoV-2, angiotensin converting enzyme 2 and transmembrane protease serine 2, in the placenta during pregnancy and in paired samples of decidua. and placenta in pregnancies complicated by preterm birth and preeclampsia (PE) compared to those without complications (13). For the first time, the expression of two key proteins for the entry of SARS CoV-2 into the placenta was determined, finding that the expression of these genes is down-regulated as gestation progresses. The expression of ECA2 or TMPRSS2 did not change in pregnancies complicated by preterm birth or PD. This pattern of expression suggests a reduced probability of virus entry into placental and decidual cells in later stages of pregnancy. However, the early stages of pregnancy may be more susceptible to SARS CoV-2 placental infection. The data from this study do not provide evidence that pregnancies complicated by preterm birth or PD are at increased risk for SARS CoV-2 placental infection (14).

It is also believed that the immune system could be related to pre-eclampsia, since it has been demonstrated by laboratory that patients positive for COVID-19 and preeclamptic state have an increase in pro-inflammatory cytokines such as interleukin (IL) -2, IL-6, IL-7 and tumor necrosis factor alpha (TNF- $\alpha$ ). However, there is limited knowledge about the immunological aspects of pre-eclampsia, for this reason it is necessary to carry out more studies to determine the relationship between COVID-19 and the development of pre-eclampsia, in turn it is suggested that obstetricians evaluate the risk of complications in pregnant women positive for SARS-CoV-2 (15). Coronado et al, report their experience in Peru on the clinical course of hypertensive disorders of pregnancy in pregnant women with SARS-CoV-2 infection. Until now, COVID-19 infection has been shown to cause systemic complications such as high blood pressure, kidney disease, thrombocytopenia, and liver injury, mediated by the action of the virus on ACE2 resulting in RAAS dysfunction. Like other authors, they share that during pregnancy ACE2 plays an important role in regulating blood pressure and that SARS-CoV-2 infection can promote a pre-eclamptic state (16). On the other hand, Prochaska et al. In a review of the literature on COVID-19 in pregnancy, share that SARS-CoV-2 can produce inflammatory and vascular changes in the placenta just like SARS-CoV and MERS-CoV. These changes can produce poor maternal vascular perfusion, poor fetal vascular

perfusion, inflammatory infiltrates, increased fibrin, among others. Consequently, placental dysfunction can induce preeclampsia, as has been reported in some cases (17). These inflammatory changes in the placenta are described by Baergen et al, in their study, where they specify the pathology and clinical information of 20 placentas whose mothers tested positive for the new Coronavirus. The placentas were fixed for 48 hours before dissection. The sections were fixed in formalin and stained with hematoxylin and eosin. None of the patients were admitted to the ICU or required intubation. In case 14, the patient presented severe pre-eclampsia (18). In pathological findings, the most common lesion was poor fetal vascular perfusion, which was observed in 45% of cases. In most cases, this was the presence of intramural fibrin deposition. Among other findings, the presence of macrophages was observed, which suggests inflammatory processes in the placenta that may be related to hypertensive disorders in pregnancy (19). The initial findings observed in this report show poor fetal vascular perfusion, in addition, patients positive for Covid-19 may have a greater propensity for thrombosis in the fetal circulation, generating important clinical implications for both the mother and the baby. However, more studies are needed to determine the significance of these initial findings (20).

## DISCUSSION

Currently, the evidence suggests two possible mechanisms that could explain the possible relationship between COVID-19 and pre-eclampsia. However, more studies are still needed that can establish this relationship, because some studies differ in terms of results and do not reach statistical significance to state that pregnant patients who have SARS-CoV-2 infection have a higher risk of developing pre-eclampsia. These results may also be due to a small sample size, study biases, or changes in methodology. However, the possibility that COVID-19 infection may have a synergistic effect and complicate patients who have spiral artery defects and predisposition to pre-eclampsia should be considered. On the other hand, new recommendations are also needed to be adopted from the first control of the pregnant woman and thus avoid a possible contagion (21). The pandemic caused by the new coronavirus continues to be extremely serious, highly contagious and has affected the world population beyond risk groups. The importance of sensitizing and making pregnant women aware of its severity is also highlighted in order to achieve prevention measures in order to reduce and control this infection. Most of the studies focused on China, as it is the country of origin of the new coronavirus. In addition, it is observed that, in most of the studies, few clinical cases were analyzed, but they deserve attention because they provide the evidence available at this time and because it is extremely important to know the main clinical manifestations to face this disease during pregnancy (22). The pandemic caused by the new coronavirus continues to be extremely serious, highly contagious and has affected the world population beyond risk groups. The importance of sensitizing and making pregnant women aware of its severity is also highlighted in order to achieve prevention measures in order to reduce and control this infection. Most of the studies focused on China, as it is the country of origin of the new coronavirus. In addition, it is observed that, in most of the studies, few clinical cases were analyzed, but they deserve attention because they provide the evidence available at this time and because it is extremely important to know the main clinical manifestations to face this disease during pregnancy (23). Taking into account that despite the high incidence of

preeclampsia associated with SARS-CoV-2 infection, in Colombia there is no official report that relates these two pathologies, therefore, the departmental and national statistical analysis was developed with little scientific evidence and unofficial data, which from our point of view this would be a point to be improved by the INS, providing a detailed and updated characterization of the relationship between COVID19 and pre-eclampsia (24).

## Conclusion

What has been exposed throughout the work allows us to conclude that the SARS-CoV-2 infection can play a fundamental role in the development of pre-eclampsia since they share a mechanism that induces an increase in blood pressure in pregnancy, accompanied by endothelial dysfunction, microvascular complications and impaired coagulation. Evidence also indicates that placental invasion by the coronavirus and its inflammatory effects lead to an even higher risk of hypertensive disorders in pregnancy. Despite the results of studies to date, more studies are suggested investigating the underlying mechanisms that lead to the development of pre-eclampsia. It should be noted that this work has some limitations such as little information available, most of the studies presented here are case reports, the methodology and designs of the studies do not allow a direct relationship between these two diseases to be established (25).

## REFERENCES

- Lan J, Ge J, Yu J, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*. 2020; 581:215-220. <https://doi.org/10.1038/s41586-020-2180-5>
- Malik Y. Properties of Coronavirus and SARS-CoV-2. *Malays J Pathol*. 2020;42(1):3-11. <https://pubmed.ncbi.nlm.nih.gov/32342926/>
- Narang K, Enninga E, Gunaratne M, et al. SARS-CoV-2 infection and COVID-19 during pregnancy: A multidisciplinary review. *Mayo Clin Proc*. 2020; 95(8): 1559-1561. <https://doi.org/10.1016/j.mayocp.2020.05.011>
- Esakandari H, Nabi M, Fakkari J, et al. A comprehensive review of COVID-19 characteristics. *Biol Proced*. 2020; 22:19. <https://doi.org/10.1186/s12575-020-00128-2>
- World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. 2020. <https://www.who.int/es/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>. Accessed 09 octubre 2020
- Icenogle T. COVID-19: Infection or Autoimmunity. *Front Immunol*. 2020; 11:20-55. <https://doi.org/10.3389/fimmu.2020.02055>
- Li MY, Li L, Zhang Y, et al. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty*. 2020;9(1):45. <https://doi.org/10.1186/s40249-020-00662-x>
- Jing Y, Run-Qian L, Hao-Ran W, et al. Potential influence of COVID-19/ACE2 on the female reproductive system. *Mol Hum Reprod*. 2020;26(6):367-373. <https://doi.org/10.1093/molehr/gaaa030>
- Todros T, Masturzo B, De Francia S. COVID-19 infection: ACE2, pregnancy and preeclampsia. *Eur J Obstet Gynecol Reprod Biol*. 2020; 253:330. <https://doi.org/10.1016/j.ejogrb.2020.08.007>
- Varga Z, Flammer A, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *2020;395(10234): 1417-1418,02*. [https://doi.org/10.1016/S01406736\(20\)30937-5](https://doi.org/10.1016/S01406736(20)30937-5).
- Johns Hopkins. COVID-19 dashboard by the center for systems science and engineering (CSSE) at Johns Hopkins University (JHU). [Disponible en: <https://coronavirus.jhu.edu/map.html>]
- Phipps E, Thadhani R, Benzing T, et al. Pre-eclampsia: pathogenesis, novel diagnostics and therapies. *Nat Rev Nephrol*. 2019; 15(5):275-289. [10.1038/s41581-019-0119-6](https://doi.org/10.1038/s41581-019-0119-6).
- Nápoles N. New interpretations in the classification and diagnosis of pre-eclampsia. 2016; 20(4):516-529.
- WJ Mol B, Roberts C, Thangaratnam S, et al. Preeclampsia. *Lancet*. 2016; 387(10022):999-1011. [https://doi.org/10.1016/S0140-6736\(15\)00070-7](https://doi.org/10.1016/S0140-6736(15)00070-7)
- ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol*. 2019; 133(1): e1-e25. [10.1097/AOG.0000000000003018](https://doi.org/10.1097/AOG.0000000000003018).
- Lopes J, Sass N, Martins S. Preeclampsia. *Rev Bras Ginecol Obstet*. 2017;39(09):496-512. <https://doi.org/10.1055/s-0037-1604471>
- Barbosa M, Morales C, Amézquina M, et al. Vigilancia de morbilidad materna extrema en una institución de referencia en Cali, Colombia, 2013-2014. *Rev Colomb Obstet Ginecol*. 2016; 67(3):215-222. <http://dx.doi.org/10.18597/rcog.769>
- Abrao A, Ibiroga E, Elrafai A, et al. Complications and outcomes of SARS-CoV-2 in pregnancy: where and what is the evidence. *J Hypert Preg*. 2020;39(3):361-369. <https://doi.org/10.1080/10641955.2020.1769645>
- Diriba K, Awulachew E, Getu E. The effect of coronavirus infection (SARS-CoV-2, MERS-CoV, and SARS-CoV) during pregnancy and the possibility of vertical maternal-fetal transmission: a systematic review and meta-analysis. *Eur J Med Res*. 2020;25(39): 1-14. <https://doi.org/10.1186/s40001-020-00439-w>
- Ukachi E, Spiegelman J, Ona S, et al. Influence of race and ethnicity on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection rates and clinical outcomes in pregnancy. *Am Obstet Gynecol*. 2020;136(5):1040-1043. <https://doi.org/10.1097/01.AOG.0000447420.16812.8>
- Ahlberg M, Neovius M, Saltvedt S, et al. Association of SARS-CoV-2 test status and pregnancy outcomes. *JAMA*. 2020; e1-e3. <https://jamanetwork.com/10.1001/jama.2020.19124>
- Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020; 370: m3320. <https://doi.org/10.1136/bmj.m3320>
- Juan J, Gil M, Rong Z, et al. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcomes: systematic review. *Ultrasound Obstet Gynecol*. 2020; 56:15-27. [10.1002/uog.22088](https://doi.org/10.1002/uog.22088).
- American College of Obstetricians and Gynecologists. Task Force on hypertension in pregnancy. *Obstetrics and Gynecology*. 2013; 122(5):1122-1131. [Disponible en: [https://journals.lww.com/greenjournal/fulltext/2013/1100/hypertension\\_in\\_pregnancy\\_executive\\_summary.36.aspx](https://journals.lww.com/greenjournal/fulltext/2013/1100/hypertension_in_pregnancy_executive_summary.36.aspx)]
- Brown M, Magee L, Kenny L, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. 2018; 13:291-310. <https://doi.org/10.1016/j.preghy.2018.05.004>.