Endothelial Function Evaluation on Pregnant COVID-19 Patients

Subjects: Health Care Sciences & Services

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Pregnancy with SARS-CoV-2 infection can raise the risk of many complications, including severe COVID-19 and maternal–fetal adverse outcomes. Additionally, endothelial damage occurs as a result of direct SARS-CoV-2 infection, as well as immune system, cardiovascular, and thrombo-inflammatory reactions. The endothelium is the key regulator of vascular homeostasis, as it determines vascular tone, smooth muscle cell proliferation, vessel wall inflammation, and platelet aggregation.

endothelial dysfunction pregnant women COVID-19 SARS-CoV-2 infection invasive testing oninvasive

1. Introduction

COVID-19 in pregnancy is still a severe risk factor for complications in both maternal (i.e., need for intensive care, death) and fetal aspects (i.e., miscarriages, preeclampsia, intrauterine growth retardation, preterm labor, stillbirth, etc.) [1], although the World Health Organisation has declared the pandemic is no longer a global concern. The higher risk of pregnancy complications associated with SARS-CoV-2 infection is probably related to cardiovascular, hormonal, and immunological amendments in pregnant women, changes that make females prone to more severe COVID-19 [1][2][3].

Some research groups reported a higher incidence of preeclampsia in SARS-CoV-2-infected women [4][5]. In addition to COVID-19, other pandemics, such as H1N1, MERS, and SARS-CoV-1, have had catastrophic consequences on pregnancy outcomes. Preterm birth, preeclampsia, preterm prelabor membrane rupture, fetal development restriction, and mode of delivery were among the ones that were noted. Fetal distress, an Apgar score below seven at five minutes, neonatal asphyxia, admission to a neonatal intensive care unit, perinatal death, and signs of vertical transmission were the perinatal outcomes seen [6]. However, other researchers questioned that incidence, suggesting careful analysis and interpretation of the available data [7].

Furthermore, it is thought that extensive endothelial dysfunction (ED) is the common and overlapping pathophysiological mechanism behind both preeclampsia and COVID-19 [8][9][10]. SARS-CoV-2 infection and preeclampsia exert symptoms related to vasoconstriction and organ ischemia. When both conditions are present, it

is difficult to determine which complications are attributed to one or the other condition, taking into account that ED is the common feature. Usually, ED is presented by elevated levels of angiotensin II (Ang-II) and the antiangiogenic sFlt-1 (FMS-like tyrosine kinase 1) and low levels of angiogenic molecule placental growth factor (PIGF). However, a high sFlt-1/PIGF ratio could propose placental dysfunction in preeclampsia, but excessive levels are observed in SARS-CoV-2-infected pregnant women [9][10].

Although the endothelium represents a simple cell monolayer, its crucial location as a vessel's inner layer determines its essential role. Healthy endothelium can respond to physical and chemical signals by producing a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation. The endothelium is the key regulator of vascular homeostasis, as it determines vascular tone, smooth muscle cell proliferation, vessel wall inflammation, and platelet aggregation [11]. An alteration in endothelial function results in the disproportionate production of relaxing and contracting factors and procoagulants. ED precedes the development of atherosclerotic changes. It is increasingly recognized as an important prognostic factor for cardiovascular events [12].

Endothelial function assessment can enhance risk stratification, improve early diagnosis, and be used to assess therapeutic response [13]. The optimal method for endothelial function evaluation should be safe, reproducible, and standardized between laboratories. Both invasive and noninvasive tests have been developed. However, some challenges arise when endothelial function has to be assessed in pregnant women.

2. Invasive Testing

In general, endothelial function assessment is mainly focused on vasoreactivity testing, as this is the most verifiable function of the vascular endothelium [14]. Assessing endothelial function in the cardiac catheterization laboratory is feasible in patients with risk factors for atherosclerotic coronary artery disease [11].

The intracoronary acetylcholine provocation test is the gold standard for vasoreactivity testing [15]. Acetylcholine binds muscarinic receptors, which leads to nitric oxide (NO) release and subsequent arterial dilatation in the case of an intact endothelium. However, acetylcholine induces arterial conduit constriction when there is an endothelium impairment. Dosing regimens for acetylcholine during provocation testing are diverse, with some doses starting at 2 µg to up to 200 µg. Notably, the current data supporting the dosing regimens of acetylcholine during provocation testing are mainly focused on coronary epicardial and microvascular vasospasm and not on endothelial dysfunction testing. ED is diagnosed when the reproduction of symptoms and ST-segment depression on ECG are apparent [16].

Additionally, the endothelial function can be invasively assessed by measuring coronary blood flow changes and, thereby, coronary flow reserve using a Doppler wire [14] or using the method of thermodilution [17]. A Doppler-tipped guidewire is most commonly positioned in a proximal segment of a coronary artery (usually at the left anterior descending coronary artery), and the Doppler flow velocity is continuously recorded. The change in blood flow velocity at rest and after provocation with acetylcholine is calculated as a measure of the preserved or impaired

ED. Although the described invasive tests are characterized by high specificity and sensitivity, they require specific technical equipment and experienced personnel. Hence, provocative invasive testing is not performed regularly [18].

3. Noninvasive Testing

The application of noninvasive tests allows for accessible and easily applicable measurements of endothelial function in everyday clinical practice. The brachial artery is the most accessible location to assess vasoreactivity, specifically its flow-mediated dilatation. The latter can be achieved through B-mode ultrasound and Doppler, evaluating flow changes in response to vasomotor stimuli such as blood pressure cuff inflation or oral/sublingual nitroglycerin [19]. Various factors, including temperature, food, caffeine, and drugs, may influence vascular reactivity. Therefore, subjects should fast for at least 12 h before the examination, and the test should be performed in a quiet, temperature-controlled room. To create a flow stimulus in the brachial artery, a sphygmomanometric cuff is positioned above the antecubital fossa. A baseline rest image is acquired, and blood flow is estimated by time-averaging the pulsed Doppler velocity signal obtained. Afterward, ischemia is induced by the arterial occlusion created from the cuff inflation to supra systolic pressure. The following cuff deflation induces a high-flow state, which increases shear stress and brachial artery dilatation. After cuff deflation, a control image and Doppler signal are obtained to assess hyperemic velocity.

Other noninvasive modalities allowing for the reproducible and safe evaluation of endothelial function are magnetic resonance imaging (MRI) and positron emission tomography (PET). Both methods provide the ability to quantify coronary blood flow. To evaluate coronary blood flow and myocardial flow reserve (MFR), different provoking tests, such as isometric handgrip exercise [20] or cold pressor tests, have been validated [21]. MFR is calculated as the ratio of stress to rest blood flow, and a value below 2.0 is considered abnormal and consistent with ED [22].

The decision for the optimal test should be made after taking into consideration each specific patient's characteristics and pathology. In the case of pregnancy, we should opt for the minimally invasive test, ideally without any provocative medication application.

Flow-mediated dilatation (FMD) and its modified version-reactive hyperemial arterial tonometry [23][24][25] are the gold standard for evaluating ED in preeclampsia among noninvasive methods.

It was shown that a severe ED was observed in pregnant women with preeclampsia, manifested with reduced FMD, compared to healthy pregnant women [23]. Usually, these differences are more prominent in the third trimester or around the 30th gestational week. However, ED will have developed weeks before the clinical manifestation of preeclampsia [26].

Imaging plays a crucial role in the diagnosis of blood vessel diseases. Diagnostics in this field has come a long way from the use of classical angiography through DSA (digital subtraction angiography), which nowadays is mainly used in invasive procedures, to computed tomography angiography (CTA) and magnetic resonance angiography

(MRA). Molecular magnetic resonance is a modern method for diagnosing vascular diseases, especially for evaluating the endothelium.

Direct in vivo study of the vascular endothelium is complex. Attempts have been made to diagnose the endothelium using physical methods, and various magnetic resonance sequences have been developed in recent years [27]. By applying gadolinium, the contrast of the vessel wall can be evaluated, which is a semiquantitative analysis of vascular permeability. One of the ways to apply contrast material is through so-called dynamic contrast enhancement (DCE), which allows evaluation of the contrast of the vascular wall in an active order. It is possible to measure the microvascular volume, contrast extravasation rate, time to peak, and peak concentration [27]. Performing a quality dynamic contrast study is challenging, even with modern devices, and requires good spatial and temporal resolution because the vessel wall is a very fine structure. A group of scientists proposes using a specific method called a quantitative MRI of endothelial permeability and dysfunction (qMETRIC). The method is a specially developed protocol that evaluates late gadolinium enhancement (LGE) and modified Look –Locker inversion recovery (MOLLI) T1. It is currently under investigation using mice but has the potential to be a useful modern biomarker assessing vascular permeability. This way, modern diagnostics is performed noninvasively and relatively quickly and is affordable. The large vessels, such as the aorta, aortic arch, and brachiocephalic and carotid arteries, are suitable for evaluation. The disadvantage is the need for a special coil and exact patient positioning. The examination must be carried out with ECG monitoring, which must also be precise [28].

However, one must acknowledge that searching for proper and valuable biomarkers for endothelial dysfunction could be challenging. Moreover, a sophisticated biomarker could be difficult to implement in clinical practice. However, it could be helpful in the research.

In recent years, different sequences have been developed to study the endothelial function of coronary vessels, one of which is the late gadolinium enhancement. Thanks to this sequence, the assessment of endothelium-dependent coronary vasomotor abnormality is possible [29].

References

1. Ntounis, T.; Prokopakis, I.; Koutras, A.; Fasoulakis, Z.; Pittokopitou, S.; Valsamaki, A.; Chionis, A.; Kontogeorgi, E.; Lampraki, V.; Peraki, A.; et al. Pregnancy and COVID-19. J. Clin. Med. 2022, 11, 6645.
2. Ferrer-Oliveras, R.; Mendoza, M.; Capote, S.; Pratcorona, L.; Esteve-Valverde, E.; Cabero-Roura, L.; Alijotas-Reig, J. Immunological and physiopathological approach of COVID-19 in pregnancy. Arch. Gynecol. Obstet. 2021, 304, 39–57.
3. Sekulovski, M.; Bogdanova-Petrova, S.; Peshevska-Sekulovska, M.; Velikova, T.; Georgiev, T. COVID-19-related liver injuries in pregnancy. World J. Clin. Cases 2023, 11, 1918–1929.

4. Di Mascio, D.; Khalil, A.; Saccone, G.; Rizzo, G.; Buca, D.; Liberati, M.; Vecchiet, J.; Nappi, L.; Scambia, G.; Berghella, V.; et al. The outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: A systematic review and meta-analysis. Am. J. Obstet. Gynecol. MFM 2020, 2, 100107.
5. Mendoza, M.; Garcia-Ruiz, I.; Maiz, N.; Rodo, C.; Garcia-Manau, P.; Serrano, B.; Lopez-Martinez, R.; Balcells, J.; Fernandez-Hidalgo, N.; Carreras, E.; et al. Pre-eclampsia-like syndrome induced by severe COVID-19: A prospective observational study. BJOG Int. J. Obstet. Gynaecol. 2020, 127, 1374–1380.
6. Zhu, H.; Wang, L.; Fang, C.; Peng, S.; Zhang, L.; Chang, G.; Xia, S.; Zhou, W. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl. Pediatr. 2020, 9, 51–60.
7. Rolnik, D. Can COVID-19 in pregnancy cause preeclampsia? Bjog 2020, 127, 1381.
8. Juan, J.; Gil, M.M.; Rong, Z.; Zhang, Y.; Yang, H.; Poon, L.C. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: Systematic review. Ultrasound Obstet. Gynecol. 2020, 56, 15–27.
9. Giardini, V.; Casati, M.; Carrer, A.; Vergani, P. Can Similarities between the Pathogenesis of Preeclampsia and COVID-19 Increase the Understanding of COVID-19? Int. J. Transl. Med. 2022, 2, 186–197.
10. Giardini, V.; Ornaghi, S.; Casati, M.; Carrer, A.; Acampora, E.; Vasarri, M.V.; Arienti, F.; Vergani, P. Imbalanced Angiogenesis in Pregnancies Complicated by SARS-CoV-2 Infection. Viruses 2022, 14, 2207.
11. Halcox, J.P.; Schenke, W.H.; Zalos, G.; Mincemoyer, R.; Prasad, A.; Waclawiw, M.A.; Nour, K.R.; Quyyumi, A.A. Prognostic value of coronary vascular endothelial dysfunction. Circulation 2002, 106, 653–658.
12. Vita, J.A.; Keaney, J.F., Jr. Endothelial function: A barometer for cardiovascular risk? Circulation 2002, 106, 640–642.
13. Flammer, A.J.; Anderson, T.; Celermajer, D.S.; Creager, M.A.; Deanfield, J.; Ganz, P.; Hamburg, N.M.; Lüscher, T.F.; Shechter, M.; Taddei, S.; et al. The assessment of endothelial function: From research into clinical practice. Circulation 2012, 126, 753–767.
14. Hasdai, D.; Lerman, A. The assessment of endothelial function in the cardiac catheterization laboratory in patients with risk factors for atherosclerotic coronary artery disease. Herz 1999, 24, 544–547.
15. Niccoli, G.; Scalone, G.; Crea, F. Coronary functional tests in the catheterization laboratory—Pathophysiological and clinical relevance. Circ. J. 2015, 79, 676–684.

16. Kunadian, V.; Chieffo, A.; Camici, P.G.; Berry, C.; Escaned, J.; Maas, A.H.E.M.; Prescott, E.; Karam, N.; Appelman, Y.; Fraccaro, C.; et al. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. Eur. Heart J. 2020, 41, 3504–3520.
17. Gallinoro, E.; Bertolone, D.T.; Fernandez-Peregrina, E.; Paolisso, P.; Bermpeis, K.; Esposito, G.; Gomez-Lopez, A.; Candreva, A.; Mileva, N.; Belmonte, M.; et al. Reproducibility of bolus versus continuous thermodilution for assessment of coronary microvascular function in patients with ANOCA. EuroIntervention 2023, 19, e155–e166.
18. Mileva, N.; Nagumo, S.; Mizukami, T.; Sonck, J.; Berry, C.; Gallinoro, E.; Monizzi, G.; Candreva, A.; Munhoz, D.; Vassilev, D.; et al. Prevalence of Coronary Microvascular Disease and Coronary Vasospasm in Patients With Nonobstructive Coronary Artery Disease: Systematic Review and Meta-Analysis. J. Am. Heart Assoc. 2022, 11, e023207.
19. Corretti, M.C.; Anderson, T.J.; Benjamin, E.J.; Celermajer, D.; Charbonneau, F.; Creager, M.A.; Deanfield, J.; Drexler, H.; Gerhard-Herman, M.; Herrington, D.; et al. International Brachial Artery Reactivity Task Force. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. J. Am. Coll. Cardiol. 2002, 39, 257–265, https://doi.org/10.1016/s0735-1097(01)01746-6. Erratum in J. Am. Coll. Cardiol.2002, 39, 1082..
20. Hays, A.G.; Hirsch, G.A.; Kelle, S.; Gerstenblith, G.; Weiss, R.G.; Stuber, M. Non-invasive visualization of coronary artery endothelial function in healthy subjects and in patients with coronary artery disease. J. Am. Coll. Cardiol. 2010, 56, 1657–1665.
21. Taqueti, V.R.; Di Carli, M.F. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. J. Am. Coll. Cardiol. 2018, 72, 2625–2641.
22. Schindler, T.H.; Dilsizian, V. Coronary Microvascular Dysfunction: Clinical Considerations and Non-invasive Diagnosis. JACC Cardiovasc. Imaging 2020, 13 Pt 1, 140–155.
23. Mannaerts, D.; Faes, E.; Goovaerts, I.; Stoop, T.; Cornette, J.; Gyselaers, W.; Spaanderman, M.; Van Craenenbroeck, E.M.; Jacquemyn, Y. Flow-Mediated Dilation and Peripheral Arterial Tonometry Are Disturbed in Preeclampsia and Reflect Different Aspects of Endothelial Function. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2017, 313, R518–R525.
24. Musz, P.; Podhajski, P.; Grzelakowska, K.; Umińska, J.M. Non-Invasive Assessment of Endothelial Function—A Review of Available Methods. Med. Res. J. 2021, 6, 53–58.
25. Meeme, A.; Buga, G.A.; Mammen, M.; Namugowa, A. Endothelial Dysfunction and Arterial Stiffness in Preeclampsia Demonstrated by the EndoPAT Method. Cardiovasc. J. Afr. 2017, 28, 23–29.

26. Impaired Flow-Mediated Dilation before, during, and after Preeclampsia|Hypertension. Available online: https://www.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.115.06554 (accessed on 6 June 2023).
27. van Hoof, R.H.M.; Vöö, S.A.; Sluimer, J.C.; Wijnen, N.J.A.; Hermeling, E.; Schreuder, F.H.B.M.; Truijman, M.T.B.; Cleutjens, J.P.M.; Daemen, M.J.A.P.; Daemen, J.-W.H.; et al. Vessel wall and adventitial DCE-MRI parameters demonstrate similar correlations with carotid plaque microvasculature on histology. J. Magn. Reson. Imaging 2017, 46, 1053–1059.
28. Lavin, B.; Andia, M.E.; Saha, P.; Botnar, R.M.; Phinikaridou, A. Quantitative MRI of Endothelial Permeability and (Dys)function in Atherosclerosis. J. Vis. Exp. 2021, 178, e62724.
29. Nakayama, M.; Yamamuro, M.; Takashio, S.; Uemura, T.; Nakayama, N.; Hirakawa, K.; Oda, S.; Utsunomiya, D.; Kaikita, K.; Hokimoto, S.; et al. Late gadolinium enhancement on cardiac magnetic resonance imaging is associated with coronary endothelial dysfunction in patients with dilated cardiomyopathy. Heart Vessel. 2018, 33, 393–402.