9. Cohen JB, Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, Rodriguez-Mori JE, Renna N, Chang TI, Corrales-Medina V, Andrade-Villanueva JF, Barbagelata A, Cristodulo-Cortez R, Díaz-Cucho OA, Spaak J, Alfonso CE, Valdivia-Vega R, Villavicencio-Carranza M, Ayala-García RJ, Castro-Callirgos CA, González-Hernández LA, Bernales-Salas EF, Coacalla-Guerra JC, Salinas-Herrera CD, Nicolosi L, Basconcel M, Byrd JB, Sharkoski T, Bendeziú-Huassasquiche LE, Chittams J, Edmonston DL, Vasquez CR, Chirinos JA. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med*. 2021 Mar;9(3):275-284. doi: [10.1016/S2213-2600\(20\)30558-0](https://doi.org/10.1016/S2213-2600(20)30558-0)

10. Lopes RD, Macedo AVS, de Barros E Silva PGM, Moll-Bernardes RJ, Feldman A, D'Andréa Saba Arruda

G, de Souza AS, de Albuquerque DC, Mazza L, Santos MF, Salvador NZ, Gibson CM, Granger CB, Alexander JH, de Souza OF; BRACE CORONA investigators. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: Impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)--The BRACE CORONA Trial. *Am Heart J*. 2020 Aug;226:49-59. doi: [10.1016/j.ahj.2020.05.002](https://doi.org/10.1016/j.ahj.2020.05.002).

11. Meylan S, Livio F, Foerster M, Genoud PJ, Marguet F, Wuerzner G; CHUV COVID Vaccination Center. Stage III Hypertension in Patients After mRNA-Based SARS-CoV-2 Vaccination. *Hypertension*. 2021 Jun;77(6):e56-e57.

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Hypertension and Pregnancy: Basic Aspects

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Hypertensive disorders affect up to 10% of pregnancies worldwide, being a major health problem for women and their infants and causing increased maternal and infant morbidity and mortality.^{1, 2} The alarming global number of deaths caused by preeclampsia or due to cardiovascular morbidities following pregnancy with preeclampsia is a result of the current lack of knowledge about its causes and the limited therapies to handle maternal blood pressure (BP) during such insults or in the postpartum period. Improving the identification and follow up of high-risk pregnancies can also significantly contribute to prevent severe outcomes associated with the development of preeclampsia.

The International Hypertension Society (ISH) recognizes these gaps and encourages a wide-ranging discussion of key topics for advancing this field. In the 2021 edition of the ISH and

European Society of Hypertension (ESH) joint meeting, international leaders in the field of hypertension in pregnancy presented their most recent contributions in discovering new mechanisms involved in preeclampsia-related placental dysfunction and in the study of emerging biomarkers of preeclampsia.

The early onset of preeclampsia is mainly driven by abnormal trophoblast invasion and impaired arterial remodeling, leading to significant oxidative stress and exacerbated immune responses in the placenta.³⁻⁵ Dr. McClements has studied therapies using mesenchymal stem cells (MSC) originated from placentas of pregnancies with preeclampsia.^{6, 7} The potential of this cell therapy is justified by the fact that placentas are rich in MSC. These cells release extracellular vesicles (EV) containing mRNA, miRNAs and proteins that can alter different aspects of placentation,

including immunomodulation, angiogenesis and redox status.^{7,8} At this meeting, Dr. McClements described that MSCs of pregnancy with preeclampsia have impaired angiogenesis capacity compared to MSCs from control pregnancies. They also identified two target miRNAs, mir-183-5p and mir-203a-3p, both related to impaired placental angiogenesis. Their results are supported by others also describing the anti-angiogenic effect of miR-183-5p by suppressing trophoblast invasion and migration through a negative regulation of metalloproteinase (MMP) 9 during preeclampsia.⁹ Likewise, miR-203a-3p has also been shown to inhibit angiogenesis by reducing VEGF availability and HIF-1 α activity, as previously described in diabetic retinopathy.¹⁰ These findings also open new avenues for testing the use of MSC-derived EVs as new therapeutic targets in preeclampsia.

Soluble vascular endothelial growth factor (VEGF) receptor-1 (sFlt-1), a well-known biomarker of preeclampsia, was also discussed at this meeting, particularly in relation to coagulation disorders in pregnancy. Although sFlt-1 is a soluble protein, it contains a binding site for heparin sulfate, a component of the extracellular matrix, which reduces the bioavailability and signaling of circulating and tissue-present VEGF.¹¹ During the ISH/ESH meeting, the study presented by Dr. Kurvanov described an increase in the concentration of sFlt1 as well as thrombocytes aggregation, longer prothrombin time and higher fibrinogen concentration, in pregnancy with preeclampsia compared to controls, suggesting an association between this soluble factor and subclinical disseminated intravascular coagulation and decreased fibrinolytic potential in preeclampsia.

In another presentation, Dr. Moore suggested otherwise that a treatment with a powerful anticoagulant heparin can stimulate the release of sFlt1 from trophoblasts and placental explants in a dose dependent manner.¹² sFlt1 was increased in the supernatant of cells treated with heparin while the non-soluble Flt-1 was reduced. In vitro findings were further confirmed by *in vivo* experiments on pregnant rats given a continuous infusion of unfractionated heparin. Treated pregnant rats exhibited increased BP and reduced VEGF bioavailability compared to vehicle-treated animals, indicating that heparin treatment is able to release sFlt1 and that this soluble factor may contribute to increase maternal BP.

The findings presented during the 2021 ISH/ESH meeting point to important advances in the discovery of potential biomarkers as well as new therapies in preeclampsia. However, as highlighted by Dr. Kotsis in his presentation, the newly discovered biomarkers must still go through a long process of preclinical testing using previous predictive models, in order to consider them effective in predicting preeclampsia, particularly in the early stages of gestation.

References:

1. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP, Souza JP, Maternal WHOMSo and Newborn Health Research N. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG : an international journal of obstetrics and gynaecology*. 2014;121 Suppl 1:14-24. DOI: [10.1111/1471-0528.12629](https://doi.org/10.1111/1471-0528.12629)
2. Bellamy L, Casas JP, Hingorani AD and Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *Bmj*. 2007;335:974. DOI: [10.1136/bmj.39335.385301.BE](https://doi.org/10.1136/bmj.39335.385301.BE)
3. Burton GJ, Charnock-Jones DS and Jauniaux E. Regulation of vascular growth and function in the human placenta. *Reproduction*. 2009;138:895-902. DOI: [10.1530/REP-09-0092](https://doi.org/10.1530/REP-09-0092)
4. Pereira RD, De Long NE, Wang RC, Yazdi FT, Holloway AC and Raha S. Angiogenesis in the placenta: the role of reactive oxygen species signaling. *BioMed research international*. 2015;2015:814543. DOI: [10.1155/2015/814543](https://doi.org/10.1155/2015/814543)
5. Reynolds LP and Redmer DA. Angiogenesis in the placenta. *Biol Reprod*. 2001;64:1033-40. DOI: [10.1095/biolreprod64.4.1033](https://doi.org/10.1095/biolreprod64.4.1033)
6. McNally R, Alqudah A, Obradovic D and McClements L. Elucidating the Pathogenesis of Pre-eclampsia Using In Vitro Models of Spiral Uterine Artery Remodelling. *Current hypertension reports*. 2017;19:93. DOI: [10.1007/s11906-017-0786-2](https://doi.org/10.1007/s11906-017-0786-2)
7. Suvakov S, Richards C, Nikolic V, Simic T, McGrath K, Krasnodembskaya A and McClements L. Emerging Therapeutic Potential of Mesenchymal Stem/Stromal Cells in Preeclampsia. *Current hypertension reports*. 2020;22:37. DOI: [10.1007/s11906-020-1034-8](https://doi.org/10.1007/s11906-020-1034-8)
8. Todd N, McNally R, Alqudah A, Jerotic D, Suvakov S, Obradovic D, Hoch D, Hombrebueno JR, Campos GL, Watson CJ, Gojnic-Dugalic M, Simic TP, Krasnodembskaya A, Desoye G, Eastwood KA, Hunter AJ, Holmes VA, McCance DR, Young IS, Grieve DJ, Kenny LC, Garovic VD, Robson T and McClements L. Role of A Novel Angiogenesis FKBPL-CD44 Pathway in Preeclampsia Risk Stratification and Mesenchymal Stem Cell Treatment. *The Journal of clinical endocrinology and metabolism*. 2021;106:26-41. DOI: [10.1210/clinem/dgaa403](https://doi.org/10.1210/clinem/dgaa403)

9.Suo M, Sun Y, Yang H, Ji J, He Y, Dong L, Wang Y, Zhang Y, Zhang Y and Hao M. miR-183-5p suppressed the invasion and migration of HTR-8/SVneo trophoblast cells partly via targeting MMP-9 in preeclampsia. Biosci Rep. 2020;40. DOI: [10.1042/BSR20192575](https://doi.org/10.1042/BSR20192575)

10.Han N, Xu H, Yu N, Wu Y and Yu L. MiR-203a-3p inhibits retinal angiogenesis and alleviates proliferative diabetic retinopathy in oxygen-induced retinopathy (OIR) rat model via targeting VEGFA and HIF-1alpha. Clin Exp Pharmacol Physiol. 2020;47:85-94. DOI: [10.1111/1440-1681.13163](https://doi.org/10.1111/1440-1681.13163)

11.Sela S, Natanson-Yaron S, Zcharia E, Vlodavsky I, Yagel S and Keshet E. Local retention versus systemic release of soluble VEGF receptor-1 are mediated by heparin-binding and regulated by heparanase. Circulation research. 2011;108:1063-70. DOI: [10.1161/CIRCRESAHA.110.239665](https://doi.org/10.1161/CIRCRESAHA.110.239665)

12.Moore KH, Chapman H and George EM. Unfractionated heparin displaces sFlt-1 from the placental extracellular matrix. Biol Sex Differ. 2020;11:34.DOI: [10.1186/s13293-020-00311-w](https://doi.org/10.1186/s13293-020-00311-w)

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Clinical Aspects of Hypertension in Pregnancy: Complications of Pregnancy as Predictors of Cardiovascular Risk

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Hypertension during pregnancy is an independent risk factor for cardiovascular events. This has clearly been documented in multiple studies¹⁻³. Recently, numerous studies have contributed to evidence on the degree of added risk these women experience.

The CALIBER study⁴ fills this gap and has reported an excess of cardiovascular complications in women at a younger age. The median age that the complications occur is less than forty years, which is below the age that traditional annual screening for hypertension and other cardiovascular risk factors is initiated. Therefore, to initiate screening at forty is too late. The data from this study were discussed by Lucy Chappell, at the ESH-ISH 2021 Joint Meeting in April 2021. As recommended

in the ISH Global Hypertension Guidance⁵, it is essential that these women are monitored from a much earlier age.

It has been observed that clinical trials are not a real life setting and the subjects enrolled in these trials are highly selected, excluding the vast majority of patients. The CALIBER data are real world data from a large cohort, with almost 1.9 million pregnancies assessed. Furthermore, the CALIBER population appears to be a realistic representation of pregnant women as demonstrated by similarities to previous populations, with similar risk factors.

A cardiovascular event occurred in 18 624 women within a median follow-up of 9.25 years. The majority (65%) of which occurred in women