International Journal of Cerebrovascular Disease and Stroke
Campbell N et al. Int J Cerebrovasc Dis Stroke 6: 154.
www.doi.org/10.29011/2688-8734.000054
www.gavinpublishers.com

Research Article

AT1-AA Infusion during Pregnancy Impairs CBF Autoregulation Postpartum

Nathan Campbell[1*], Luke Strong[1], Xing Fang[1], Jane J Border[1], Owen Herrock[1], Ty Turner[1], Evangeline Deer[1], Lorena Amaral[1], Ralf Dechend[3], Richard J Roman[1], Babbette LaMarca[1,2*]

[1]Department of Pharmacology & Toxicology, University of Mississippi Medical Center, Jackson, MS, USA

[2]Department of Obstetrics and Gynecology, University of Mississippi Medical Center, Jackson, MS, USA

[3]Charité, Campus Buch, Experimental and Clinical Research Center, HELIOS Clinic, Berlin-Buch, Germany

***Corresponding author:** Nathan Campbell, Department of Pharmacology & Toxicology, University of Mississippi Medical Center, Jackson, MS, USA

Citation: Campbell N, Strong L, Fang X, Border JJ, Herrock O, et al. (2023) AT1-AA Infusion during Pregnancy Impairs CBF Autoregulation Postpartum. Int J Cerebrovasc Dis Stroke 6: 154. DOI: https://doi.org/10.29011/2688-8734.100154

Received Date: 05 July, 2023**; Accepted Date:** 14 July, 2023**; Published Date:** 17 July, 2023

Abstract

Preeclampsia (PE), new-onset hypertension during pregnancy alongside organ dysfunction, is a leading cause of morbidity and mortality for the mother and fetus. PE women have activated B cells that produce agonistic autoantibodies to the angiotensin II type 1 receptor (AT1-AA). AT1-AA impairs cerebral blood flow (CBF) autoregulation during pregnancy. Although AT1-AA often remains elevated up to 8 years postpartum, AT1-AA's effect on CBF autoregulation postpartum is unknown. This study examined whether elevated AT1-AA during pregnancy impairs CBF autoregulation postpartum and if this was augmented by infusion of AT1-AA postpartum. AT1-AA was infused into 12-week-old timed-pregnant Sprague Dawley rats beginning on gestational day 14. Uterine artery resistance index (UARI) was measured on gestational day 18 as a measure of endothelial dysfunction associated with PE. Dams were allowed to deliver. One group was given a second infusion of AT1-AA (50% perinatal dose mimicking levels observed in postpartum PE women) at 9 weeks postpartum. After postpartum week 10, mean arterial pressure (MAP) was measured in conscious rats and CBF autoregulation was measured by laser Doppler flowmetry. AT1-AA during pregnancy increased UARI ($P<0.05$). AT1-AA during pregnancy did not affect MAP postpartum but did impair CBF autoregulation postpartum. Infusion of AT1-AA postpartum significantly elevated blood pressure ($P<0.01$) but did not further impair CBF autoregulation. This study demonstrates that circulating AT1-AA during pregnancy causes impairment of CBF autoregulation well into the postpartum period indicating that elevated AT1-AA leads to long-term cerebrovascular consequences. Targeting AT1-AA may prevent cerebrovascular effects associated with PE during pregnancy and postpartum.

Keywords: Autoantibodies; Blood pressure; Cerebral blood flow; Inflammation; Preeclampsia

Introduction

PPreeclampsia (PE) is defined as new-onset hypertension during the third trimester accompanied by other-organ dysfunction [1,2]. PE affects between 5-10% of pregnancies in the United States and worldwide. The best treatment for PE is the delivery of the fetoplacental unit. Current treatments focus on maintaining the pregnancy for as long as possible to improve fetal development. The leading cause of mortality for women with PE is cerebrovascular events including cerebral edema, hemorrhage, or ischemic stroke[3,4]. In fact, 40% of maternal deaths in PE patients are related to complications in the cerebrovasculature [5]. PE also increases the risk for vascular dementia postpartum [6,7]. Although the mechanisms leading to the increased cerebrovascular dysfunction are unclear, there is evidence in both patients and

animal models that implicates impaired cerebral blood flow (CBF) autoregulation [8,9].

The brain requires that there is constant blood flow to meet its metabolic needs even during changes in perfusion pressure [10]. The blood flow is regulated through changes in the vascular resistance. The CBF can be regulated at perfusion pressures between 60 and 160 mmHg [11,12]. CBF autoregulation is an important mechanism that maintains constant cerebral blood flow and prevents transmission of elevated pressure to vulnerable capillaries over a range of systemic mean arterial pressures (MAP) [13]. In the setting of hypertension when blood pressures rise above the regulatory range, increased pressure overcomes the myogenic vasoconstriction of the vessels causing them to lose their ability to provide resistance that regulates the CBF [12,14-16]. A significant concern following impaired CBF autoregulation is blood-brain barrier disruption and cerebral edema which leads to neurological complications, including strokes and cognitive dysfunction[7,17]. Impaired CBF autoregulation can lead to increased transmission of elevated systemic pressure to capillaries and other small blood vessels in the brain. Increased pressure in the brain capillaries is associated with the disruption of the blood brain barrier [18]. One system that may be responsible for impaired autoregulation during PE is the renin-angiotensin system (RAS). During normal pregnancies, activation of the RAS plays a role in the expansion of extracellular fluid volume but blood pressure typically decreases due to reduced vascular sensitivity to angiotensin II [19]. However, PE pregnancies are characterized by increased vascular sensitivity to angiotensin II [20]. One explanation for this increased sensitivity is the presence of circulating agonistic autoantibodies to the angiotensin II type 1 receptor (AT1-AA) [21,22]. AT1-AA was first discovered in the serum of PE patients by Wallukat et al. [21] and since then AT1-AA has been shown to contribute to endothelial dysfunction in the placenta and kidney in PE [22,23]. AT1-AA also may contribute to the impairment of CBF autoregulation during pregnancy [9]. Circulating AT1-AA levels are known to be elevated for up to 8 years postpartum following a PE pregnancy [24] however, the cerebrovascular consequences of this sustained presence are unknown. AT1-AA exposure during pregnancy increases susceptibility to ischemic injury and other cardiovascular morbidities in the heart postpartum [25-27]. Previous studies in animal models of PE found that autoregulation of CBF is impaired during pregnancy [9,28, 29]. Angiotensin II receptor blockers have attenuated impaired CBF autoregulation in the reduced uterine perfusion pressure (RUPP) model of PE implicating the AT1 receptor and its agonists including AT1-AA [9]. Additionally, a 'n7AAc' peptide, which blocks the actions of AT1-AA, improves postpartum cardiac outcomes in the RUPP model [27] and also improves CBF autoregulation in the RUPP model during pregnancy [29]. Taken together, these studies implicate AT1-AA during pregnancy and in postpartum impairment of CBF.

In the present study, we infused purified RUPP AT1-AA into pregnant Sprague Dawley rats which has previously been shown to induce a PE-like phenotype [30,31] including increased uterine artery resistance index (UARI) associated with hypertension and increased Endothelin-1 and Reactive Oxygen Species, mitochondrial dysfunction, and sFlt-1. AT1-AA has also been shown to play a role in impaired CBF autoregulation during pregnancy and in the reduced uterine perfusion pressure (RUPP) model of PE [9,29]. However, the effect of AT1-AA infusion during pregnancy on CBF autoregulation and blood pressure during the postpartum period is unclear. Thus, the objective of the current study was to determine if elevated circulating AT1-AA levels during pregnancy have a sustained effect to impair CBF autoregulation in the postpartum period and if this effect is augmented by secondary infusion of AT1-AA postpartum to mimic levels observed in postpartum preeclamptic women.

Methods

All procedures involving animals in this study were performed in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the University of Mississippi Medical Center. Animal experiments were conducted on twelve-week-old timed-pregnant Sprague Dawley rats (Envigo, Indianapolis, IN) that were housed in a temperature-controlled (23°C) facility under a 12:12-h light-dark cycle and fed a standard laboratory chow diet.

AT1-AA administration to pregnant rats

The AT1-AA was purified as previously described [32]. AT1-AA was extracted from the serum of RUPP rats by column purification of the IgG fraction and the AT1-AA epitope binding site. Pregnant rats were implanted with osmotic minipumps intraperitoneally (model 2002; Alzet Osmotic Pumps, Cupertino, CA) containing purified AT1-AA diluted 1:40 in saline or saline alone beginning on gestational day (GD) 14. Rats were anesthetized with 2% isoflurane delivered by a vaporizer (Ohio Medical Products, Champaign, IL) and treated with carprofen to reduce post-operative pain. The rats were allowed to deliver their litters between GD21-23. Pups were weaned at 3 weeks postpartum. During postpartum week 9, a group of rats infused with AT1-AA during pregnancy were randomly selected and implanted with a second osmotic minipump that infused AT1-AA, diluted 1:80 with saline to mimic the elevated AT1-AA levels seen in PE women postpartum [24,33].

Assessment of uterine artery resistance index

On GD18, the uterine artery resistance index (UARI) of pregnant rats was measured by Doppler ultrasound as a non-invasive measure of vascular function to confirm a PE phenotype. The rats were anesthetized with isoflurane and fixed on a platform of a Vevo 770 ultrasound imaging system (FUJIFILM VisualSonics, Toronto, ON, Canada) with a 30-Hz transducer. Doppler velocimetry profiles were obtained from the uterine arteries of each uterine horn. Waveforms representing the peak systolic velocity (PSV) and the end-diastolic velocity (EDV) were captured and the velocities were measured. Three waveforms were measured per frame. The UARI = (PSV-EDV)/PSV was calculated as seen in clinical settings.

Assessment of mean arterial pressure

On postpartum week 10, rats from each group were anesthetized with 2% isoflurane delivered with a vaporizer (Ohio Medical Products, Champaign, IL) and a PE50 catheter was implanted in the right carotid artery and exteriorized through the back of the neck. The rats were treated with carprofen to manage post-operative pain. The following day, blood pressure was measured in conscious rats in restrainers using a pressure transducer after an equilibration period of 30 minutes and a reading time of 30 minutes (Cobe II Transducer CDX Sema, Birmingham, AL).

Assessment of cerebral blood flow autoregulation

CBF autoregulation was measured by laser Doppler flowmetry 12 weeks postpartum in a second group of randomly selected animals from each group as we have previously described [34,35]. Briefly, postpartum week 12 rats were anesthetized with Ketamine (30 mg/Kg, i.m.) and Inactin (50 mg/Kg, i.p.). Catheters were implanted in the femoral artery and vein for measurement of MAP and iv infusions. The trachea was cannulated for artificial ventilation and monitoring of end-expired PCO_2. The head was immobilized in a stereotaxic apparatus and a 4mm x 4mm closed cranial window was created by thinning the bone over the parietal cortex, using a dental drill until the underlying vasculature was visible. The ventilation rate was adjusted to maintain end-expired PCO_2 levels between 30-35 mmHg. MAP and baseline CBF were measured using a Laser Doppler flowmeter (PF5000, Perimed Instruments). Autoregulation of CBF was measured as MAP was increased in graded steps of 20 mmHg from 100 to 180 mmHg using iv infusion of phenylephrine (0.5-5 µg/min). The infusion of phenylephrine was then terminated to allow MAP to return to 100 mmHg and CBF was measured as MAP was reduced from 100 to 40 mmHg by graded hemorrhage in steps of 20 mmHg. Changes in CBF were expressed relative to baseline (100 mmHg) values as a percentage.

Statistical Analysis

Data are expressed as mean values ± standard error (SEM). A paired t-test was used to determine the significance of changes in UARI. One-way analysis of variance with a Bonferroni post hoc test was used for statistical comparison of MAP. A two-way analysis of variance for repeated measures with a Bonferroni post hoc test was used for statistical comparison of CBF. A P value < 0.05 was considered statistically significant.

Results

AT1-AA infusion increases uterine artery resistance index

As a measure of a PE phenotype, UARI was performed on pregnant rats. The rats infused with AT1-AA (n=7) showed significantly increased uterine artery resistance index (UARI) defined by (PSV-EDV)/PSV, on GD18 compared with normal pregnant (NP) rats (n=5) (P<0.05) [36] (Figure 1).

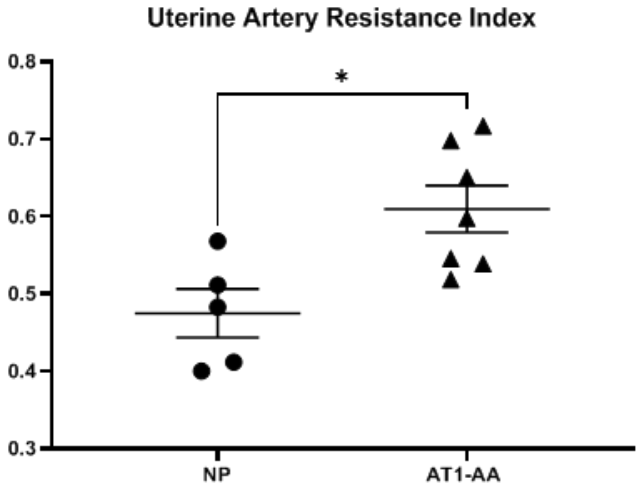

Figure 1: Uterine Artery Resistance Index is Increased Following AT1-AA Infusion.

AT1-AA infusion (n=7) during pregnancy significantly increased uterine artery resistance index (UARI) compared to NP (n=5, p<0.05). * indicates P<0.05. A paired t-test was used for statistical analysis. The data are presented as mean values ± standard error.

AT1-AA infusion postpartum increases mean arterial pressure

MAP was measured at 10 weeks postpartum. There was no change in postpartum MAP in the rats infused with AT1-AA during pregnancy (n=6) compared to NP (n=5) (Figure 2). However, blood pressure significantly increased in the rats that received a second infusion of AT1-AA postpartum (n=5) compared to NP (P<0.01) rats and those infused with AT1-AA only during pregnancy (P<0.01) (Figure 2).

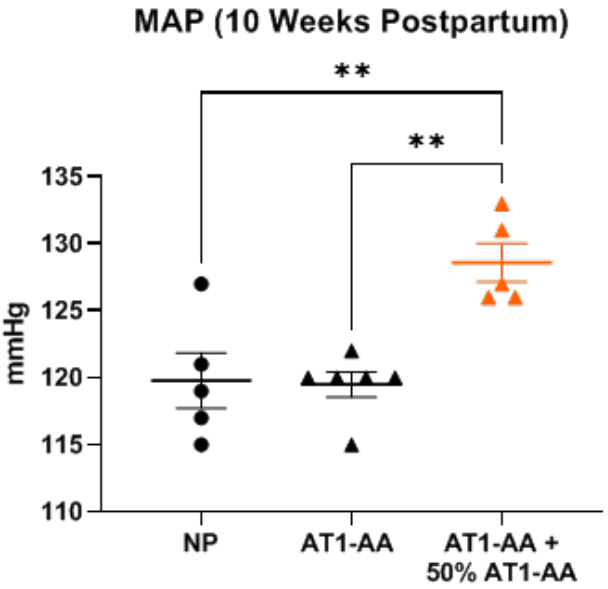

Figure 2: Secondary Infusion of AT1-AA Increases Postpartum Blood Pressure.

AT1-AA infused rats that received a secondary infusion of 50% AT1-AA (n=5) had increased mean arterial pressure (MAP) compared to NP (n=5, P<0.01) or rats infused with AT1-AA during pregnancy (n=6, P<0.01). ** indicates P<0.01. A one-way analysis of variance with a Bonferroni post hoc test was used for statistical analysis. The data are presented as mean ± standard error.

AT1-AA infusion during pregnancy impairs CBF autoregulation postpartum

Autoregulation of CBF was compared in NP rats (n=8), rats infused with AT1-AA during pregnancy alone (n=8), and those that received a second infusion of AT1-AA postpartum (n=10). Infusion of AT1-AA during pregnancy significantly impaired CBF autoregulation 12 weeks postpartum (Figure 3). CBF increased by only 25% when pressure was increased from 80 to 180 mmHg in the NP animals. In contrast, CBF doubled in the animals infused with AT1-AA during pregnancy. A second infusion of the AT1-AA in the postpartum period also impaired CBF but did not have a greater effect on CBF autoregulation compared with the rats infused with the AT1-AA during pregnancy alone (Figure 3).

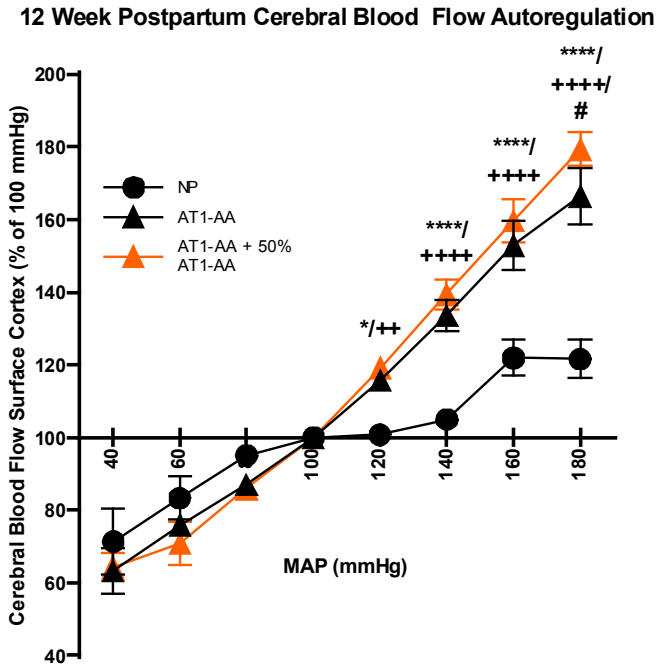

Figure 3: AT1-AA Infusion Impairs Cerebral Blood Flow Autoregulation.

Rats infused with AT1-AA (n=8) during pregnancy alone and those that receive a second infusion of AT1-AA + 50% AT1-AA (n=10) in the postpartum period exhibited impaired autoregulation of CBF in response to elevations in MAP above 120 mmHg as compared to normal pregnant NP rats (n=8). * indicates p<0.05 versus corresponding values in AT1-AA vs NP. **** indicates P<0.0001 AT1-AA vs NP. ++ indicates P<0.01 AT1-AA + 50% AT1-AA vs NP. ++++ indicates P<0.0001 AT1-AA + 50% AT1-AA vs NP. # indicates P<0.05 AT1-AA vs AT1-AA + 50% AT1-AA. A two-way analysis of variance with a Bonferroni post hoc test was used for statistical analysis. The data are presented as mean ± standard error.

Discussion

AT1-AA administration has been used as a model for PE in multiple studies showing increased blood pressure, UARI, [30,32,37,38], oxidative stress [22,39,40], endothelial dysfunction[30,32,41,42], renal dysfunction [22,30,43] and

impaired CBF autoregulation [9]. In this study, we demonstrated AT1-AA infusion causes uterine artery dysfunction during pregnancy, confirming a PE phenotype during pregnancy as previously published [23,36,37]. We associated this uterine vascular dysfunction with sustained cerebrovascular dysfunction demonstrated by impaired CBF autoregulation in the postpartum period in rats that no longer had increased blood pressure. Importantly, we show that infusion of AT1-AA to levels to mimic that seen in previously PE women causes hypertension and impaired CBF postpartum. Studies that have investigated the postpartum period following PE have focused on whether there are prolonged effects on blood pressure or cardiac function [25-27], but to our knowledge, this is one of the first studies to examine factors that may be responsible for cerebrovascular dysfunction postpartum for PE women.

Although the role of AT1-AA in PE has been studied extensively, the results from this study are the first to link impaired CBF autoregulation postpartum with the presence of circulating AT1-AA during pregnancy. In conjunction with data published by Duncan et al. [29] and Warrington et al. [9] we demonstrated that circulating AT1-AA during pregnancy results in significant impairment of CBF autoregulation postpartum. Importantly, we demonstrated that this CBF autoregulatory impairment does not resolve after the delivery of the placenta as many PE symptoms do. This data supports the hypothesis that circulating AT1-AA contributes to the impairment of the autoregulatory process to maintain normal CBF. Furthermore, we demonstrated that CBF autoregulation was impaired to the same degree regardless of sustained hypertension with a second infusion of AT1-AA in the postpartum period [24,33]. This leads us to believe that the mechanism by which AT1-AA impairs CBF autoregulation occurs during pregnancy and is significant enough to last long after the resolution of the pregnancy. Interestingly, the second infusion of AT1-AA led to higher blood pressure in the postpartum rats compared to rats that only received AT1-AA during pregnancy. This indicates that the population of postpartum women that produce AT1-AA up to 8 years postpartum may be at increased risk for hypertension [24,33]. However, this study also raises awareness that previously PE women that do not have hypertension postpartum are also at risk for long-term neurovascular dysfunction. Our study contributes some insight into epidemiological studies showing an increased risk of hypertension as well as neurovascular disorders later in the life of women who suffered from PE [44]. AT1-AA has been implicated in non-pregnancy-related forms of hypertension, renal allograft rejection, and Covid-19 [21,45,46]. Our data adds to the evidence showing that AT1-AA can contribute to hypertension and other diseases beyond the context of pregnancy [47-55].

Conclusion

Our data indicates that AT1-AA during pregnancy causes changes in CBF hemodynamics that are sustained, even in the absence of hypertension in the postpartum period. Elevated circulating AT1-AA during the postpartum period is associated with elevated blood pressure and impaired CBF autoregulation. This implicates AT1-AA in the long-term cardiovascular and cerebrovascular outcomes for PE women. AT1-AA may be a potential target for the treatment of PE and postpartum disease following PE.

Source of Funding

This study was supported in part by NIH grants HD067541 (BL), H13865 (RJR) and P20GM121334 (BL, LMA), and F31 HD110230-01(N.C.), RD is funded by the German Research Foundation DFG 631/15-1 (RD).

Conflict of Interest Statement

The authors report no conflict of interest.

Author Contributions

Conceived and designed research, R.J.R and B.L.; Performed experiments, N.C., L.S., X.F., J.J.B., O.H., T.T., R.J.R.; Analyzed data, N.C., L.S., X.F., J.J.B., O.H., T.T.; Interpreted Results, N.C., R.J.R., and B.L.; writing—original draft preparation, N.C.; writing—review and editing, N.C., L.S., X.F., J.J.B., O.H., T.T., E.D., L.A., R.D., R.J.R., and B.L.; All authors have read and agreed to the published version of the manuscript.

References

1. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, et al. (2018) Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension 72: 24-43.
2. Obstetricians, A.C.O. and Gynecologists (2019) ACOG practice bulletin no. 202: Gestational hypertension and preeclampsia. Obstet Gynecol 133: e1-e25.
3. Duley L (2009) The global impact of pre-eclampsia and eclampsia. Semin Perinatol 33: 130-137.
4. Bartal MF, Sibai BM (2020) Eclampsia in the 21st century. Am J Obstet Gynecol 226: S1237-S1253.
5. MacKay AP, Berg CJ, Atrash HK (2001) Pregnancy-related mortality from preeclampsia and eclampsia. Obstet Gynecol 97: 533-538.
6. Basit S, Wohlfahrt J, Boyd HA (2018) Pre-eclampsia and risk of dementia later in life: Nationwide cohort study. BMJ 363.
7. Miller EC (2019) Preeclampsia and cerebrovascular disease: The maternal brain at risk. Hypertension 74: 5-13.
8. van Veen TR, Panerai RB, Haeri S, Griffioen AC, Zeeman GG, Belfort MA (2013) Cerebral autoregulation in normal pregnancy and preeclampsia. Obstet Gynecol 122: 1064-1069.
9. Warrington JP, Fan F, Duncan J, Cunningham MW, LaMarca BB, et al. (2019) The angiotensin II type I receptor contributes to impaired cerebral blood flow autoregulation caused by placental ischemia in pregnant rats. Biol Sex Differ. 10: 58.
10. Cipolla MJ (2009) The cerebral circulation. Integrated systems physiology: From molecule to function 1: 1-59.
11. Phillips SJ, Whisnant JP (1992) Hypertension and the brain. Arch intern med 152: 938-945.
12. Busija DW, Heistad DD (1984) Factors involved in the physiological

regulation of the cerebral circulation. Rev Physiol Biochem Pharmacol 101: 161-211.

13. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H (1989) Cerebral autoregulation dynamics in humans. Stroke 20: 45-52.

14. Johansson B, Li CL, Olsson Y, Klatzo I (1970) The effect of acute arterial hypertension on the blood-brain barrier to protein tracers. Acta Neuropathologica 16: 117-124.

15. Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, et al. (1978) Responses of cerebral arteries and arterioles to acute hypotension and hypertension. Am J Physiol 234: H371-H383.

16. Kontos HA, Wei EP, Dietrich WD, Navari RM, Povlishock JT, et al. (1981) Mechanism of cerebral arteriolar abnormalities after acute hypertension. Am J Physiol 240: H511-H527.

17. Obermeier BR, Daneman R, Ransohoff RM (2013) Development, maintenance and disruption of the blood-brain barrier. Nat Med 19: 1584-1596.

18. Baumbach GL, Heistad DD (1985) Regional, segmental, and temporal heterogeneity of cerebral vascular autoregulation. Ann Biomed Eng 13: 303-310.

19. West CA, Sasser JM, Baylis C (2016) The enigma of continual plasma volume expansion in pregnancy: Critical role of the renin-angiotensin-aldosterone system. Am J Physiol Renal Physiol 311: F1125-F1134.

20. Gant NF, Daley GL, Chand S, Whalley PJ, MacDonald PC (1973) A study of angiotensin II presso response throughout primigravid pregnancy. J Clin Invest 52: 2682-2689.

21. Wallukat G, Homuth V, Fischer T, Lindschau C, Horstkamp B, et al. (1999) Patients with preeclampsia develop agonistic autoantibodies against the angiotensin AT 1 receptor. J Clin Invest 103: 945-952.

22. Cunningham Jr MW, Williams JM, Amaral L, Usry N, Wallukat G, et al. (2016) Agonistic autoantibodies to the angiotensin II type 1 receptor enhance angiotensin II–induced renal vascular sensitivity and reduce renal function during pregnancy. Hypertension 68: 1308-1313.

23. Cunningham Jr MW, Castillo J, Ibrahim T, Cornelius DC, Campbell N, et al, (2018) AT1-AA (angiotensin II type 1 receptor agonistic autoantibody) blockade prevents preeclamptic symptoms in placental ischemic rats. Hypertension 71: 886-893.

24. Rieber-Mohn AB, Sugulle M, Wallukat G, Alnæs-Katjavivi P, Størvold GL, et al. (2018) Auto-antibodies against the angiotensin II type I receptor in women with uteroplacental acute atherosis and preeclampsia at delivery and several years postpartum. J Reprod Immunol 128: 23-29.

25. Wang HP, Zhang WH, Wang XF, Zhu J, Zheng YQ, et al. (2014) Exposure to AT1 receptor autoantibodies during pregnancy increases susceptibility of the maternal heart to postpartum ischemia-reperfusion injury in rats. Int J Mol Sci 15: 11495-11509.

26. Jin Z, Zhang W, Yang H, Wang X, Zheng Y, et al. (2013) Maternal treatment with agonistic autoantibodies against type-1 angiotensin II receptor in late pregnancy increases apoptosis of myocardial cells and myocardial susceptibility to ischemia-reperfusion injury in offspring rats. PLoS One 8: e80709.

27. Booz GW, Kennedy D, Bowling M, Robinson T, Azubuike D, et al. (2021) Angiotensin II type 1 receptor agonistic autoantibody blockade improves postpartum hypertension and cardiac mitochondrial function in rat model of preeclampsia. Biol Sex Differ 12: 1-12.

28. Maeda KJ, McClung DM, Showmaker KC, Warrington JP, Ryan MJ, et al. (2021) Endothelial cell disruption drives increased blood-brain barrier permeability and cerebral edema in the Dahl SS/jr rat model of superimposed preeclampsia. Am J Physiol Heart Circ Physiol 320: H535-H548.

29. Duncan JW, Azubuike D, Booz GW, Fisher B, Williams JM, et al. (2020) Angiotensin II type 1 receptor autoantibody blockade improves cerebral blood flow autoregulation and hypertension in a preclinical model of preeclampsia. Hypertens Pregnancy 39: 451-460.

30. Brewer J, Liu R, Lu Y, Scott J, Wallace K, et al. (2013) Endothelin-1, oxidative stress, and endogenous angiotensin II: Mechanisms of angiotensin II type I receptor autoantibody-enhanced renal and blood pressure response during pregnancy. Hypertension 62: 886-92.

31. Parrish MR, Murphy SR, Rutland S, Wallace K, Wenzel K, et al. (2010) The effect of immune factors, tumor necrosis factor-α, and agonistic autoantibodies to the angiotensin II type I receptor on soluble fms-like tyrosine-1 and soluble endoglin production in response to hypertension during pregnancy. Am J hypertens 23: 911-916.

32. LaMarca B, Parrish M, Ray LF, Murphy SR, Roberts L, et al. (2009) Hypertension in response to autoantibodies to the angiotensin II type I receptor (AT1-AA) in pregnant rats: Role of endothelin-1. Hypertension 54: 905-909.

33. Hubel CA, Wallukat G, Wolf M, Herse F, Rajakumar A, et al (2007) Agonistic angiotensin II type 1 receptor autoantibodies in postpartum women with a history of preeclampsia. Hypertension 49: 612-617.

34. Wang S, Jiao F, Border JJ, Fang X, Crumpler RF, et al. (2022) Luseogliflozin, a sodium-glucose cotransporter-2 inhibitor, reverses cerebrovascular dysfunction and cognitive impairments in 18-mo-old diabetic animals. Am J Physiol Heart Circ Physiol 322: H246-H259.

35. Wang S, Lv W, Zhang H, Liu Y, Li L, et al. (2020) Aging exacerbates impairments of cerebral blood flow autoregulation and cognition in diabetic rats. Geroscience 42: 1387-1410.

36. Faulkner JL, Amaral LM, Cornelius DC, Cunningham MW, Ibrahim T, et al. (2017) Vitamin D supplementation reduces some AT1-AA-induced downstream targets implicated in preeclampsia including hypertension. Am J Physiol Regul Integr Comp Physiol 312: R125-R131.

37. Ashraf UM, Hall DL, Campbell N, Waller JP, Rawls AZ, et al. (2022) Inhibition of the AT1R agonistic autoantibody in a rat model of preeclampsia improves fetal growth in late gestation. Am J Physiol Regul Integr Comp Physiol.323:R670-R681.

38. LaMarca B, Wallukat G,Llinas M, Herse F, Dechend R, et al. (2008) Autoantibodies to the angiotensin type I receptor in response to placental ischemia and tumor necrosis factor α in pregnant rats. Hypertension, 52: 1168-1172.

39. Parrish MR, Wallace K, Tam Tam KB, Herse F, Weimer A, et al, (2011) Hypertension in response to AT1-AA: role of reactive oxygen species in pregnancy-induced hypertension. Am J Hypertens, 24: 835-40.

40. Deer E, Ramana Vaka V, McMaster KM, Wallace K, Cornelius DC, et al. (2021) Vascular endothelial mitochondrial oxidative stress in response to preeclampsia: A role for angiotension II type 1 autoantibodies. Am J Obstet Gynecol MFM.3:100275.

41. Parrish MR, Ryan MJ, Glover P, Brewer J, Ray L, Dechend R, et al. (2011) Angiotensin II type 1 autoantibody induced hypertension during pregnancy is associated with renal endothelial dysfunction. Gend Med, 8:184-8.

42. Yang X, Wang F, Lau WB, Zhang S, Zhang S, et al. (2014) Autoantibodies isolated from preeclamptic patients induce endothelial dysfunction via interaction with the angiotensin II AT1 receptor. Cardiovasc Toxicol.14:21-9.

43. Cunningham MW, Vaka VR, McMaster K,Ibrahim T, Cornelius DC, et al. (2019) Renal natural killer cell activation and mitochondrial oxidative stress; new mechanisms in AT1-AA mediated hypertensive pregnancy. Pregnancy Hypertens, 215:72-77.

44. Lee G, Tubby J. (2015) Preeclampsia and the risk of cardiovascular disease later in life–A review of the evidence. Midwifery, 31:1127-1134.

45. Dragun D, Müller DN, Bräsen JH, Fritsche L, Nieminen-Kelhä M, et al. (2005) Angiotensin II type 1–receptor activating antibodies in renal-allograft rejection. N Engl J Med.352:558-69.

46. Rodriguez-Perez AI, Labandeira CM, Pedrosa MA, Valenzuela R, Suarez-Quintanilla JA, et al, (2021) Autoantibodies against ACE2 and angiotensin type-1 receptors increase severity of COVID-19 J Autoimmun.122:102683.

47. Irani RA, Zhang Y, Zhou CC, Blackwell SC, John Hicks M, et al. (2010) Autoantibody-mediated angiotensin receptor activation contributes to preeclampsia through tumor necrosis factor-α signaling. Hypertension, 55:1246-1253.

48. Zuo Y, Estes SK, Ali RA, Gandhi AA, Yalavarthi S, et al. (2020) Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. Sci Transl Med.12:eabd3876.

49. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, et al. (2020) Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science, 370: eabd4585.

50. Wang EY, Mao T, Klein J, Dai Y, Huck JD, et al, (2021) Diverse functional autoantibodies in patients with COVID-19. Nature, 595:283-288.

51. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, et al, (2021). Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine.38:101019.

52. Ceban F, Ling S, Lui MW L, Lee Y, Gill H, et al, (2022) Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. Brain Behav Immun. 101:-135.

53. Wallukat G, Hohberger B, Wenzel K, Fürst J, Schulze-Rothe S, et al. (2021) Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. Journal of Translational Autoimmunity, 4: 100100.

54. Sotzny F, Filgueiras IS, Kedor C, Freitag H, Wittke K, et al. (2022) Dysregulated autoantibodies targeting vaso-and immunoregulatory receptors in Post COVID Syndrome correlate with symptom severity. Frontiers in immunology, 13:5182.

55. Freitag H, Szklarski M, Lorenz S, Sotzny F, Bauer S, et al. (2021) Autoantibodies to vasoregulative G-protein-coupled receptors correlate with symptom severity, autonomic dysfunction and disability in myalgic encephalomyelitis/chronic fatigue syndrome. J Clin Med.10:3675.