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Preeclampsia and the Brain: Neural Control of Cardiovascular Changes During Pregnancy and Neurological Outcomes of Preeclampsia

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Abstract

Preeclampsia (PE) is a form of gestational hypertension that complicates ~ 5 percent of pregnancies worldwide. Over 70 percent of the fatal cases of PE are attributed to cerebral edema, intracranial hemorrhage, and eclampsia. The etiology of PE originates from abnormal remodeling of the maternal spiral arteries, creating an ischemic placenta that releases factors that drive the pathophysiology. An initial neurological outcome of PE is the absence of the autonomically regulated cardiovascular adaptations to pregnancy. PE patients exhibit sympathetic overactivation, in comparison to both normotensive pregnant and hypertensive non-pregnant females. Moreover, PE diminishes baroreceptor reflex sensitivity (BRS) beyond that observed in healthy pregnancy. The absence of the cardiovascular adaptations to pregnancy, combined with sympathovagal imbalance and a blunted BRS leads to life-threatening neurological outcomes. Behaviorally, the increased incidences of maternal depression, anxiety, and post-traumatic stress disorder (PTSD) in PE are correlated to low fetal birth weight, intrauterine growth restriction (IUGR) and premature birth. This review addresses these neurological consequences of PE that present in the gravid female both during and after the index pregnancy.

Keywords

Pregnancy; hypertension; preeclampsia; sympathovagal imbalance; disinhibition

Introduction

Preeclampsia (PE) is a distinct form of gestational hypertension that typically presents after the 20th week of gestation and complicates ~5 percent of pregnancies worldwide (1, 2), with developing countries having an incidence almost seven times higher than that of industrialized nations (3). The current diagnostic criteria classifies PE (in the absence of proteinuria) as hypertension associated with thrombocytopenia (platelet count less than 100,00 / microliter), liver dysfunction with liver transaminase blood levels at least double the

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normal concentration, elevated serum creatinine in excess of 1.1 mg/dL, pulmonary edema, and /or new-onset cerebral or visual impairments (4). PE results in more than 60,000 maternal deaths per year (3, 5), with over 70 percent of these fatal cases being neurological in cause, and are attributed to cerebral edema, intracranial hemorrhage, and eclampsia (3, 5–7). The exact etiology of PE is unknown, but the disorder originates from abnormal remodeling of the spiral arteries at the maternal-placental interface, creating an ischemic placenta that releases factors that drive the pathophysiology (8, 9). An initial neurological outcome of PE is the impairment of visceral motor autonomic control of maternal hemodynamics (Table 1), such that the cardiovascular physiological adaptations characteristic of healthy pregnancy are absent (10–14). One of these critical adaptations is the biphasic alteration of autonomic firing patterns, which adjusts sympathovagal balance to meet the metabolic demands of pregnancy (15, 16). PE is distinguished by sympathetic overactivation, where sympathetic firing is three times higher than in normotensive pregnant females, and quadruple the rate of hypertensive non-pregnant females (17, 18). Moreover, PE blunts baroreceptor reflex sensitivity (BRS) beyond that observed in healthy pregnancy (14, 19–21).

In the absence of the cardiovascular adaptations to pregnancy (Figure 1), the combination of an impaired BRS, sympathovagal imbalance, and pathogenic factors from the ischemic placenta advance the sequelae of life-threatening white matter lesions (22–24), cerebral edema and hemorrhaging (25–27) that can lead to executive dysfunction (28–30). Furthermore, PE establishes predispositions to anxiety (31–33), depression (34–36), and PTSD (37–42) in the gravid female, which are significantly correlated to low fetal birth weight, IUGR, and premature birth (32–36, 38). This review examines the neural control of blood pressure in healthy pregnancy, and addressess the resulting neurological outcomes of PE that present both during and after the index pregnancy.

The Autonomic Regulation of Cardiovascular Physiological Adaptations of Healthy Pregnancy vs. the Maternal Hemodynamics of PE

One of the initial and most dramatic changes observed in the gravid female is an expanded blood volume (43). To prepare for a typical blood loss of 500 ml (vaginal) to 1 liter (Cesarean) during delivery, osmoregulatory brain circuity (44) acts via neuroendocrine mechanisms to elicit increases in total blood volume beginning at 6 weeks gestation (45). During pregnancy, the plasma osmolality threshold for stimulating osmoreceptors is lowered from the normal 285 to 270 mOsm/kg (46). Relaxin secreted by the corpus luteum (47) acts on the organum vasculosum of the lamina terminalis (OVLT) and the subfornical organ that project to and excite the magnocellular neurons in the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus (48). Axons of these PVN and SON cell bodies project into the posterior pituitary, where they release vasopressin into the general circulation (44, 49, 50). Vasopressin acts on renal V_2 receptors to upregulate aquaporin-2 water channel expression on the cells of the distal convoluted tubule and collecting duct, thereby increasing the amount of water reabsorbed from urine and returning it to the blood volume (51, 52). As a result, by 32 weeks gestation 1.2 -1.6 liters has been added to the total blood volume (53), which is almost exclusively increased plasma volume (43). In stark contrast, preeclamptic

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women exhibit an increase of only ~ 200 mL in blood volume, which is directly correlated to the low birth weight and intrauterine growth restriction (54, 55) seen in children that are born during the index pregnancy (10).

Another critical adaptation that occurs in response in to this expanded blood volume is an increase in cardiac output (CO) (56). The metabolic demands of the fetoplacental unit require that 25% of the CO be allotted to arterial blood flow to the uterus (57). To increase the CO, the RVLM of the brain stem sends excitatory inputs to the cardiac preganglionic sympathetic nerves, residing in the intermediolateral cell column (IMLCC) of the spinal cord at thoracic levels T1–T4 (58–60). Exiting the cord via spinal nerves at the same levels, these cardiac preganglionic nerves synapse with postganglionic fibers within paravertebral ganglia (59–61). Cardiac postganglionic sympathetic fibers project to the sinoatrial and the atrioventricular nodes of the heart, and release norepinephrine that binds to β_1 adrenergic receptors (60, 62). The resulting signaling pathway increases cyclic AMP and activates protein kinase A, which leads to increased cardiac output (58, 60, 63, 64).

Influenced by this autonomic input, the CO increases early in the 1st trimester of normal pregnancy so that by 37–42 weeks gestation the average output is 6 L/minute (65–67). Three factors contribute to this increase in CO, each varying in dominance over the time course of gestation. Beginning in the 1st trimester, stroke volume and preload, both associated with the expansion in total blood volume, participates in the augmentation of CO (65, 68–70). Conversely, in the 2nd and 3rd trimesters, the HR, increased by 15 to 20 beats/min, becomes the primary cause of the increased CO which enables adequate nutrient/waste exchange to the developing fetus (65, 71). In clinical cases of preeclampsia, however, cardiac output is significantly reduced with an increase in peripheral vascular resistance (72, 73). This pathophysiological reduction in CO is manifested in preeclamptic patients by asymmetrical remodeling and hypertrophy of the left ventricle (74, 75). Moreover, increased levels of atrial and brain natriuretic peptides are directly correlated to the degree of left ventricular dysfunction in preeclampsia (12).

Within the context of the increases in blood volume and CO, the adaptation of a decrease in the peripheral vascular resistance (PVR) occurs in healthy pregnancy. The visceral motor autonomic innervation of the systemic vasculature produces forceful vasoconstriction by increasing the PVR (76, 77). Postganglionic sympathetic nerves terminate in the tunica adventitia of arteries and arterioles and release NE that diffuses into the tunica media to bind to α_1 or α_2 adrenergic receptors expressed on vascular smooth muscle cells producing vasoconstriction (59–61). In healthy pregnancy, this vasoconstriction is attenuated, and PVR is reduced by complex neurohormonal interactions that diminish the sensitivity to angiotensisn II (AngII) (78–80), offsetting the vasoconstrictive effects of thromboxane (81), and lowering both plasma osmolarity and arterial load (82–84). Moreover, starting at the fifth week of gestation, progesterone and prostaglandin levels promote vasodilation, and as a result the PVR decreases ~10% from baseline levels (76, 85, 86). The PVR reaches its lowest level at 20 weeks' gestation, ~ 35% decrease from baseline levels, and persists at this level through week 32 (65, 77, 87). Prostacyclin, an endothelium-derived eicosanoid, counteracts the vasoconstrictive effects of AngII during pregnancy (79, 80). Moreover, enhanced release of nitric oxide attenuates the actions of thromboxane by preventing the

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phosphorylation of myosin light chains in vascular smooth muscle (88, 89). In addition, production of relaxin increases during the first trimester and at term (82, 84). This peptide contributes both to the reduction in PVR and to the increase in CO (82, 84). Thus, despite the presence of increased AngII levels during normal pregnancy, a decreased sensitivity to AngII results (90–92).

However, in PE the PVR is elevated due to a heightened sensitivity to AngII (93), contributing to the hypertensive state. Several studies suggest that agonistic autoantibodies against the AngII AT_1 receptor (AT_1R-AABs) are associated with enhanced AngII sensitivity (94–98). AT_1R-AABs have been observed to increase production of the NF-κB / NADPH oxidase-mediated formation of reactive oxygen species (ROS) (99), plasminogen activator inhibitor, (100, 101), and soluble fms-related tyrosine kinase-1 (sFlt-1) (102). However, this significant correlation between AT_1R-AAB titer and elevated PVR is observed mostly in severe cases of PE (103, 104). In addition, levels of the vasodilatory heptapeptide angiotensin 1–7 (Ang 1–7), which attenuates the vasoconstrictive properties of AngII, are significantly diminished in PE (91). Further amplifying AngII sensitivity in PE is the increased expression of the angiotensin 1 receptor - bradykinin 2 receptor (AT_1-B_2) heterodimer on blood cells and omental vessels (105–107), that increase the PVR by accentuating AngII-mediated vasoconstriction. The pathological elevations in PVR observed in PE are manifested by increased arterial stiffness that not only reveals endothelial dysfunction, but also indicates the vulnerability to left ventricular hypertrophy and cardiac irregularities (74, 108, 109), all of which contribute to the hypertension associated with PE.

Critical to understanding the characteristic enhanced AngII sensitivity of PE are the changes that occur to the renin-angiotensin-aldosterone systems (RAAS) in both the kidney (110–113) and more importantly the placenta (114–131). Mistry et al., (119) observed that the placental RAAS exhibits the same degree of autonomy as the renal RAAS, but whose components are derived from both maternal and fetal sources. Rising estrogen plasma levels during pregnancy activate the placental RAAS, with concurrent increases in angiotensinogen (AGT) and renin levels (110, 114, 120, 132). Compared to the chorionic villi, the maternal decidua produces greater amounts of both total and active renin (114, 123). The hallmark placental ischemia observed in PE triggers increased expression of prorenin receptors (PRRs), which promote the generation of angiotensin I from AGT, and the subsequent cleavage of AngII from Ang I by angiotensin converting enzyme (ACE) (119). Morover, the binding of prorennin to PRRs exerts nearly a four-fold increase in the catalytic efficiency of PRR (117, 133).

The placental RAAS demonstrates high sensitivity to tissue levels of reactive oxygen species (ROS), which serve as a signal for both angiogenesis (116) and placental development (117). Overactivation of the placental RAAS, such as in cases of placental ischemia, results in excess local production of AngII, which acting on AT1Rs expressed by placental trophoblasts (124), can lead to the deleterious effects of low birthweight and intrauterine growth restriction (119). Recently, Zhou et al., (130) have elucidated the mechanism between placental RAAS overactivation and the enhanced pressor response observed in PE. The AGT protein maintains a state of equilibrium between its oxidized and reduced forms (130). Excessive ROS production by the ischemic placenta catalyzes a disulfide linkage in

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the angiotensin portion of AGT, and this oxidized form of AGT results in the four-fold incease in Ang I production (117, 130), subsequent cleavage to AngII, and then enhanced pressor response brought about by the vasoconstrictive properties of AngII (119, 134). Thus, maternally derived AngII produced from the uterine placental bed acts in an endocrine manner to produce vasoconstriction of the uterine spiral arteries, further exacerbating placental ischemia (114, 115).

As observed by Nartita et al. (120), overactivation of the placental RAAS by placental ischemia leads to increased AngII-mediated pressor response and sympathetic nerve activity. If left untreated, the resulting hypertension can increase the risk of the loss of CBF autoregulation, increase in cerebral perfusion pressure, and eventual damage to the blood brain barrier (135, 136). These initial neurological outcomes resulting from overactivation of the placental RAAS can lead to life threatening neurological consequences, which will be addressed later in the text.

The above described cardiovascular hemodynamic alterations of pregnancy are mediated by the sympathetic and parasympathetic divisions of the autonomic nervous system via sympathovagal balance (137, 138). Sympathovagal balance has been assessed in healthy pregnant and preeclamptic women by spectral analysis of heart rate variability (HRV) by comparing the ratio of the low frequency (0.04–0.15 Hz) to high frequency (0.15–0.40 Hz) domains of the HRV, termed the LF:HF ratio (139–142). During the first trimester of normal healthy pregnancy, a dominant HF exists (0.15–0.40 Hz), which is consistent with a robust vagal control of heart rate (16). By the third trimester, however, a gradual increase in the LF:HF ratio indicates that a biphasic change in autonomic inputs occurs, characterized by a vagal withdrawal over heart rate and a dominant sympathetic tone (15, 16, 143). Kuo et al., observed that this biphasic shift towards augmented sympathetic tone in late pregnancy is in part attributed to aortocaval compression by the gravid uterus (16, 144, 145). In these cases, the gravid uterus compresses upon the maternal abdominal aorta and inferior vena cava, resulting in both a decrease in cardiac output and venous return, and eliciting compensatory changes in sympathetic tone (146).

In PE, however, the abnormal uterine perfusion adversely affects autonomic control of cardiovascular function (14, 147), such that the LF:HF ratio is elevated beyond that seen in normotensive pregnant females (140, 142, 148), indicative of sympathetic overactivation and sympathovagal imbalance (11, 17, 149–151). Thus, the impaired regulation of heart rate and blood pressure by sympathetic overactivation (141, 152) further exacerbates the abnormal placental perfusion and renal blood flow in preeclamptic women (153). This sympathetic overactivation may be the result of placental pathogenic factors (e.g., inflammatory cytokines) acting primarily on brainstem nuclei that govern sympathovagal balance (154–156) of cardiovascular physiology. In other forms of hypertension, the mechanism is disinhibition of the RVLM by upregulating the expression of $GABA_B$ receptors in the regions of the nucleus of the solitary tract that receive baroreceptor afferents (Figure 2) (157–163). Whether this mechanism is active in PE is an area ripe for new research.

Despite the routine clinical use of the LF:HF ratio in assessing sympathovagal balance, caution should be taken when interpreting data due to confounding non-neural factors and

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mathematical influences (164). For instance, the HF peak, typically associated with parasympathetic activity, may exhibit up to a 10% change in frequency due to augmented sympathetic nerve activation (164–166). Conversely, the upper limits of sympathetic activation may be offset by cardiac parasympathetic input, such as that observed during the "diving reflex" (167), where marked bradycardia occurs despite a robust increase in sympathetic nerve output (164, 168). Mathematical confounding variables (169) can occur when the heart rate variability (HRV) is not divided by the average R-R interval (164, 170). Moreover, respiratory influences on the LF:HF ratio, as is observed in heart transplant patients that lack cardiac innervation (164), exhibit an atrial stretch contributioin to the LF:HF ratio during the respiratory cycle (164, 171). Given these limitations of the LF:HF ratio, microneurography of skeletal muscle sympathetic nerve activity (MSNA) may be an alternative method of accurately evaluating sympathovagal balance.

Microneurography clinically assesses multiunit sympathetic activity of the peripheral vasculature by performing percutaneous recordings of action potentials conducted by peripheral nerves (172, 173). Sex-dependent differences are observed in MSNA recordings, such that women exhibit β-adrenergic vasodilation that counteracts the vasoconstrictive properties associated with increased MSNA (174). This effect has been observed in normotensive pregnant women, who demonstrated enhanced MSNA in spite of no significant change in blood pressure (141, 152, 172). Microneurographic studies of preeclamptic women reported amplified MSNA when compared to normotensive pregnant women, but were not significantly different from women diagnosed with pregnancy-induced hypertension (PIH), suggesting that sympathetic hyperactivity is not solely responsible for the renal dysfunction presented in cases of PE (172, 175). These data emphasize that it is unclear whether sympathetic hyperactivity actually causes gestational hypertension, or if it is a mechanistic consequence of angiogenic imbalance and endothelial dysfunction (172, 176).

The Baroreceptor Reflex in Healthy Pregnancy and Preeclampsia

Though it was once regarded as a short-term regulator of abrupt changes in blood pressure, the BR reflex is now considered to play an integral role in chronic hypertensive states (177).

Basic Circuitry of the Baroreceptor Reflex

Located within the arterial walls of the aortic arch and immediately rostral to the bifurcation of the common carotid artery within the carotid sinus (178) stretch-sensitive baroreceptors (BRs) detect beat-to-beat fluctuations in arterial pressure (62, 179, 180). Aortic BRs transmit impulses via the vagus nerve (CN X), while the carotid BRs send afferent signals via the glossopharyngeal nerve (CN IX). The cell bodies of the aortic BRs and carotid BRs reside in the nodose and petrosal ganglia, respectively, and they both make excitatory (glutamatergic) synapses on neurons in the dorsomedial region of the caudal NTS (62, 181, 182). The NTS receives and integrates these BR afferent inputs, and projects excitatory terminals to the caudal ventrolateral medulla (CVLM) (62, 181, 182). In turn, the CVLM excites preganglionic parasympathetic neurons in the nucleus ambiguus (NA), which also receives excitatory input from the NTS, and projects (via the vagus nerve) to the heart to reduce the heart rate and stroke volume (62, 181). More importantly, the CVLM projects inhibitory

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(GABAergic) projections to the “vasomotor center” of cardiovascular system, the RVLM (59, 181, 183). The RVLM projects to and synapses on preganglionic sympathetic neurons located in the IMLCC of the spinal cord (59, 179, 182). Inhibition of the RVLM reduces the sympathetic tone to IMLCC, and it is this decrease in sympathetic nerve activity to the blood vessels, heart, and kidneys, that produces a corresponding decrease in mean arterial pressure (180, 181, 183).

Alterations of the BR Reflex in Healthy and Preeclamptic Pregnancies

The CNS nuclei of the BR reflex circuitry express receptors for sex hormones (184). Estradiol has been observed to affect BRS, while progesterone modulates the sympathetic output of the RVLM (184). The neurosteroid 3-α-hydroxydihydroprogesterone (3-α-OH-DHP), a metabolite of progesterone, augments inhibitory GABAergic tone of the RVLM by binding to $GABA_A$ receptors expressed by RVLM neurons, and increasing Cl^- conductance (185, 186). Through this hormonal modulation of neural excitability, normal pregnancy is characterized by a reduction in BRS (185, 187–190).

Conversely, the BR reflex is impaired in PE beyond that observed in healthy pregnancy (14, 19), and presents with beat-to-beat variations in blood pressure, heart rate, and BRS that are utilized clinically to predict cases of PE (191, 192). When combined with Doppler sonography (for detection of reduced uterine perfusion), analysis of these beat-to-beat variations in blood pressure, heart rate, and BR reflex sensitivity, PE is predicted with a positive predictive accuracy of over 71% (21).

These clinical observations of BR reflex pathophysiology associated with PE provide the rationale for future studies on the regions of the NTS that receive and integrate BR afferents inputs. Indeed, a variety of hypertensive models have demonstrated mechanistic alterations occurring on NTS neurons (160–163, 193–201). While none of these studies modeled PE, the molecular pathways implicated in the increased pressor response warrant investigation in an animal model of PE (202). The electrophysological alterations that were observed in NTS neurons in these animal models are summarized below.

Diverse Models of Hypertension Demonstrate Electrophysiological Alterations Occuring in the NTS

$GABA_B$ receptors ($GABA_B$Rs) are metabotropic G-protein coupled receptors (GPCRs) (203, 204) that hyperpolarize the neuron (Figure 2) presynaptically (205, 206) and postsynaptically (203–206). NTS neurons hyperpolarized by increased $GABA_B$R activity cannot excite the CVLM and NA, nor can the CVLM sufficiently excite the preganglionic parasympathetic neurons of the NA (158, 180, 195, 207). As a result, the NA provides insufficient parasympathetic input to the heart, and the CVLM no longer inhibits the RVLM, creating a sympathovagal imbalance that leads to vasoconstriction, increased heart rate, and enhanced renal sympathetic nerve activity (158, 180, 195, 207). Pharmacologic studies in spontaneously hypertensive rats (SHRs) (162, 208–210), and hypertensive Sprague-Dawley rats induced with a one-kidney figure-8 renal wrap (163, 195, 198, 201, 211) have demonstrated that the enhanced expression and activation of $GABA_B$Rs in the regions of the

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NTS that receive and integrate BR afferent inputs results in hypertension. Additionally, transfer of the $GABA_BR$ gene into the NTS of normotensive rats resulted in rapid onset of hypertension, increased heart rate, and increased plasma norepinephrine levels, all of which remained elevated for the duration of the 14-day study (157). This $GABA_BR$-mediated pressor response is potentiated by the actions of AngII on NTS neurons (161).

NTS neurons express angiotensin II Type 1 receptors (AT_1Rs) with one of the highest receptor densities within the BBB (212, 213), and AngII acts at these receptors to dampen the BR afferent inputs in both hypertensive and normotensive animals (214, 215). Moreover, AngII increases the expression of $GABA_BRs$ on NTS neurons (161) and synergistically enhances the pressor response (160). Thus, AngII blunts BR afferent inputs by augmenting the $GABA_BR$-mediated inhibitory currents on NTS neurons, leading to disinhibition of the RVLM and increased sympathetic tone to the heart, vasculature, and kidneys (160, 163, 180, 207). Therefore, given the heightened AngII sensitivity observed in PE (216), and that the NTS neurons that receive BR afferent inputs exhibit one of the highest AT_1R expression levels within the BBB (212, 213), these $GABA_BRs$ on NTS neurons would serve as prime mechanistic targets for future studies employing an animal model of PE (202).

In addition to $GABA_BRs$, alpha2-adrenoreceptors (α_2-adrenoreceptors) represent an alternative mechanistic target for blood pressure control in PE. The activation of alpha2-adrenoreceptors (α_2-adrenoreceptors) expressed by astrocytes residing in the NTS elicits a decrease in blood pressure (197, 217, 218). However, when these astrocytic α_2-adrenoreceptors engage in cross-talk with neuronal adenosine-1 receptors (A1Rs) (196), or form heterodimers with μ-opoid receptors (197), hypertension can occur. Synaptic release of norepinephrine activates astrocytic α_2-adrenoreceptors, which triggers the extracellular release of ATP, that is then hydrolyzed to adenosine (196, 219, 220). The adenosine binds to presynaptic A1Rs and induces hyperpolarization by inactivating Ca^{2+} inward channels and activating K^+ channels (196, 221). Studies employing SHRs observed increased A1R expression in the NTS (194, 222), with enhanced sensitivity to adenosine (222) that blunted BRS resulting in a hypertensive state (193, 196, 223, 224). A hypertensive response in the NTS can also occur when μ-opioid receptors form heterodimers specifically with the α_{2A} class of α_2-adrenoreceptors (α_{2A}-ARs) (197, 225). Pharmacologic studies of SHRs demonstrated this hypertensive effect by microinjecting a μ-opioid agonist into the NTS, in which the μ-opioid-α_{2A}-AR heterodimers blocked nitric oxide-mediated vasodilation (197). Conversely, administration of a μ-opioid antagonist into the NTS prohibits the formation of μ-opioid-α_{2A}-AR heterodimers, resulting in a decrease in blood pressure in SHRs but not in WKY rats (197, 226). These results in rat models of primary hypertension implicate $GABA_BRs$ and alpha2-adrenoreceptors as prime candidates for mechanistics studies examining the neurogenic control of blood pressure in PE.

Cerebrovascular and Higher Function Neurological Consequences of PE

In addition to the neural control of cardiovascular maladaptations that occur in PE, PE also induces deleterious neurological outcomes to affected mothers. Next, we examine the effects PE has on brain volume, cerebral hemodynamics, white matter lesions, electrophysiological profile, (Table 2) and cognitive and behavioral impairments.

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Volume Changes in the Brains of Preeclamptic Women During the Peripartum Period

Observed in humans (227), and in rodents (228), healthy gravid females undergo a reduction in both gray and white matter volumes of the brain, while the volume of the lateral ventricles are increased. These changes in volume in the brain and ventricular spaces begin at the moment of placental implantation, peak at term, and slowly reverse months after delivery. Moreover, human studies have shown that while the brain decreased in volume, there were also concomitant volume increases in the heart, kidneys, thyroid gland, and extracellular fluid, with all changes reversing within six months postpartum (227, 228). However, these volumetric changes were even more pronounced in human PE patients (227, 228). Women in the PE group had significantly smaller brain volumes, with corresponding increases in lateral ventricular volumes. A recent study involving a large multiethnic and racially diverse sample observed that women with a history of hypertensive pregnancy had smaller brain volumes and larger degrees of atrophy decades after the index pregnancy (229). While not a sole indicator of neurological dysfunction, these alterations in brain size and volume are accompanied by changes in cerebral hemodynamics, electrophysiology, cognition, and behavior in human PE patients.

Cerebral Hemodynamics in Healthy vs. Preeclamptic Gravid Females

In normotensive individuals, cerebral blood flow (CBF) is maintained at ~50 mL per 100 g of brain tissue per minute, given that the cerebral perfusion pressure (CPP) and intracranial pressure is in the range of 60 to 150 mm Hg (61, 135, 136). When the CPP exceeds 150 mm Hg, autoregulation can no longer be maintained and “breakthrough” occurs, such that the decrease in cerebrovascular resistance (CVR) results in hyperperfusion, blood brain barrier (BBB) disruption, and vasogenic edema (61, 135, 136), which can contribute to neurological complications associated with hypertensive encephalopathy and eclampsia (61, 135, 136). Significant changes in cerebral hemodynamics have been observed in both clinical (230–232) and animal model (233) studies of PE. Compared to normotensive pregnant women, PE patients exhibit augmented CPP in the middle (231), anterior, and posterior (230) cerebral arteries, with accompanying changes in cerebral artery resistance indices (230). An animal model PE study confirmed that placental ischemia was the driving force of the CBF pathology, and that the increased brain water content was the result of increased BBB permeability and smaller diameter cerebral vessels being burdened with increased pressure (233). Thus, it is possible that the PE-decreased CVR and hyperperfusion causes the brain to be susceptible to vasogenic edema by creating an unfavorable hydrostatic pressure gradient when pressure is elevated (61, 135, 136).

Anatomical Distribution and Volume of White Matter Lesions in PE

White matter lesions (WMLs) are a common neurological corollary that result from the altered hemodynamics of PE (5, 234, 235). Diagnostic imaging reveals that these WMLs can persist for years after the index pregnancy (22–24, 229). Counterintuitively, the pattern of distribution of WMLs associated with preeclampsia differs from that of Posterior Reversible Encephalopathy Syndrome (PRES). PRES is more often associated with eclampsia (7, 234). The WMLs resulting from PRES tend to predominate in the occipital, parietal, and frontal lobes, are hemispheric, and bilaterally symmetric (25). The WMLs seen in PE patients are

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distributed in the frontal lobes (24), and tend to dominate in cases of early-onset PE (23). Interestingly, a relationship exists between WML distribution patterns and the degree of sympathetic innervation supplied to the brain regions most at risk for sustaining WMLs (236). Myogenic and neurogenic elements comprise cerebral autoregulation, in which proper neurogenic function is dependent upon sympathetic innervation (236). In PRES, elevated blood pressure weakens myogenic homeostatic mechanisms via vascular endothelial dysfunction, causing cerebral autoregulation to rely more upon its neurogenic component (236–238). As a result, brain regions with robust sympathetic innervation (e.g. frontal lobe) are relatively safeguarded against serum extravasation through vasoconstriction. This contrasts with regions such as the occipital lobe, which receives meager sympathetic innervation, that are more susceptible to developing WMLs after being exposed to acute oscillations in cerebral blood pressure (236, 239).

There is a strong correlation between the presence and distribution of WMLs and poor neurological outcome in PE, particularly when accompanied by cerebral edema, intracranial hemorrhage, and eclampsia (6, 7). Moreover, during the peripartum period 47% of ischemic strokes are the result of severe PE, and these strokes account for 12% of the annual maternal death rate globally (240–243). One quarter of PE patients that suffer an ischemic stroke will incur permanent brain damage (5). Diagnostic imaging studies of PE patients that sustained a cerebrovascular accident demonstrate white matter lesions in the frontal, parietal, insular, and temporal lobes in women 10–26 years after being diagnosed with PE or eclampsia (23, 24).

Electrophysiological Changes Exhibited by Healthy, Preeclamptic, and Eclamptic Gravid Females

The electroencephalogram (EEG) is sensitive enough to distinguish if an intra-partum seizure has resulted from eclampsia or if the mother suffered an epileptic seizure during labor (244, 245). Furthermore, hypertensive PE and eclamptic women exhibit changes in EEG recordings compared to normotensive pregnant and non-pregnant females (244). PE and eclamptic women demonstrate both diffuse and focal slowing of delta and theta waves, typically localized to the occipital lobe (234, 244–247). Eclamptic women exhibit a significantly greater number of spike discharges than PE patients (234, 244–247). Collectively, these anatomical, hemodynamic, histopathological, and electrophysiological changes that result from PE are manifested in cognitive and behavioral impairments.

Cognitive and Behavioral Impairments in PE: Associations with Increased Risk of Low Fetal Birth Weight, Intrauterine Growth Restriction, and Premature Birth

Maternal cognitive dysfunction is associated with PE (Figure 3) (28–30), where impairment severity correlates to the total number of eclamptic seizures (248). A pilot study suggested that these self-reported deficits from formerly PE women exhibited auditory-verbal memory deficits, impaired learning, and delayed recall, all of which were independent of depression or anxiety (29). However, a long-term follow up study found no evidence of neurocognitive dysfunction despite the self-reporting of impairments, but the investigators did conclude that this increase in self-reported deficits is an indicator for cognitive impairment and/or dementia later in life (28). A more recent study concluded that hypertensive pregnancy

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disorders may be independent risk factors of cognitive decline, after adjusting for cardiovascular disease and known cardiovascular disease risk factors (229). Human subjects with a mean age of ~61 years, from a large multiracial sample, demonstrated significant deficits in processing speed decades after the index pregnancy, even when the results were adjusted for abnormal estimated glomerular filtration rate (eGFR) (229).

The indices for depression (31, 249, 250) and anxiety (31, 38, 249) are elevated in PE, while the frequency of PTSD is increased for several years after the index pregnancy (37–42). One clinical study observed that the risk for postpartum depression was associated not to the severity of PE, but rather to its consequences (e.g., perinatal death), even after adjusting for the confounding variables of age, ethnicity, and educational level of the mother (250). While resilience shielding against psychological stress (251) and psychotherapeutic treatment (252) can attenuate the duration of the episode, a previous history of depression coupled with experiencing a preeclamptic index pregnancy can significantly contribute to the onset of PTSD and exacerbate the anxiety of planning future pregnancies (39). The deleterious effects of prenatal maternal psychosocial stressors on fetal development are well documented, where increased incidences of maternal depression (34–36) and anxiety (31–33) are significantly correlated to low fetal birth weight, IUGR, and premature birth (32–36, 38).

Conclusion

First reported over a century ago (253), the ischemic placenta was identified as the source of pathogenic factors that generate the clinical presentations of PE. Moreover, experiments performed in 1940 confirmed that delivery/removal of the ischemic placenta results in full regression of the maternal syndrome (9, 254). Current research continues to focus on the ischemic placenta by targeting the pathogenic factors that drive angiogenic imbalance (255), increases in reactive oxygen species (ROS) (256), and peripheral inflammation (257). These approaches are based upon the recommendations of the 2013 Task Force on Hypertension in Pregnancy, which concluded that current FDA-approved antihypertensive therapies have no effect on the progression of PE, may further exacerbate placental ischemia, and expose both the expectant mother and developing fetus to possible deleterious side effects (4).

To be sure, while PE is initiated at the maternal-placental interface, the poor patient outcomes are predominantly neurological and occur in the brain. As illustrated in Figure 1, the absence of the autonomically-regulated adaptations to pregnancy contributes to the development of potential life-threatening neuropathology, including increased BBB permeability and brain water content, the appearance of white matter lesions, and the loss of cerebrovascular regulation. Finally, the poor outcomes of PE are manifested as executive dysfunction, cognitive impairment, depression, anxiety, and PTSD. These behavioral outcomes are significantly associated with low fetal birth weight, IUGR, and premature birth.

In parallel with the current ischemic placental studies of PE pathophysiology, we have proposed that future studies of PE should address the neural control of blood pressure in animal models, and how known circulating factors (for example, anti-angiogenic proteins,

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angII, and inflammatory cytokines) influence activity of brainstem nuclei controlling blood pressure. The intent of these proposed studies is to identify mechanistic targets, and to direct therapeutic agents against these targets so as to reduce both the neurological outcomes and the number of fatal cases of PE.

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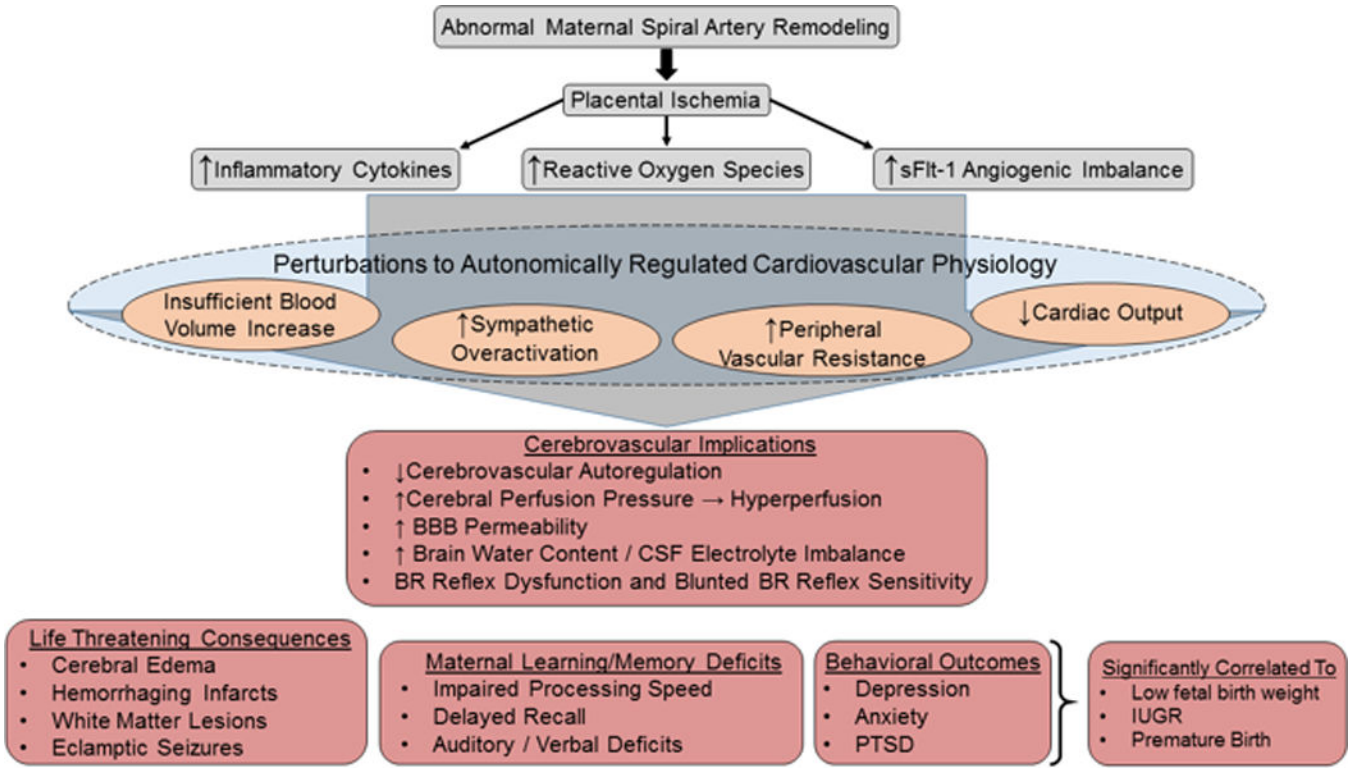

Figure 1.

The neurological consequences and life-threatening implications of PE. The initial pathophysiology of PE (gray boxes) originates from abnormal remodeling of the spiral arteries at the maternal-placental interface that creates placental ischemia/hypoxia. The ischemic placenta releases inflammatory cytokines, reactive oxygen species, and the anti-angiogenic factor sFlt-1. Furthermore, in the absence of the autonomically regulated cardiovascular adaptations to pregnancy, perturbations in cardiovascular physiology (orange circles) result. The combination of ischemic placental pathogenic factors and the lack of cardiovascular adaptations to pregnancy, lead to cerebrovascular implications (middle red box) that include autoregulatory breakthrough, increased BBB permeability, CSF electrolyte imbalance, BRS impairment, sympathovagal imbalance. The life-threatening consequences (bottom left red box) include white matter lesions, cerebral edema, hemorrhaging infarcts, and eclamptic seizures. Executive dysfunction (bottom middle and right red boxes) include impaired processing speed that can persist for decades after the index pregnancy, delayed recall, and auditory /verbal memory impairments. The behavioral outcomes of depression, anxiety, and PTSD are all significantly associated with low fetal birth weight, IUGR, and premature birth.

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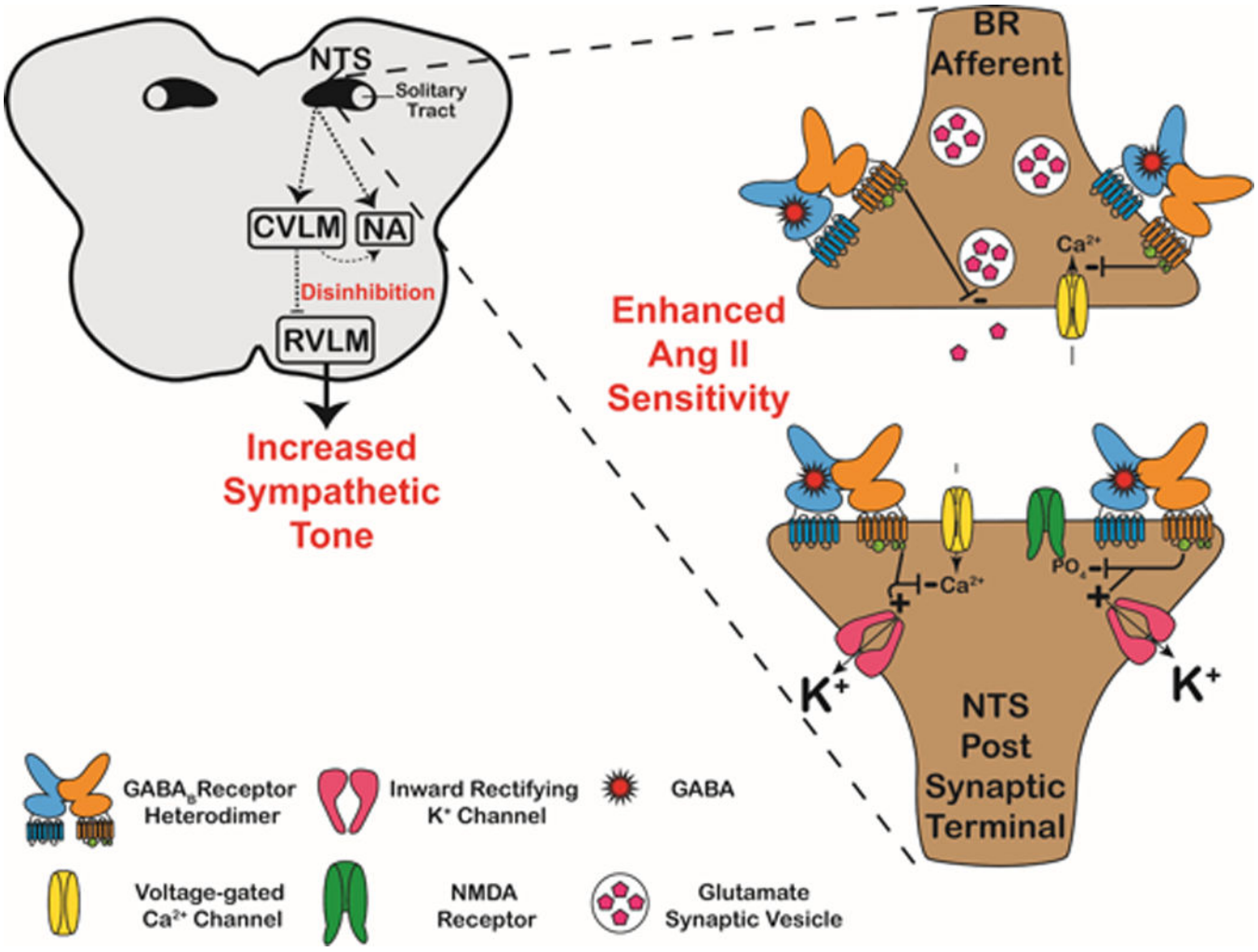

Figure 2.

$GABA_BR$-mediated disinhibition of the RVLM as a proposed mechanistic target for future PE studies. Neurons in the dorsomedial regions of the caudal NTS receive and integrate BR afferent inputs. Normally, BR inputs excite these NTS neurons, which in turn, excites the caudal ventrolateral medulla (CVLM). The CVLM reduces sympathetic tone using dual circuitries. First, the CVLM excites preganglionic parasympathetic neurons in the nucleus ambiguus (NA) which projects (via the vagus nerve) to the heart to reduce the heart rate and stroke volume. Secondly, the CVLM projects inhibitory (GABAergic) projections to the "vasomotor center" RVLM. Inhibition of the RVLM reduces the sympathetic tone to the blood vessels, heart, and kidneys. However, in several hypertensive studies, $GABA_BR$-mediated inhibition of these NTS neurons occurs (expanded synapse in figure). In the presence of AngII, upregulated expression of $GABA_BR$ occurs on NTS neurons. Presynaptically, $GABA_BRs$ inhibit N-type ($Ca_V2.2$) & P/Q-type ($Ca_V2.1$) Ca^{2+} channels, and thus reduce the probability of glutamate release into the synaptic cleft. Postsynaptically, $GABA_BRs$ hyperpolarize NTS neurons by activating inward-rectifying K+ channels, inhibiting L-type Ca^{2+} channels, and producing a voltage-sensitive Mg^{2+} block of NMDA receptors, as well as preventing their phosphosphorylation by protein kinase A (PKA).

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Hyperpolarization of NTS neurons by $GABA_BRs$ result in insufficient excitatory input (dashed arrows) to the NA and CVLM. Decreased parasympathetic input to the heart via the NA results in increases in heart rate and stroke volume. More importantly, the hyperpolarized NTS neurons cannot excite the CVLM, resulting in a disinhibition of the RVLM. No longer governed by the GABAergic tone from the CVLM, the RVLM increases sympathetic tone to the vasculature, heart, and kidneys. Given that PE is characterized by enhanced AngII sensitivity, an impaired BR reflex, and sympathetic overexcitation, this $GABA_BR$-mediated disinhibition of the RVLM is proposed as a mechanistic target for future PE studies.

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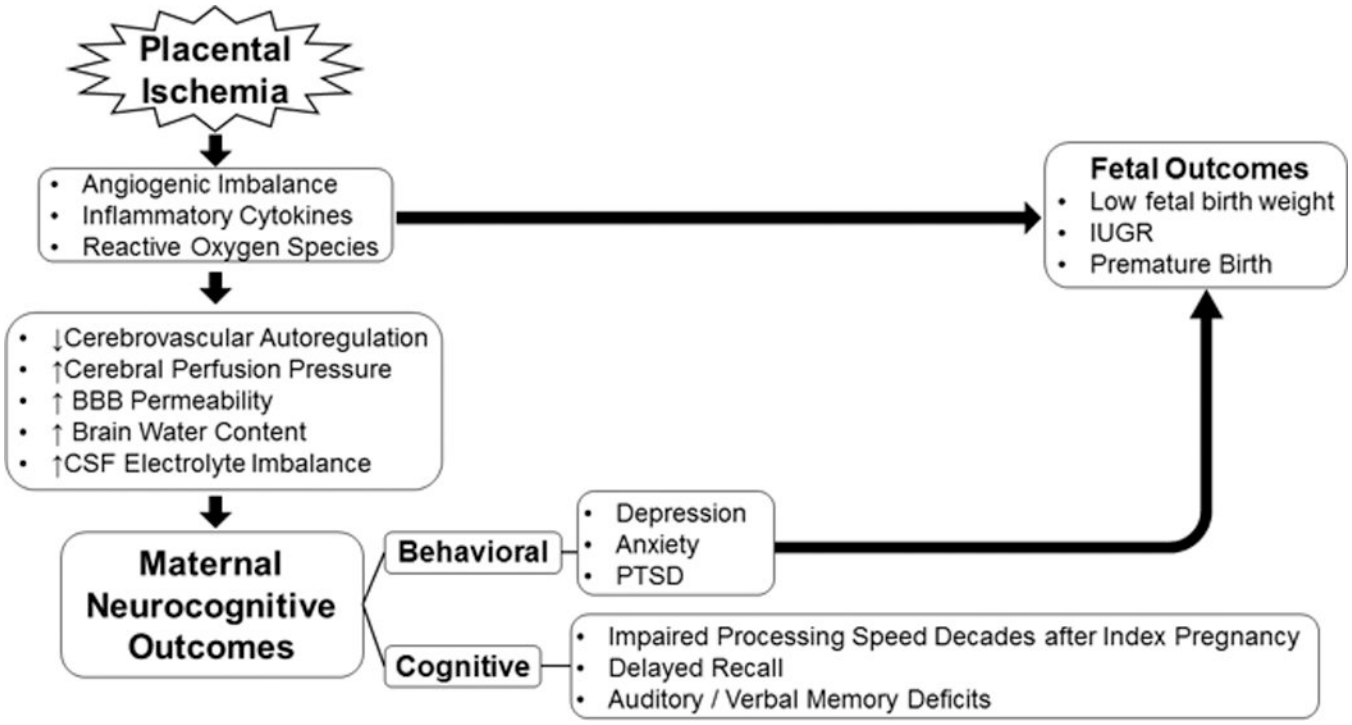

Figure 3.

Cognitive and behavioral deficits associated with preeclampsia, and their relationship to fetal outcomes. The ischemic placenta releases a myriad of pathogenic factors that lead to endothelial dysfunction. The resulting pathophysiology, if left untreated, can develop into cerebrovascular abnormalities which include a loss of autoregulation, increase in BBB permeability, with a resulting imbalance in CSF electrolyte composition. Collectively, these insults to the CNS can manifest into learning and memory deficits that can persist for decades after the index pregnancy. Moreover, behavioral outcomes of depression, anxiety, and PTSD are significantly associated with low fetal birth weight, IUGR, and preterm birth.

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Table 1

The visceral motor autonomic influence of the cardiovascular physiological adaptations of pregnancy vs. the maternal hemodynamics of PE. In healthy pregnancy, higher brain centers direct autonomic neural circuitry to produce an expanded blood volume, increased cardiac output, decreased peripheral vascular resistance, and biphasic alterations in sympathetic firing. However, in PE, these adaptations are absent, resulting in an insufficient blood volume increase, decreased cardiac output, increased peripheral vascular resistance, and sympathetic overexcitation.

Autonomic Influence of the Cardiovascular Physiological Adaptations of Pregnancy				
Cardiovascular Physiological Component	**Higher Brain Inputs**	**Key Neural Circuitry**	**Adaptive Mechanism of Healthy Pregnancy**	**Maladaptive Perturbations of PE**
Blood Volume	Circumventricular Organs of the Lamina Terminals	• PVN and SON magnocellular neurons excite the hyperosmotic sensitive neurons of the posterior pituitary, which secrete vasopressin	• Vasopressin binding to renal V_2 receptors promotes water reabsorption • Stimulation of thirst mechanism • Increase in total blood volume of 1.2–1.6 liters (mostly Plasma)	• Insufficient increase (− 200 mL) in blood volume that is directly correlated to low birth weight and IUGR
Cardiac Output (CO)	Rostral Ventro-lateral medulla (RVLM)	• RVLM excites cardiac preganglionc sympathetics located in the IMLCC at spinal cord levels T1–T4 • Cardiac preganglionc sympathetic neurons exit the cord at T1–T4 via spinal nerves • Cardiac preganglionc sympathetic neurons release ACh on cardiac postganglionic sympathetic neurons in paravertebral ganglia • Cardiac postganglionic sympathetics project to the cardiac sinoatrial (SA) and atrioventricular (AV) nodes	• Cardiac postganglionic sympathetic nerves release NE that binds to β_1 adrenergic receptors expressed on the cardiac SA and AV nodes • Increased CAMP and PKA signaling increases CO via increases in stroke volume, contractility, and heart rate	• Decreased CO with concurrent increase in PVR • Asymmetrical remodeling and left ventricular hypertrophy

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Autonomic Influence of the Cardiovascular Physiological Adaptations of Pregnancy				
Cardiovascular Physiological Component	**Higher Brain Inputs**	**Key Neural Circuitry**	**Adaptive Mechanism of Healthy Pregnancy**	**Maladaptive Perturbations of PE**
Peripheral Vascular Resistance (PVR)	RVLM	• RVLM excites preganglionic sympathetics located in the IMLCC at spinal cord levels T1–L2 • Preganglionc sympathetic neurons exit the cord at T1–L2 via Spinal nerves, and release ACh on postganglionic neurons in paravertebral ganglia • Postganglionic fibers terminate in the tunica adventia layer of arteries and arterioles, and release NE • NE diffuses to tunica media to bind to α_1/α_2 receptors	• Prostacyclin counteracts AngII vasoconstriction • Nitric oxide release counteracts thromboxane by preventing the phosphorylation of myosin light chains in vascular smooth muscle • Progesterone, relaxin, and prostaglandins promote vasodilation • Decreased PVR	• Increased PVR due to enhanced AngII Sensitivity • AT_1R-AABs and AT1-B2 heterodimers contribute to increased AngII sensitivity • Decreased Ang 1–7 levels fail to Counteract AngII vasoconstriction
Sympatho-vagal Balance	Solitary Tract Nucleus (NTS), Caudal Ventro-lateral Medulla (CVLM), RVLM	• Dorsomedial regions of the caudal NTS receive BR inputs via CNs IX and X • Caudal NTS projects to and excites CVLM • Based upon BR inputs, CVLM inhibits RVLM, in addition to exciting preganglionic parasympathetic inputs to the heart in the nucleus ambiguus (NA)	• Reduced LF:HF ratio in 1st trimester • Vagal withdrawal and dominant sympathetic tone in 3rd trimester (increased LF:HF ratio)	• LF:HF ratio is higher than normotensive pregnant females and hypertensive non-pregnant females • Impaired placental perfusion and renal blood flow

Abbreviations: PVN, paraventricular nucleus; SON, supraoptic nucleus; IUGR, intrauterine growth restriction; IMLCC, intermediolateral cell column; T1–T4, thoracic spinal cord levels 1–4; ACh, acetylcholine; NE, norepinephrine; cAMP, cyclic AMP; PKA, protein kinase A; T1–L2, thoracic spinal cord levels T1–L2; AT_1R-AABs, agonistic autoantibodies to the angiotensin AT_1 receptor; AT_1-B_2 heterodimer, AT_1 receptor – Bradykinin-2 receptor heterodimer; Ang 1–7, Angiotensin 1–7; CN IX, cranial nerve X (glossopharyngeal nerve); CN X, cranial nerve X (vagus nerve); BR, baroreceptor; LF:HF, low frequency to high frequency ratio (index of sympathovagal balance).

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Table 2

Alterations in brain volume, cerebral hemodynamics, white matter integrity, and electrophysiological profile observed in maternal brains after a preeclamptic index pregnancy. Normal pregnancy is associated with a reduction in both gray and matter volumes, and an enlargement of the ventricular spaces, with these changes reversing postpartum. However, in preeclampsia this atrophy in brain volume and expansion of the ventricles can persist for decades. In moderate to severe case of PE, cerebrovascular autoregulation is lost, resulting in increased BBB permeability, brain water content, and an exacerbated risk of vasogenic edema. The pattern and distribution pattern of white matter lesions correlate to neurological outcome. The occipital lobe, a region of interest in visual disturbances, exhibits electrophysiological changes as a result of preeclampsia.

CNS Component		Healthy Pregnancy	Preeclampsia
Brain Volume	Gray Matter	Atrophy reverses postpartum	Atrophy persists decades after index pregnancy
	White Matter		
	Ventricular Spaces	Expansion reverses postpartum	Enlarged ventricles persist decades after index pregnancy
Cerebral Hemodynamics	Cerebrovascular Autoregulation	---	Decreased
	Cerebral Perfusion Pressure	---	Increased
	BBB Permeability	---	
	Brain Water Content	---	
	Risk of Vasogenic Edema	---	
White Matter Lesions (WMLs)	WML Distribution Pattern	---	Strong correlation to neurological outcome
	Sympathetic Innervation	---	Regions with meager innervation (e.g., occipital lobe) are more susceptible to WMLs
Electrophysiology	EEG	---	Diffuse and focal slowing of delta and theta waves in occipital lobe