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HAEMODYNAMIC CONTRIBUTIONS TO THE PATHOGENESIS OF PREECLAMPSIA AND ECLAMPSIA

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Current hypotheses regarding the origins of preeclampsia have focused on the "Two stage model"[1]. This model suggests that the primary steps in the pathophysiologic sequence of preeclampsia are initiated by abnormal placentation including the classic finding of abnormal trophoblast invasion of maternal decidual spiral arteries. The second stage of the sequence includes the elaboration of a single or multiple substances from these disordered placentas which contribute to the generalized maternal systemic illness, eventually manifesting as endothelial injury, hypertension and proteinuria. Recent studies have focused on the role of pro and anti-angiogenic peptides as potential placentally derived aetiologic agents in this pathophysiologic sequence[2,3] although other placental products have been highlighted in recent research.[4,5] Despite the fact that this modeling of preeclampsia has widespread support significant limitations to this hypothesis can be identified.

The two stage model as proposed does not specifically outline a mechanism through which placentation is disturbed. Abnormal placentation is viewed as the starting point of disease but the proposed pathway must have antecedent elements to constitute a complete pathophysiologic sequence. Additionally the finding that placental disease, with lesions identical to those observed with maternal preeclampsia, can and often do exist in the absence of the maternal syndrome of preeclampsia poses problems for the hypothesis.[6] Maternal factors contributing to a heterogeneity in response to the placental signal(s) have not been broadly examined nor even widely considered. Perhaps more importantly, and in distinction to the absence of disease in those with placental pathology, placental disease does not appear to be required to create disease. In a study that compared placental bed biopsies obtained from women with a normal pregnancy outcome to a group with severe preeclampsia, trophoblastic invasion of the spiral arteries was examined. Trophoblastic invasion of the decidual segment of the

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spiral arteries was observed in 100% of the normal placentas and 44% of placentas from women with severe preeclampisa. Examining the myometrial arterial segments, trophoblastic vascular invasion occurred in only 75% of the normal pregnancies compared with 18% of the severely preeclamptic placentas. Importantly, nearly half of the placentae from women with severe preeclampsia demonstrated a relatively normal appearance to the decidual spiral arteries.[7]

Direct studies of the placenta reveal similar findings[8,9]. In a review of 350 placentas of women with clinically defined preeclampsia the characteristic histopathologic vascular lesions of preeclampsia, maternal atherosis and fibrinoid medial necrosis, were observed in only 21.4% of the placentas examined[8]. A separate study compared normal placentas to those from a group of 158 women with preeclampsia, most of whom (67%) had severe disease[9]. Increases in specific placental lesions were observed. Placentas from preeclamptic pregnancies were more likely to have arteriolopathy, villus hypermaturity, intervillous thrombi and central infarction. However none of these specific findings were present in more than 46% of the placentas from women with preeclampsia. Of interest the frequency of placental findings was inversely associated with the gestational age at onset of maternal disease, supporting the notion of distinct preeclamptic phenotypes[9].

The two stage hypothesis of preeclampsia also suggests that the placenta produces and releases a substance or substances which result in systemic maternal endothelial injury. Recent evidence however suggests that evidence of endothelial injury is not uniform in the maternal vasculature. In a group of women with severe early onset preeclampsia and evidence of elevated markers of endothelial injury in plasma samples, no direct evidence of endothelial injury could be detected in the vasculature of several organs including myometrium, abdominal fascia and subcutaneous fat[10]. This finding implies that additional factors, beyond the presumptive placental products, are active within the maternal circulation for endothelial injury to manifest. Finally, epidemiologic studies of preeclampsia have pointed to the likelihood of at least two distinct phenotypes which have been segregated by either the gestational age at onset of disease or by the presence or absence of associated fetal growth restriction[11–13]. This suggestion of distinct phenotypes is supported by the observation that the frequency of placental disease in preeclampsia in inversely related to gestational age[9]. The two stage hypothesis does not specifically accommodate these observations of discriminant phenotypes.

In 1998 we proposed an alternative view to the pathophysiologic sequence associated with preeclampsia focusing on haemodynamic adaptations during pregnancy. This model suggested that a specific prepregnancy disposition and an associated intolerance to volume expansion were important contributors to the development of preeclampsia[14]. The pathologic sequence of preeclampsia was proposed to be produced by a response to the physiologic adaptation of pregnancy superimposed on a specific prepregnancy phenotype. The critical physiologic signal of pregnancy is volume expansion and the prepregnancy phenotype is characterized by reduced plasma volume. The original hypothesis further suggested that two distinct mechanisms could lead to the hypertension and proteinuria observed with clinical preeclampsia. One is women with low plasma volume prior to pregnancy. We suggested that chronic low plasma volume could produce poor vascular compliance that results in increased pressure/volume relationship as the volume expansion of pregnancy proceeds. This prepregnancy phenotype was hypothesized to be most strongly associated with the preeclamptic phenotype characterized by both preterm birth and fetal growth restriction. A second mechanism for the development of hypertension in pregnancy is where volume expansion exceeds the capacity of a relatively normal prepregnancy vasculature to accommodate the expansion. This second phenotype is supported by the finding of an increased risk for preeclampsia in both molar pregnancies and twin gestations[15,16] since both of these conditions represent situations in which there is evidence that the volume expansion of pregnancy is augmented[17,18,19].

The origins of this hypothesis were sparked by the work of Ward et al[20] who demonstrated that a specific polymorphism in the angiotensingen gene was associated with an elevated risk for preeclampsia. This polymorphism had been previously linked to chronic hypertension in adults and to angiotensinogen over-expression.[21] We demonstrated that women who possessed the predisposing polymorphism (AGT TT 235) had reduced plasma volume prior to a first pregnancy[22]. This observation was combined with specific observations from the published works of Easterling and Schobel. Easterling and his colleagues demonstrated that the development of preeclampsia was associated with increased cardiac output as early as the first trimester[23], and Schobel et al[24] demonstrated that preeclampsia was associated with evidence of elevated sympathetic tone[23]. In composite we suggested the novel hypothesis that chronic low plasma volume is associated with increased sympathetic tone prior to pregnancy and poor vascular compliance in the face of the volume expansion of pregnancy. Further, reduced vascular compliance would manifest in both the arterial and venous compartments. On the venous side this results in disproportionate cardiac filling and increased cardiac output as plasma volume expands in early pregnancy. Arterial hypertension would then result as this exaggerated cardiac output interfaced with limited arterial compliance. We further suggested that this pathophysiologic sequence might be restricted to species of upright posture where an adaptation to the orthostatic stress included increased peripheral vasoconstrictor tone mediated through the autonomic nervous system. This accommodation is likely a response to gravitational influences on blood flow and might explain the uniqueness of the preeclamptic syndrome to the human species.

This general hypothesis regarding the pathophysiologic underpinning to hypertension finds support in the work of Julius et al[25,26] who studied young borderline hypertensive males and demonstrated that low plasma volume was associated with elevated cardiac output and augmented autonomic nervous system activity. These observations support the apparent contradiction in Easterlings' observation that low plasma volume could be associated with high cardiac output as part of the pathophysiologic sequence of hypertension. In light of these findings it is likely that disease resolution is a function of the loss of intravascular volume resulting from postpartum diuresis. Further, remodelling of the cardiovascular system in response to pregnancy would reduce the risk for preeclampisa in subsequent pregnancies. The suggestion that pregnancy imparts a sustained cardiovascular remodelling effect was based on the observations of Clapp and Capeless[27]. These authors examined cardiovascular parameters in 30 women beginning prior to pregnancy and prospectively followed until a full year postpartum. Cardiac output remained elevated and peripheral resistance stayed reduced when compared to prepregnancy values at one year postpartum. This evidence of physiologic remodelling of the cardiovascular system in response to pregnancy supports the hypothesis that the recurrence risk for preeclampsia may be at least partially dependent on both the degree and duration of these pregnancy induced cardiovascular adaptations. Individual women may enter subsequent pregnancies in a different physiologic state than they entered their first pregnancy placing them at a modified risk for the development of hypertensive complications.

Over the last 10 years we have been working to characterize the elements of the pre-pregnancy phenotype. We and others have begun to examine how prepregnancy phenotype contributes to the progress and pathologies of pregnancy. These investigations are described below.

PREPREGNANCY PHENOTYPE

Examining women who had never been pregnant we demonstrated that reduced plasma volume is associated with increased sympathetic responsiveness[28]. We measured plasma volume employing Evans blue dye dilution in a group of 40 young, healthy non-smoking, women after an overnight fast and after 72 hours of stabilizing dietary management and expressed the plasma volume per unit of body mass index to correct for variations in subject size. Sympathetic responsiveness was estimated by evaluating the maternal blood pressure response to Valsalva's manoeuvre. Continuous non-invasive blood pressure recordings were obtained with auto-standardization to brachial artery measurements. We estimated the Phase II-late response to Valsalva's manoeuvre which is an index of alpha adrenergic activation[29,30]. Importantly we identified an inverse relationship of supine plasma volumes to both resting heart rate and phase II late response to Valsalva's manoeuvre suggesting higher sympathetic activation in the setting of reduced plasma volume. These observations have been expanded to include over 80 nulligravid women and the relationships between low plasma volume, elevated pulse rate and phase II-Late adrenergic responsiveness remain highly significant (Figure 1). In support of these findings Courtar and her colleagues[31] in Maastricht examined the relationship of plasma volume to sympathetic tone in a group of formerly preeclamptic women. These women, who were not pregnant at the time of study, demonstrated changes in beat-to-beat blood pressure and heart rate recordings consistent with heightened sympathetic activity that were inversely related to plasma volume. These observations confirm the basic physiologic association of low plasma volume with elevated sympathetic tone.

We further examined reduced prepregnancy plasma volume as the hub of the phenotype of interest by examining the relationship of platelet concentration and

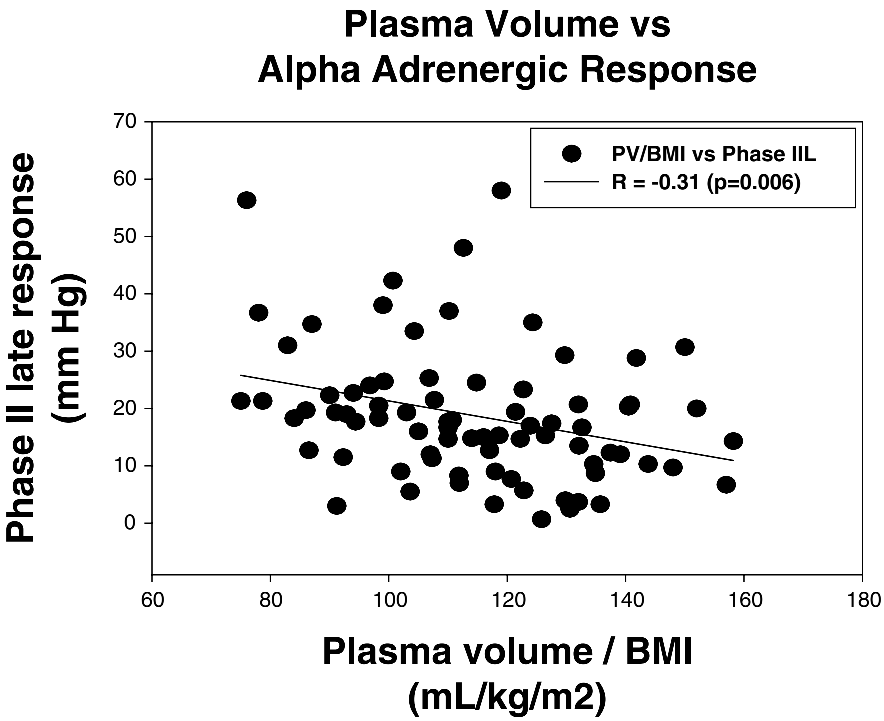

Figure 1 Negative relationship of supine resting plasma volume, corrected for each individual's body mass index, to the phase II - late blood pressure response, reflecting alpha adrenergic activation, measured during a Valsalva manoeuvre in young healthy nulliparous women. These measurements were collected using a continuous non-invasive tonometric blood pressure monitor during a sustained Valsalva manoeuvre to 40 mm Hg lasting 20 seconds.

platelet activation in a group of 37 young nulligravid healthy non-smoking women of reproductive age[32]. Heightened platelet activation is common in preeclampsia and has been demonstrated to be present prior to the clinical recognition of disease[33–35]. We hypothesized that, prior to a first pregnancy, there is a relationship of heightened platelet activation to low plasma volume, both findings observed in preeclampsia. We measured plasma volume employing Evans blue dilution and examined 2 distinct markers of platelet activation. The percentage of platelets expressing CD 63 and the percentage of platelet monocyte aggregates demonstrating combined CD61-CD14 expression were measured by flow cytometry. This combination of markers allowed us to identify both isolated platelet activation and the formation of platelet-monocyte aggregates which are also an index of platelet activity. Plasma volume was expressed as plasma volume per unit of body mass index (PV/BMI). We compared data from the lowest PV/BMI quartile, to the combined middle two quartiles and the upper quartile. We identified no significant relationship of platelet concentration to PV/BMI between quartile groups ($p = 0.944$). However, there was a significant difference between quartiles for percentage CD63 expression and for CD61/CD14 expression, with those subjects with the lowest quartile of PV/BMI demonstrating the most platelet activation for both markers of activity.

More recently we examined the relationship of both sympathetic tone and plasma volume to pro-inflammatory cytokines in 76 young healthy non-smoking nulliparous women. Elevated levels of pro-inflammatory cytokines, including CRP, IL-6 and TNF-alpha have been identified in patients with preeclampsia[36,37]. Some of these cytokines, particularly CRP has been observed to be elevated prior to the clinical recognition of disease[38]. There has been speculation linking the increased levels of proinflammatory cytokines with abnormal placentation and as contributors to placental damage and the resulting oxidative stress and endothelial cell damage. However, it is still unclear exactly how early in pregnancy the elevation of inflammatory cytokines observed with preeclampsia occurs, and whether it might even precede the pregnancy. Interestingly, we found a significant difference when examining the relationship between plasma volume (corrected for body mass index) and inflammatory cytokines. Mean CRP levels in the non-pregnant subjects with the lowest PV/BMI quartile were significantly elevated when compared to the middle two quartiles, suggesting the relationship between pro-inflammatory cytokines and the preeclamptic phenotype may predate pregnancy.[39]

Studying women with prior preeclampsia, but at least 6 months postpartum, the Maastricht group has examined a series of different haemodynamic endpoints with the goal of understanding how these physiologic observations translate into future pregnancy performance. Aardenburg et al[40] examined the response to volume loading in a group of women with prior preeclampsia and a low plasma volume following pregnancy. They observed that the former preeclamptic women who had reduced plasma volume, when compared to a control group of parous subjects, demonstrated a greater rise in pulse rate, cardiac output and alpha atrial natriuretic peptide concentration in response to volume loading. These findings are all consistent with the early pregnancy observations of women destined to develop preeclampsia[23,41].

Spaanderman et al[42], also working in Maastricht, examined former preeclamptic women and found that plasma volume and renal plasma flow was reduced in the subset of non-thrombophilic, normotensive, prior preeclamptics. This group of former preeclamptic women had heightened angiotensin II sensitivity and an inverse association of plasma volume with sensitivity to angiotensin II infusion.

Together these data all support reduced plasma volume as a valuable marker of numerous systemic maternal changes associated with preeclampsia. These assessments, all performed outside of pregnancy, point to the importance of understanding the relationship of prepregnancy phenotype to the pathophysiologic findings of pregnancy.

ADAPTATIONS TO PREGNANCY BASED ON PRE-PREGNANCY PHENOTYPE

Remarkably there are limited data examining the details of the maternal physiologic state prior to a first pregnancy and its implications for pregnancy course. The association of the prepregnancy phenotype, following a pregnancy complicated by preeclampsia, and the clinical course of pregnancy has been most comprehensively examined by the group in Maastricht led by Louis Peeters. This group has demonstrated that low inter-pregnancy plasma volume predisposes to increase risk for hypertensive complications in future pregnancies.

Aardenburg et al[40] examined women at least 6 months postpartum following a pregnancy complicated by either preeclampsia or HELLP syndrome. He segregated this group of 316 women into those with low plasma volume and normotensive, normal plasma volume and normotensive and hypertensive. Postpartum differences within the normotensive group comparing the low plasma volume (low PV) and normal plasma volume (normal PV) subsets included the observations that those with low plasma volume had a higher body mass index, were more likely to have positive family history for cardiovascular disease (low PV 59.2% vs normal PV 39.7%) were more likely to be smokers, had a lower mean gestational age at birth and had a higher rate of preterm birth less than 32 weeks. The lower plasma volume group also had a lower non-pregnant stroke volume, cardiac index and total vascular compliance and greater indices of insulin resistance. These same women were followed into subsequent pregnancies. Those with low plasma volume between pregnancies and prior preeclampsia had lower birth weight and more recurrent preeclampsia (34.8%) when compared to than those with normal plasma volumes (13.3%)[40].

More recently, Aardenburg et al[43] in a small case-control study examined two groups of women with prior preeclampsia who went on to subsequent pregnancies. In this group of fourteen women seven developed recurrent hypertensive disease and seven women did not. Inter-pregnancy and early pregnancy physiology was compared between these two groups. There was no difference between the groups in prepregnancy blood pressure, heart rate or body mass index. Interestingly the authors identified reduced inter-pregnancy plasma volume and reduced venous capacitance in those who went on to develop recurrent hypertensive disease of pregnancy. The difference in plasma volume in this study completely discriminated between those who would go on to recurrent hypertensive disease of pregnancy and those who subsequently had normal pregnancies. The rise in plasma volume in early pregnancy, through 12 weeks, was not different between groups. In addition the haemodynamic response to bicycle exercise did not differ between groups either at the inter-pregnancy time point or at 12 weeks gestational age in the follow-up pregnancies. The primary difference between those who went on to recurrent hypertensive disease of pregnancy was in the inter-pregnancy plasma volume and the inter-pregnancy venous capacitance.

UTERINE BLOOD FLOW AND EARLY PLACENTATION

The source of abnormal placentation that often accompanies both preeclampsia and fetal growth restriction is unknown. We have hypothesized that reduced prepregnancy uterine blood flow in association with increased sympathetic tone underlies this phenomenon. Detailed data from microsphere studies in sheep, and supportive studies in rats, have demonstrated that there is significant variation in regional blood flow in response to systemic catecholamine stimulation[44,46]. These cross-species studies confirm a heightened vasoconstrictor response within the uterine circulation to alpha adrenergic stimulation. Where some vascular beds, including liver and fat, experience vasodilation in the face of increased catecholamine exposure, the reproductive tract (with the exception of the ovary) undergoes a disproportionate reduction in blood flow. Our own studies in young nulliparous women confirm this observation by examining the influence of the adrenergic blocking agent phentolamine on uterine blood flow during the follicular phase of the menstrual cycle. We compared the changes observed in the uterine circulation to a control vascular bed[47]. We demonstrated that adrenergic blockade results in a substantial increase in uterine blood flow compared to upper extremity radial blood flow. These data suggest an important contribution of sympathetic tone to baseline uterine perfusion. Consistent with this we demonstrated a tendency for the change in uterine blood flow, in the face of adrenergic blockade, to be inversely related to baseline uterine blood flow and directly related to mean arterial pressure. Together with findings of elevated adrenergic activity in preeclampsia[24,48–51] and the association of low non-pregnant plasma volume with increased sympathetic tone the hypothesis that poor uterine perfusion promotes abnormal placentation becomes attractive.

Many features of early placentation and the primary factors controlling the interaction of invading trophoblast with the maternal uterine vasculature leading to adequate utero-placental perfusion remain unknown. Recent data suggest that local shear stress may be an important modulator of trophoblast migration[52]. Shear stress is the frictional force produced by blood moving across the endothelial surface and is a function of the velocity gradient of blood near the endothelial surface. The magnitude of shear stress is directly proportional to blood flow and blood viscosity and inversely proportional to the cube of the radius. Shear stress is known to regulate arterial wall remodelling. It is important to note that reduced uterine blood flow in early pregnancy would result in reduced shear stress, an effect that could potentially limit signaling to the invading trophoblast for directed and coordinated migration into the spiral arteries. This could contribute to the underlying mechanism for abnormal placentation.

While first trimester measures of human endometrial/decidual vascular shear stress rates are not available there are third trimester data available. Magness et al[53] have recently demonstrated that uterine shear stress rates, estimated by a combination of uterine artery colour Doppler ultrasound measurements and direct measure of blood viscosity, are significantly lower in the third trimester of pregnancy in women presenting with preeclampsia when compared to controls. Examining pregnant women in Bolivia at sea level and at altitude they demonstrated that women in the third trimester with preeclampsia had reduced uterine blood flow and lower shear stress compared to non-preeclamptic controls.

ECLAMPSIA

The obstetrical literature defines eclampsia as the new onset of seizures in a woman with preeclampsia[1]. While it is seizure that defines eclampsia, neurologic signs and symptoms can precede the onset of seizure, including persistent headaches, nausea, vomiting and even cortical blindness[54–56]. There has been considerable debate as to whether the neurologic symptoms of eclampsia arise from "overautoregulation" contributing to vasospasm and ischaemia, or from hyperperfusion that causes cerebral oedema formation[57]. This uncertainty over the cause of eclampsia results because clinical findings of eclampsia have shown varying degrees of vasculopathy, cerebral oedema, haemorrhage and ischaemia[54,58,59]. However, there is considerable evidence to suggest that eclampsia is similar to hypertensive encephalopathy in which an acute elevation in pressure causes autoregulatory failure that promotes hyperperfusion and oedema formation.

The major cerebrovascular changes in eclampsia have been shown to be similar to those described for hypertensive encephalopathy, including loss of cerebral blood flow (CBF) autoregulation, hyperperfusion and oedema[58–62]. In fact, the neurological symptoms of eclampsia are often interpreted as a form of hypertensive encephalopathy[58,63–65]. Clinical and neuroimaging findings during eclampsia are consistent with oedema, which is thought to result from a rapid rise in blood pressure that causes breakthrough of autoregulation and blood-brain barrier (BBB) disruption[62,66–68]. For example, the neuroradiologic hallmarks of eclampsia are reversible abnormalities that appear on computed tomography (CT), T_2-weighted magnetic resonance (MR) and diffusion-weighted images with high apparent diffusion coefficient (ADC), all suggestive of oedema[65,67–74]. In addition, the reversibility of clinical neurological signs and neuroradiologic lesions within a few days or weeks postpartum in most cases argues against the existence of true cerebral ischaemic necrosis.

The primary explanation for the pathogenesis of neurological symptoms and oedema formation during eclampsia is that it represents a form of reversible posterior leukoencephalopathy syndrome (RPLS)[75] or posterior reversible encephalopathy syndrome (PRES)[76]. The formation of cerebral oedema in hypertensive encephalopathy and PRES is caused by pathologically increased blood hydrostatic pressure that disrupts the BBB and increases hydraulic conductivity (water filtration) into the brain tissue[77–79]. The fact that the BBB is disrupted under these conditions suggests that it is vasogenic oedema that occurs in eclampsia. Unlike cytotoxic oedema in which the brain tissue swells at the expense of the extracellular space, vasogenic occurs when cerebrovascular permeability is increased due to BBB disruption that allows an influx of plasma constituents into the brain and expansion of the extracellular space. Because the increase in brain water content occurs within the closed space of the skull, vasogenic oedema causes brain compression and the neurological symptoms associated with eclampsia (headache, nausea, vomiting, cortical blindness, and convulsions)[61,80]. Importantly, the oedematous brain can also displace brain structures and reduce perfusion, ultimately leading to infarction or herniation, common causes of death in eclampsia[69,81,82].

Under normal conditions, the cerebral endothelium that forms the BBB is unique in that in the intact brain there is very low hydraulic conductivity and essentially no ionic flux, due to the presence of specialized tight junctions that prevent the passage of ions[77,83]. This configuration makes osmotic forces negligible in mediating water flux under normal conditions and is protective against vasogenic brain oedema[77]. However, under conditions in which there is an acute rise in blood pressure that causes autoregulatory breakthrough, the resulting decreased cerebrovascular resistance (CVR) increases hydrostatic pressure in the microcirculation, causing endothelial cell damage, increased BBB permeability and vasogenic oedema[77]. This type of vasogenic oedema is termed hydrostatic brain oedema and underlies the neurologic complications of hypertensive encephalopathy and eclampsia[78].

It is clear that the cerebral circulation has a central role in the development of eclampsia. In fact, it has been estimated that cerebrovascular involvement is the direct cause of death in approximately 40% of patients[56,84]. While the vascular changes that occur during pregnancy have been the subject of intense study in many organs[55,85–88], our own studies suggest a significant effect of pregnancy on cerebrovascular structure and function that can promote some of the signs and symptoms of eclampsia when blood pressure is elevated, including oedema[89,90]. Using a model of hypertensive encephalopathy during late-gestation as a model of eclampsia, we compared cerebral blood flow autoregulatory curves and the pressure at which breakthrough occurred between nonpregnant and late-pregnant rats[89]. We found that the pressure at which breakthrough occurred was not different in pregnancy, however, only the late-pregnant animals developed oedema. These results demonstrate that pregnancy alone predisposes the brain to eclampsia by promoting hydrostatic brain oedema during acute hypertension. These important results have led to further investigation of how normal pregnancy and hypertension in pregnancy affect cerebrovascular structure and function in ways that promote oedema. In addition, the influence of normal pregnancy on cerebrovascular function, including haemodynamics and BBB properties, might explain the occurrence of eclampsia at relatively normal blood pressures[91,93].

One mechanism by which pregnancy may predispose the brain to oedema formation is through an effect on cerebral haemodynamics and CVR. Increase in CVR is a protective mechanism that limits transmission of damaging hydrostatic pressure to the microcirculation[94]. In our own studies, we found evidence of diminished CVR during pregnancy[90]. Third-order posterior cerebral arteries isolated from late-pregnant rats underwent forced dilatation at significantly lower pressures compared to nonpregnant animals. The increased diameter at high pressures in late-pregnant animals could decrease CVR and cause hyperperfusion because flow is related to the fourth power of vessel diameter. Interestingly, we found that the penetrating parenchymal arterioles were also significantly larger during pregnancy and underwent forced dilatation at lower pressures, similar to the posterior cerebral arteries. These small arterioles had decreased myogenic tone compared to nonpregnant animals, an effect that likely caused the larger lumen diameters. The diminished tone and myogenic activity in these small arterioles would be predicted to decrease small vessel resistance and promote hyperperfusion especially under conditions when vessels are maximally dilated, such as during acute hypertension.

While studies of isolated arteries and arterioles may predict cerebral haemodynamics, we measured CBF *in vivo* and calculated CVR in late-pregnant and nonpregnant rats and found that pregnancy was associated with diminished CVR and hyperperfusion during acute hypertension[95]. In further studies employing microspheres to measure absolute CBF and calculate CVR in nonpregnant and late-pregnant animals at normotension and after autoregulatory breakthrough, we found that there was no difference in CBF or CVR under basal conditions. However, when blood pressure was acutely elevated by infusion of phenylephrine, both groups of animals had a significant increase in CBF. However, the increase in CBF was considerably greater in late-pregnant animals. CBF increased 181% in nonpregnant, but 238% in late-pregnant animals in response to the same acute change in pressure. Hyperperfusion in late-pregnant animals was likely due to the fact that pregnancy was associated with significantly decreased CVR compared to nonpregnant animals at the higher pressure. These studies importantly demonstrate that pregnancy has a profound effect on cerebral haemodynamics, including decreased CVR and hyperperfusion under conditions of acute hypertension. Together, these results suggest that gestation-induced changes in cerebrovascular haemodynamics may predispose the brain to oedema by diminishing protective mechanisms that increase CVR during acute hypertension.

While many of our previous studies have focused on normal pregnancy, because women who develop eclampsia are, in general, normotensive and asymptomatic prior to pregnancy[91–93], hypertension that develops prior to pregnancy poses significant risks for superimposed preeclampsia during pregnancy and elevated pregnancy related morbidity and mortality. Chronic hypertension is associated with cerebrovascular remodelling that is thought to be protective of the brain[96,97]. Medial hypertrophy of both large and small cerebral arteries and arterioles occurs during chronic hypertension. In addition, hypertension increases the wall:lumen ratio and serves to normalize circumferential wall stress that is elevated due to increased blood pressure[96–100]. Both hypertrophy and remodelling of large and small cerebral arteries attenuate the increased pressure in downstream microvessels, thereby protecting the BBB from disruption[101]. Importantly, while medial hypertrophy of cerebral arteries is considered protective of the BBB, pregnancy appears to prevent this response to hypertension, potentially increasing the susceptibility to oedema formation. Our own study examined how hypertension during pregnancy, induced by nitric oxide synthase (NOS) inhibition, affected medial hypertrophy of posterior cerebral arteries[102]. NOS inhibition for just 7 days significantly raised blood pressure in both nonpregnant and late-pregnant rats and caused medial hypertrophy in posterior cerebral arteries only from nonpregnant animals. In contrast, cerebral arteries from late-pregnant animals did not undergo medial hypertrophy in response to hypertension. The fact that pregnancy prevents hypertensive remodelling and medial hypertrophy was confirmed using another model of hypertension during pregnancy. A study that used Dahl salt-sensitive rats made hypertensive by feeding a high salt diet for the last half of pregnancy (2 weeks), also found that only the nonpregnant rats (treated for the same time period) underwent remodelling, i.e., the pregnant animals lacked any structural response to hypertension[103].

In a recent study, we examined whether or not pregnancy could *reverse* preexisting remodelling[104]. We compared cerebrovascular structural changes in nonpregnant Sprague Dawley rats that were hypertensive for two weeks by NOS inhibition prior to breeding and then remained on L-NAME for the entire gestation to nonpregnant animals that were hypertension for two or five weeks. Nonpregnant animals that were normotensive served as controls. We found that 2 and 5 weeks of hypertension caused significant inward remodelling of posterior cerebral arteries, demonstrated by decreased inner and outer lumen diameters compared to normotensive controls. However, late-pregnant animals that had preexisting hypertension for 2 weeks prior to pregnancy had inner and outer diameters similar to controls. Because these animals were hypertensive for 2 weeks prior to pregnancy and would have had remodelling similar to the nonpregnant hypertensive animals, these results suggest that pregnancy reverses hypertensive remodelling of cerebral arteries. If these results translate to women with hypertension in pregnancy, they have profound implications. Unlike their nonpregnant counterparts in which hypertension-induced medial hypertrophy and remodelling would shift the autoregulatory curve to higher pressures and protect the microcirculation during acute hypertension, pregnant women lack this protective response. Therefore, women with elevated blood pressure during pregnancy are particularly vulnerable to forced dilatation and damaging hyperperfusion that can lead to BBB disruption and oedema formation.

While alterations in haemodynamics likely contribute to hydrostatic brain oedema during acute hypertension by decreasing CVR, pregnancy also has a significant effect on the cerebral endothelium to cause more severe BBB disruption independent of changes in hydrostatic pressure. Using isolated and pressurized cerebral arteries from nonpregnant and late-pregnant rats, we compared BBB permeability in response to an acute elevation in pressure that caused forced dilatation of myogenic tone[105]. While arteries from both groups of animals had modest permeability at a normal pressure of 75 mm Hg, only the arteries from late pregnant animals responded to the increased pressure with a marked increase in permeability. This differential response to the same pressure step suggests that the BBB is more permeable in response to hydrostatic pressure independent of alterations in haemodynamics. These results also suggest that one mechanism by which pregnancy predisposes the brain to oedema during acute hypertension is through increased BBB disruption.

The importance of understanding how pregnancy and hypertension in pregnancy affect the cerebral circulation in ways that can promote eclampsia relates to potentially treating this condition to limit hyperperfusion and/or BBB disruption. It is interesting that the standard of care for eclampsia prevention is magnesium sulphate[106]. This treatment is given routinely despite unclear mechanisms of action. While it has been previously suggested that magnesium sulphate causes cerebral vasodilation and reversal of vasospasm associated with severe preeclampsia[107], there are likely other mechanisms by which magnesium protects the brain. In a recent study we showed that rats treated with magnesium sulphate every 4 hours for 24 hours prior to acute hypertension had significantly decreased BBB permeability to Evan's blue[108]. The effect of magnesium sulfate on the BBB was most pronounced in the posterior circulation, a region in the brain most susceptible to oedema formation. While it is likely that magnesium sulphate has multiple actions that lead to eclampsia prophylaxis, the fact that it limits BBB permeability during acute hypertension suggests that this treatment is protective of the BBB and can limit hydrostatic brain oedema.

POSTPARTUM REMODELLING, DISEASE RECURRENCE AND BEYOND

Clapp and Capeless[27] studied women beginning prior to pregnancy and continued their observations into pregnancy through one year postpartum. These investigators demonstrated that parous women showed a greater increase in their cardiac output during the course of pregnancy than women in their first pregnancy. In addition cardiac output remained elevated, and peripheral vascular resistance reduced compared to prepregnancy values when measured a year postpartum. Contributing to this change in cardiac output one year postpartum was a persistent increase in end-diastolic left atrial size suggesting that augmented preload contributed to this change. The stability of blood pressure over this same time course implied an increase in arterial compliance. In 2005 we examined sequential pregnancies in a group of 47 women for whom the results of blood pressure measurement within each trimester of pregnancy for both their first and subsequent pregnancies was available[109]. We hypothesized that pregnancy stimulates a persistent improvement in arterial compliance. Therefore a reduction in blood pressures across all trimesters would be observed when comparing subsequent to first pregnancies. Subsequent pregnancies appeared to be an optimal time to evaluate the impact of first pregnancies on residual postpartum compliance in the light of the substantial volume expansion challenge that pregnancy imparts. We also examined whether differences in blood pressure, if they existed, changed as a function of the elapsed time between pregnancies. We demonstrated significant reductions in blood pressure in all three trimesters in subsequent pregnancies when compared to first pregnancies. These reductions were detected despite the likelihood that the subsequent pregnancies were associated with a substantially greater cardiac output, as noted by Clapp and Capeless[27], suggesting that these women had increased arterial compliance. In addition, we observed that a short interval between pregnancies was associated with a greater increase in compliance. (i.e. a short inter-pregnancy interval was associated with the greatest difference in blood pressures between pregnancies and that this difference waned over time). The differences in third trimester mean arterial pressure between pregnancies were noted to approach zero at 4–5 years following a previous pregnancy (Figure 2).

Epidemiologic studies suggest that the interval between pregnancies is an important contributor to the risk of preeclampsia in women with prior pregnancies[110–111]. Of interest, while new paternity has long been identified as a contributor to preeclampsia

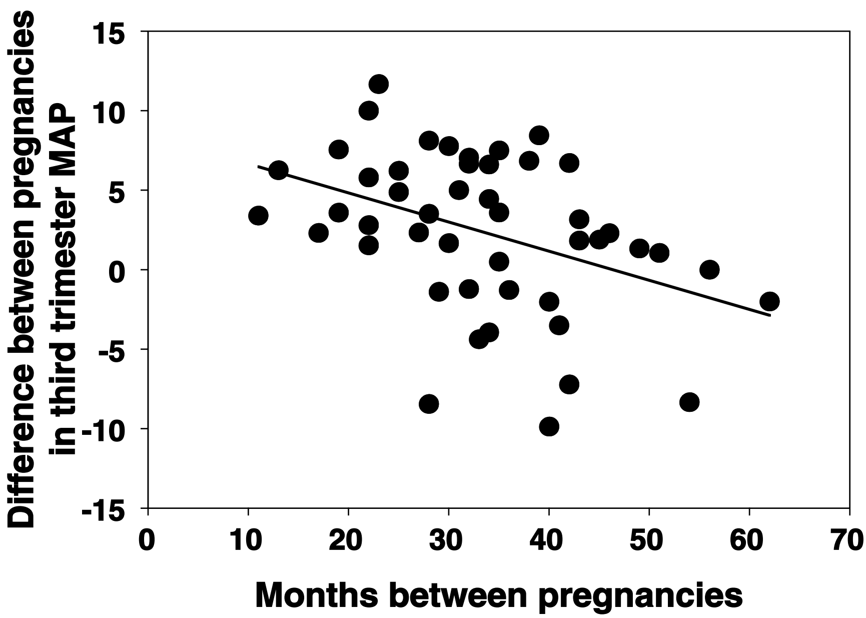

Figure 2 The difference in third trimester mean arterial pressure comparing first and subsequent pregnancies as a function of the interval between pregnancies.

in parous women[112–113], in these two large and distinct data bases, when the interval between pregnancies was considered as an independent risk factor for the occurrence of preeclampsia, there was no longer any independent influence of new paternity. Perhaps not surprisingly, new paternity was found to be significantly associated with an increase in length between pregnancies.

The association of preeclampsia with long term cardiovascular risk including the appearance of hypertension and ischaemic heart disease[114–116] is gaining widespread recognition. These associations can be viewed as either the result of preeclamptic pregnancy creating a new predisposition to cardiovascular disease or that preeclampsia uncovers preexisting predispositions. We hypothesized that the preexisting condition includes a prepregnancy phenotype incorporating reduced plasma volume with reduced arterial compliance, increase sympathetic tone, platelet activation and a pro-inflammatory cytokine environment. Importantly, these physiologic elements have all been linked to an increased risk of cardiovascular disease[117–119]. This cohort phenotype which can be identified in young healthy women prior to a first pregnancy supports the hypothesis that preeclampsia represents an uncovering of latent tendencies for cardiovascular risk.

SUMMARY

The pathophysiologic sequence of preeclampsia has been tightly linked to the presumed presence of a pathologic molecule of placental origin, the most recent Toxin of Toxaemia. While it is clear that the presence of the placenta is required for disease because placental removal initiates recovery, the specific placental signal centrally involved in this sequence remains unknown. There are significant limitations to the proposed "two stage" theory of preeclampsia which is hypothesized to be initiated by disordered placental invasion. Alternative to this hypothesis is that the placental signal of importance in the development of maternal hypertension and proteinuria is a physiologic one and involves the drive towards volume expansion. Evidence in animal models of pregnancy further suggest that normal physiologic changes in pregnancy occurring within the cerebral circulation may predispose to the development of vasogenic oedema without the need for additional explanatory toxins or pathways. When these physiologic events are superimposed on a specific prepregnancy phenotype, preeclampsia results. Similar to the way that gestational diabetes uncovers prepregnancy predispositions to diabetes and is associated with the development of diabetes mellitus in later life preeclampsia appears to uncover a predisposition to cardiovascular disease. Some elements of this predisposition may be identified through prepregnancy evaluation. These elements include platelet activation, augmented sympathetic tone and a pro-inflammatory cytokine environment which may likewise contribute to the development of cardiovascular disease in later life.

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