Review Article

Prevention of Vascular Dysfunction after Preeclampsia: A Potential Long-Term Outcome Measure and an Emerging Goal for Treatment

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Received 29 July 2011; Accepted 15 September 2011

Academic Editor: Christos Iavazzo

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Preeclampsia is increasingly being recognised as more than an isolated disease of pregnancy. In particular, preeclampsia has emerged as an independent risk factor for maternal cardiovascular disease and has recently been recognised as a risk factor for cardiovascular disease in children exposed in utero. Preeclampsia and cardiovascular disease may share important pathophysiological and molecular mechanisms and further investigation into these is likely to offer insight into the origins of both conditions. This paper considers the links between cardiovascular disease and preeclampsia and the implication of these findings for refinement of the management of patients whose care is complicated by preeclampsia.

1. Introduction

Although traditionally preeclampsia has been viewed as a condition that resolves completely with the delivery of the placenta, there is now increasing evidence that preeclampsia may constitute a condition with significant long-term health implications for both the mother and child. In particular preeclampsia has recently emerged as an independent risk factor for maternal cardiovascular disease 10–15 years after the index pregnancy [1–3]. A history of preeclampsia is therefore now considered a relevant factor in the cardiovascular risk assessment in women [4] and is associated with an increase in risk similar in magnitude to a history of dyslipidemia [5]. Meta-analysis has demonstrated that in the 10–15 years following a preeclamptic pregnancy women have an increased risk of developing hypertension (RR 3.7 95% C.I. (2.7–5.05, $P < 0.001$)), coronary artery disease (RR 2.16 95% C.I. (1.86–2.52, $P = 0.001$)), and stroke (RR 1.81 95%

C.I. (1.45–2.27, $P = 0.00$) [1]. Additionally, it has been demonstrated that there is a graded relationship between the risk of cardiac disease and the severity of preeclampsia with maternal risk being greatest with early onset or severe preeclampsia [6]. Children born to preeclamptic women have also been demonstrated to have elevated blood pressure in childhood and adolescence [7–12].

This highlights potentially important pathophysiological or molecular links between preeclampsia and cardiovascular disease. Greater insight into these links may identify new opportunities to understand disease predisposition and treatment and may also raise the possibility that prevention of vascular dysfunction should be an important long-term goal of preeclampsia management. This paper will consider the current literature considering the links between cardiovascular disease and preeclampsia and the implication of these findings for refining the management of patients whose care is complicated by preeclampsia.

2. What Links Preeclampsia and Cardiovascular Disease?

The aetiology of preeclampsia remains incompletely understood, though disturbed placentation and placental functioning in early pregnancy remains the leading hypothesis [31]. During normal placental development, fetal cytotrophoblasts invade the maternal spiral arteries transforming them to high-caliber capacitance vessels providing low resistance placental perfusion adequate to sustain fetal growth [32]. However, inadequate spiral artery remodeling in preeclampsia is thought to lead to chronic placental ischaemia or intermittent flow through the narrow muscular arteries thereby creating an ischaemia-reperfusion phenomenon [33].

Reactive oxygen species and cytokines released from the ischaemic placenta trigger a systemic oxidative stress [34] and contribute to the exaggerated systemic inflammatory reaction in preeclampsia [33, 35]. Syncytiotrophoblasts undergoing apoptosis also shed increased numbers of microparticles in the maternal circulation which contribute to this process. The release of cytokines and acute phase proteins, such as TNF α , leptin, and PAI-1, not only enhance the inflammatory response but also induce some of the observed metabolic disturbances in preeclampsia including insulin resistance, lipolysis, and hyperlipidaemia [33, 34].

Furthermore, hypoxic oxidative stress and inflammatory stimuli provoke the release of antiangiogenic factors (via NF- κ B pathways) [33, 36–38]. Soluble Fms-Like Tyrosine kinase-1 (sFLT-1), a circulating truncated form of VEGF receptor, binds and reduces levels of VEGF and PlGF in the maternal circulation thereby inhibiting angiogenesis and vasodilatation [39]. This aberrant vasculature is thought to lead to a cascade of events which end in symptomatic systemic endothelial dysfunction [40]. Soluble endoglin, a TGF- β coreceptor, is one of the antiangiogenic factors that enhances vascular permeability and may possibly affect nitric oxide synthesis and vasodilatation via altered downstream signalling in the TGF- β pathway contributing to the endothelial dysfunction [35] (Figure 1).

Consistent with these biological changes, reduced endothelial-dependent vasodilatation in conduit and resistance arteries [21, 41–47] has been demonstrated in women who have preeclampsia. They also appear to have increased arterial stiffness [13], increased atherosclerosis [48], and diminished capillary density [49]. Biochemical markers of endothelial activation and dysfunction are also elevated in preeclampsia [34, 50]. Maternal endothelial dysfunction is also present in conduit vessels before the onset of clinical disease [42] and up to three years after an affected pregnancy [24, 51, 52]. The increase in cardiovascular risk following preeclampsia may be a consequence of the pro-atherogenic impact of persistent endothelial dysfunction, a result of subclinical endothelial injury at the time of pregnancy, or to preexisting differences in endothelial function that predispose to both conditions (Figure 2).

Dysfunction of the vascular endothelium is a key factor in the development of atherosclerotic cardiovascular disease and has been demonstrated to precede clinically identifiable

structural changes in the vasculature [53]. Peripheral dysfunction of the vascular endothelium has been demonstrated to correlate with increased risk of clinical events [54] and all cause mortality [55] and associates with many traditional cardiovascular risk factors including hypertension, diabetes mellitus, insulin resistance, hypercholesterolemia, and smoking [56]. In addition to this, endothelial dysfunction has been demonstrated in young adults predisposed to hypertension without clinical evidence of arterial disease [57]. Endothelial health and nitric oxide synthase activity are crucial in modulating arterial distensibility [58–60] and carotid intima media thickness [61, 62] independent of risk factors [62] as well as myocardial hypertrophic responses in animals [63–65]. Left ventricular mass, another powerful independent predictor of mortality and morbidity in adults free of clinical disease [66], has a graded relationship with vascular endothelial vasomotor responses in hypertensive adults [67–72]. The strong relationship between endothelial dysfunction and cardiovascular outcomes and risk factors make it an interesting pathophysiological endpoint in the evaluation of therapies designed to modify long-term cardiovascular risk.

3. Maternal Vascular Function as an Intermediate Endpoint in the Management of Preeclampsia

As women who have experienced preeclampsia constitute a relatively young group, and there is potentially a prolonged period between exposure and clinical outcome, intermediate measures which may indicate a potentially modifiable change in risk are of particular value. Noninvasive measures of vascular function are widely used as surrogate markers of cardiovascular risk [73, 74]. For example, increasing arterial stiffness, demonstrated by an increase in pulse wave velocity, is an antecedent factor in elevated blood pressure, predicts the future cardiovascular risk of adults, and correlates strongly with the presence of atherosclerosis [75]. Similarly, early evidence of atherosclerosis demonstrated by increased thickness of the arterial wall is correlated with coronary artery disease and is predictive of future infarction and stroke [75, 76]. Changes in these parameters may therefore also offer unique insight into the cardiovascular risk of women and children following a preeclamptic pregnancy.

Several relatively small-scale studies have also demonstrated vascular dysfunction after pregnancy complicated by preeclampsia with evidence of endothelial dysfunction in the macrocirculation [14, 16, 18, 22–24, 26] up to a median of 3 years and the microcirculation up to 25 years later [15, 27, 30], as well as increased arterial stiffness [13, 14, 16, 17] up to almost 5 years after the index pregnancy and atherosclerosis over 3 months postpartum [19]. Elevation of systemic biomarkers of endothelial injury and inflammation have also been described between 6 weeks [77] and 20 years [78–80] following preeclampsia. The characteristics and results of current literature considering the impact of preeclampsia on vascular structure and function are summarised in Table 1. There is, however, some disparity in results with some studies demonstrating no change in vascular function following

TABLE 1: Studies assessing the long-term impact of preeclampsia on vascular function. AIx (augmentation index) and PWV (pulse wave velocity) are robust surrogate markers of aortic stiffness. Endothelial-mediated vasodilatation was measured in conduit arteries by FMD (flow-mediated dilatation) and in the resistance arteries using VOP (venous occlusion plethysmography) to measure FBF (forearm blood flow) or peripheral arterial tonometry (PAT) to measure RHI (reactive hyperaemic index). Microvascular endothelial responses were quantified in the microcirculation using LDF (laser Doppler flowmetry) and iontophoresis. SGA refers to small for gestational age.

Study	Subjects (Preeclampsia/control)	Interval after delivery	Vascular measures	Results in women with previous preeclampsia
<i>Aortic stiffness</i>				
Robb et al. 2009 [13]	15/22	7 weeks	AIx, PWV	Elevated PWV and AIx.
Yinon et al. 2010 [14]	24/16	6–24 months	AIx	Increased AIx in women with early onset preeclampsia.
Evans et al. 2011 [15]	18/50	6–36 months	PWV	No significant differences in central arterial stiffness.
Páez et al. 2009 [16]	20/20	2 years	PWV, AIx	Elevated PWV and AIx.
Elvan-Taşpınar et al. 2005 [17]	44/46	4–56 months	PWV	Elevated PWV.
Lampinen et al. 2006 [18]	30/21	5–6 years	AIx	No significant differences in AIx.
<i>Subclinical atherosclerosis</i>				
Blaauw et al. 2006 [19]	22/22	≥ 3 months	Femoral and carotid IMT	Increased IMT with early onset preeclampsia.
<i>Conduit artery endothelial function</i>				
Kusu et al. 2003 [20]	15/11	2 and 6 weeks	FMD	Reduced FMD both during pregnancy and postpartum (no control data postpartum).
Noori et al. 2010 [21]	45/21	12 weeks	FMD	No significant differences in FMD compared to controls.
Yinon et al. 2010 [14]	24/16	6–24 months	FMD	Reduced FMD in women with early onset preeclampsia.
Hamad et al. 2007 [22]	18/17	15 ± 3 months	FMD	Reduced FMD and endothelial independent dilatation in women with severe preeclampsia.
Germain et al. 2007 [23]	25/22	16 ± 3.5 months	FMD	Reduced FMD.
Páez et al. 2009 [16]	20/20	2 years	FMD	Reduced FMD.
Chambers et al. 2001 [24]	113/48	3 years median	FMD	Reduced FMD particularly in women with recurrent preeclampsia and recovery of endothelial function with ascorbic acid.
<i>Resistance artery endothelial function</i>				
Lommerse et al. 2007 [25]	32/10	0.64–1.6 years	VOP	No significant difference in FBF.
Agatisa et al. 2004 [26]	16/14	9.9 ± 0.5 months	VOP	Reduced endothelium-mediated FBF.
Evans et al. 2011 [15]	18/50	6–36 months	VOP	Reduced FBF in response to mental stress.
Lampinen et al. 2006 [18]	30/21	5–6 yrs	VOP	Significantly reduced FBF to acetylcholine (ACh) and sodium nitroprusside (SNP).
Kvehaugen et al. 2011 [27]	26/17	5–8 years	PAT	RHI comparable between preeclamptic women and controls. Women with SGA baby had significantly lower RHI.
<i>Cutaneous microvascular function</i>				
Khan et al. 2005 [28]	15/54	6 weeks	LDF and iontophoresis	No significant differences between women in endothelial dependent or independent microvascular dilatation.
Blaauw et al. 2005 [29]	25/23	7.0 ± 2.8 months	LDF and iontophoresis	Greater microvascular vasodilator responses in preeclampsia.
Ramsay et al. 2003 [30]	10/10	16–25 years	LDF and iontophoresis	Reduced response to endothelial-dependent and -independent dilatation.

FIGURE 1: Molecular and vascular mechanisms of endothelial dysfunction in preeclampsia. Defective placentation, a common feature of preeclampsia, triggers a cascade of events including oxidative stress and exaggerated inflammatory reaction and angiogenic imbalance which exacerbate endothelial dysfunction. Impaired endothelial function plays a central role in the clinical manifestations of preeclampsia such as hypertension and proteinuria.

FIGURE 2: Theoretical timelines of impairment of endothelial function and development of cardiovascular disease following preeclamptic pregnancy. (1) In the normal individuals there is a gradual age-related reduction in endothelial function, which can be exacerbated by the presence of cardiovascular risk factors and associates with the future risk of clinical cardiovascular disease. (2) Women who experience preeclamptic pregnancies are known to have impaired endothelial function during pregnancy and up to 3 years following an affected pregnancy. It is possible that these women begin life with normal endothelial function, which is acutely impaired during a preeclamptic pregnancy. This followed by ongoing age-related decreases in endothelial function may relate to the increased incidence of cardiovascular disease in these individuals. (3) Alternatively, women who develop preeclampsia may have primary endothelial dysfunction which both puts them at risk of preeclampsia, this may then be exacerbated by the preeclamptic pregnancy (solid line), or simply persist (dotted line), in either case leading to higher incidence of cardiovascular disease.

preeclampsia [21, 25, 28, 81]. This may in part reflect heterogeneity in patient cohorts, severity of preeclampsia, size of cohorts, the timing of the studies following the affected pregnancy, as well as differences in the vascular beds studied and the techniques employed. In the future more detailed long-term follow-up studies of such women may clarify changes in cardiovascular physiology and inform future treatment.

4. Offspring Vascular Function Following Preeclampsia

Even more than their mothers, children born following a preeclamptic pregnancy, constitute a cohort where early life preventative strategies may have a profound impact on future cardiovascular risk. Furthermore, adults whose mothers had preeclampsia themselves have a higher risk

of the condition. Therefore, in this group evidence of subtle changes in vascular physiology indicating changes in risk are of particular importance. The body of literature considering cardiovascular outcomes in the offspring of preeclamptic pregnancies is sparse when compared to that considering maternal health. A single 60-year-follow-up study of individuals born to preeclamptic women demonstrated an increased risk of stroke in later life (RR 1.9 95% C.I. (1.2–3.0, $P = 0.01$)) [82]. Offspring of hypertensive pregnancies have also been shown to have an increased risk of hypertension as adults [82, 83] as well as having increased, although not pathological, blood pressure in childhood and adolescence [84]. Meta-analysis suggests that the magnitude of this increase in young individuals for systolic blood pressure is 2.3 mmHg and for diastolic blood pressure is 1.7 mmHg [84]. Although such increases are unlikely to be clinically recognisable, it may have significant public health significance as a 2 mmHg rise in systolic blood pressure has been associated with a 7% increase in ischaemic heart disease mortality and a 10% increase in stroke [85].

Preterm offspring born to hypertensive pregnancies demonstrate a distinct cardiovascular phenotype, characterised by reduced conduit artery endothelial function and increased evidence of early atherosclerosis, compared to individuals born preterm to normotensive women [7]. A finding which has now been replicated in other groups [27, 86, 87] and may be similar to the vascular dysfunction seen in women following preeclamptic pregnancies [27]. Although the underlying mechanisms remain unknown, there is substantial evidence of “programming” of aspects of vascular biology during fetal development, in particular endothelial responses [88] and arterial stiffness [89]. The risk to the offspring is likely to be mediated through changes in maternal blood pressure, vascular resistance in the placenta, or exposure to maternal factors (such as antiangiogenic factors [90], vasoactive substances [91], and reactive oxygen species) in the fetomaternal circulation. Optimal management of preeclampsia may have indirect benefits to reduce cardiovascular risk in the offspring of such pregnancies [92]. Hence, better understanding of the long-term vascular changes in offspring of preeclampsia may allow assessment of novel and previously unrecognised long-term outcomes of preeclampsia with important public health significance.

5. Conclusions and Future Directions

It is now becoming clear that preeclampsia is more than an isolated disease of pregnancy. The long-term health implications of this condition for both the women and their children are increasingly being recognised and incorporated into clinical risk assessments [4]. Both women and children exposed to preeclampsia exhibit an adverse vascular phenotype, a propensity to subclinical atherosclerosis, and increased risk of adverse cardiac and vascular events in future life. As preeclampsia affects 2–5% of the population this altered risk is relevant to the health of 1.2 to 3 million people in the UK and 6 to 15 million people in the USA. Optimal management of preeclampsia may be able to improve

short and long-term vascular outcomes in these individuals. While we remain unable to effectively prevent preeclampsia attempts to reduce its long-term impact on those exposed are of potential importance. Future studies that define the detailed cardiovascular phenotype of those exposed to preeclampsia may allow identification of potential targets for future preventative strategies. Furthermore, studies into the mechanisms underlying the altered cardiovascular phenotype may provide unique insight into pathophysiological or molecular links between preeclampsia and cardiovascular disease, which may direct us to novel treatment strategies for both conditions. Vascular dysfunction is an early marker of cardiovascular risk, correlating with future risk of cardiac events and preceding structural vascular change [53]. Improvement in vascular function would therefore be a valuable intermediate endpoint in studies aiming to reduce risk in this potentially young and generally asymptomatic population before the onset of clinical disease.

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