Pre-eclampsia and long-term maternal health

David Williams PhD FRCP

Consultant Obstetric Physician, Department of Maternal Medicine, Institute for Women's Health, University College London Hospital, London, UK

Summary: Pre-eclampsia is a syndrome of pregnancy, defined by the gestational-onset of hypertension and proteinuria, which resolves postpartum. This definition does not consider the variable multiorgan involvement of a syndrome that can include seizures, fulminating hepatic necrosis and a consumptive coagulopathy. These disparate clinical features are a consequence of an accelerated but transient metabolic syndrome with widespread maternal endothelial dysfunction and inflammation. A trigger to this maternal state is the relatively ischaemic placenta. As pregnancy progresses, the concentration of vaso-toxic factors released by the relatively ischaemic placenta gradually builds up in the maternal circulation. Those predisposed to endothelial dysfunction, e.g. women with risk factors for cardiovascular disease, are more sensitive to these placental derived factors and will develop pre-eclampsia before natural onset of labour. A woman's vulnerability to pre-eclampsia is therefore composed of a unique balance between her pre-existing maternal endothelial and metabolic health and the concentration of placental derived factors toxic to maternal endothelium. Delivery of the placenta remains the only cure.

Years later, women who had pre-eclampsia are at increased risk of chronic hypertension, ischaemic heart disease, cerebrovascular disease, kidney disease, diabetes mellitus, thromboembolism, hypothyroidism and even impaired memory. This article describes how a brief, usually single episode of this acute pregnancy syndrome might both identify those vulnerable to chronic disease in later life and in some cases initiate chronic disease.

Keywords: pre-eclampsia, metabolic syndrome, endothelium, hypertension, diabetes

INTRODUCTION

During pregnancy, almost every organ of the mother's body has to work harder in order to meet the demands of the developing fetus.¹ Women with chronic disease may struggle to fulfil these physiological demands and when this occurs pregnancy outcome is compromised. Gestational syndromes such as pre-eclampsia usually occur in women who have no past history of illness. Maternal health may be threatened during pregnancy, but usually recovers completely postpartum. In these circumstances, the pregnancy has transiently unmasked a previously unrecognized subclinical vulnerability to long-term disease.²

Pre-eclampsia affects between 2% and 7% of first time pregnancies, with marked differences in incidence across nations.³ Early-onset pre-eclampsia is thought to develop when the relatively ischaemic placenta expresses factors that cause or facilitate maternal endothelial dysfunction. These include soluble fms tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), which have the potential to disrupt maternal endothelium, increase maternal blood pressure and damage the fenestration of glomerular capillaries, causing proteinuria. Late-onset pre-eclampsia is thought to occur in the second half of pregnancy when physiological haemodynamic and metabolic changes overwhelm her

ability to maintain a normal blood pressure and insulin metabolism. Childbirth leads to transient remission, but the effects of aging and weight gain gradually unmask a latent vulnerability to insulin resistance and the metabolic syndrome culminating in a spectrum of premature, but preventable clinical diseases in later life. This article describes how a history of pre-eclampsia might predict or predispose women to a range of chronic diseases, years after an affected pregnancy.

During healthy pregnancy a woman is propelled into an increasingly pro-atherogenic metabolic state.^{4,5} Shortly after conception she develops a high cardiac output,⁶ hypercoagulability⁷ and increased inflammatory activity.⁸ After 20 weeks there is insulin resistance^{5,9} and hyperlipidaemia.¹⁰ These gestational changes are usually more pronounced in women who later develop pre-eclampsia.⁴⁻¹² This is partly due to pre-existing, subclinical, cardiovascular risk factors in 'healthy' women who go on to develop pre-eclampsia.¹³⁻¹⁶ These women are more likely to be overweight,^{13,15-17} have higher lipid levels,¹⁸ higher blood pressure,^{15,16,19} insulin resistance²⁰ and are more likely to have a thrombophilia,¹⁴ compared with women who go on to have a normotensive pregnancy.

A woman's prepregnancy metabolic and endothelial health partly dictates her vulnerability to pre-eclampsia, which in turn is a transient expression of her future risk of metabolic and cardiovascular disease.

Correspondence to: Dr David Williams, The Institute for Women's Health, University College London Hospital, Medical School Building, 74 Huntley Street, London WC1E 6AU, UK
Email: d.j.williams@ucl.ac.uk

Within days of delivery following a pre-eclamptic pregnancy, blood pressure usually returns to normal. On average blood pressure returns to normal in 16 days, but for those who had

early-onset, severe pre-eclampsia it can take up to three months.²¹ A proportion of women who had pre-eclampsia will remain hypertensive, most are presumed to have had previously unidentified chronic hypertension, but some will have secondary causes of hypertension.²² Despite their recovery to a normal blood pressure, many women who have had pre-eclampsia have evidence of subclinical endothelial dysfunction²³ and remain at increased risk of developing cardiovascular disease in later life.^{24–27}

NORMOTENSIVE PREGNANCY AND RISK OF FUTURE CARDIOVASCULAR DISEASE

There is a consistent association between increasing parity and risk of future coronary heart disease. Women who have had six or more pregnancies have a significantly increased risk of future heart disease compared with nulliparous women.²⁸ In order to establish whether this association is due to biological processes related to pregnancy or life-style factors influenced by family size, an association between number of children and coronary heart disease in both the fathers and mothers of pregnancies was sought.²⁹ In both sexes, lifestyle risk factors associated with child-rearing were found to lead to obesity and result in increased coronary heart disease, but after adjustment for obesity and metabolic risk factors, only for women did some association remain. This suggests that the biological changes that follow multiple pregnancies increase a woman's vulnerability to future cardiovascular disease.²⁹ In particular, only women showed an adverse lipid profile and risk of diabetes with increasing number of children.²⁹

Weight retention or gain after pregnancy is associated with an increased risk of pre-eclampsia in a subsequent pregnancy compared with women who returned back to their prepregnancy weight.³⁰ This observation not only supports the association between maternal overweight and pre-eclampsia risk, but also the stronger association between recurrent pregnancies affected with pre-eclampsia and future cardiovascular disease.³¹

FUTURE CARDIOVASCULAR HEALTH AFTER PRE-ECLAMPSIA

A vulnerability to future cardiovascular disease following a pre-eclamptic pregnancy has been recognized for many years.^{23–26,31–39} Following a pregnancy affected by pre-eclampsia there is evidence of subclinical pathology recognized as components of the metabolic syndrome. This includes obesity,^{16,17,27} endothelial dysfunction,²³ over-activity of the sympathetic nervous system,⁴⁰ increased peripheral vascular and renovascular resistance,⁴¹ insulin resistance^{27,42} and hyperlipidaemia.^{27,43} These subclinical pathophysiological changes are then followed by often-silent conditions that include hypertension,^{25,26,41} diabetes^{27,44–46} and renal impairment.^{37,41,47} Left untreated, these conditions lead to premature coronary artery disease,⁴⁸ overt renal disease⁴⁹ and a reduced life-expectancy.⁵⁰

Systematic reviews and meta-analyses have drawn together these numerous studies and quantified the risk of future cardiovascular disease after pregnancy.^{25,26} In general, women who had pre-eclampsia are more than twice as likely to develop future ischaemic heart disease (IHD) compared with women who have a normotensive pregnancy. A similar risk exists for future cerebrovascular accident, venous thromboembolism (VT) and peripheral vascular disease.^{25,26} The onset of these

diseases may be mediated through an increased risk of chronic hypertension RR 3.70 (95% confidence intervals (CI) 2.70–5.05).

Preterm pre-eclampsia (<37 weeks), severe pre-eclampsia and recurrent pre-eclampsia are risk factors for cardiovascular disease that independently and additively give an enhanced risk of future cardiovascular disease.^{25,26,31,34,37} In one meta-analysis, preterm pre-eclampsia was associated with a calculated RR of death from future cardiovascular disease, RR 7.71 (95%CI 4.40–13.52) compared with women who had a normotensive pregnancy.²⁵ Recurrent pre-eclampsia is also associated with a very high risk of future hypertension and kidney disease in later life.^{31,37}

There appears to be a graded association between the severity of pre-eclampsia, as judged by pregnancy outcome and future risk of IHD.²⁶ Compared with women who had a normotensive pregnancy, women who had mild pre-eclampsia have an RR of future IHD of 2.00 (95%CI 1.83–2.19), for women who had moderate pre-eclampsia 2.99 (2.51–3.58) and for those who had severe pre-eclampsia RR 5.36 (3.96–7.27).²⁶

PRE-ECLAMPSIA AND CARDIOVASCULAR RISK; CAUSE OR EFFECT?

Accumulating evidence is now clarifying our understanding of whether a pregnancy affected by pre-eclampsia does irreparable harm, which eventually leads to clinically apparent maternal cardiovascular and metabolic disease, or whether the pregnancy transiently unmasks a woman's chronic underlying vulnerability to future disease.

Before a woman has ever been pregnant, those at risk of pre-eclampsia can be identified from their profile of classical cardiovascular, renovascular and metabolic risk factors.^{13,15,16} Even a woman's own birth weight gives an indication as to her risk of future pre-eclampsia.⁵¹ A low birth weight is associated with a doubling of future pre-eclampsia risk, just as low birth weight is associated with an increased risk of future cardiovascular risk.⁵¹

Later in life, prepregnancy bariatric surgery for morbidly obese women dramatically reduces the rate of pre-eclampsia odds ratio (OR) 0.20 (95% CI 0.09–0.44),⁵² just as it reduces the predicted risk of future coronary heart disease in non-pregnant individuals.⁵³

The importance of prepregnancy cardiovascular phenotype on future cardiovascular health was demonstrated in a study of 3225 women who were investigated before and after pregnancy. This study confirmed that women, who had pre-eclampsia or gestational hypertension, had higher postpartum body mass index (BMI), blood pressure and lipid levels compared with women who had a normotensive pregnancy.¹⁶ However, after adjustment for prepregnancy BMI, the difference in postpartum BMI was attenuated by >65% and the differences in blood pressure and unfavourable lipid profile were attenuated by approximately 50%.¹⁶ This evidence supports the premise that a woman's prepregnancy risk of cardiovascular disease is transiently unmasked by the development of pre-eclampsia.^{2,16}

It is possible that there are other, as yet unrecognized risk factors that explain the remainder of the association between pre-eclampsia and future cardiovascular disease. For example, high circulating levels of the soluble receptor to vascular endothelial derived growth factor (sFlt-1), released by the relatively ischaemic placenta targets the fenestrated endothelium of

glomerular and thyroid capillaries resulting in long-term micro-albuminuria and hypothyroidism, respectively (see later).^{54,55} Furthermore, although low placental growth factor (PLGF) levels are evident during a pre-eclamptic pregnancy,⁵⁶ they are elevated post-partum,⁵⁶ which is associated with an increased risk of cardiovascular disease.⁵⁷

Pre-eclampsia therefore appears to both unmask a latent risk of cardio-reno-vascular disease and to a more limited extent, may itself be responsible for irreparable maternal endothelium dysfunction, especially of the fenestrated capillaries of the renal glomerulus and thyroid gland.

WHAT ADVICE SHOULD BE GIVEN TO WOMEN WITH AN OBSTETRIC HISTORY OF PRE-ECLAMPSIA?

The CHAMPS study (Cardiovascular Health And Maternal Placental Syndromes),³³ suggests that a pregnancy affected by a maternal placental syndrome, which includes pre-eclampsia and fetal growth restriction (FGR), adds a further level of cardiovascular risk, over and above that recognized by classical cardiovascular risk factors. To this end, a woman's obstetric history becomes an important consideration towards her cardiovascular risk assessment. If factored into current algorithms that guide the need for prophylaxis against cardiovascular disease, middle-aged women with previous pre-eclampsia, especially if recurrent and severe, may benefit from prophylaxis with statins at a level of risk that was previously considered undeserving of such prophylaxis.⁵⁸ Prospective studies to investigate this possibility are still required.

In general, women who have had a term-normotensive pregnancy have been the main comparators against which the incidence of future cardiovascular disease in women who have had pre-eclampsia has been compared. However, when comparisons include women who have never been pregnant (nulliparas) and a general age-matched population, women who have had a term normotensive pregnancy go on to have the lowest blood pressures and presumably the lowest risk of future cardiovascular disease.^{34,37,45} Women who have a normotensive pregnancy might therefore be considered to have a superior cardiovascular status, whilst women who

have had pre-eclampsia should be assessed more frequently for hypertension, hyperlipidaemia and weight gain.

GESTATIONAL HYPERTENSION AND FUTURE CARDIOVASCULAR DISEASE

Women who had gestational hypertension, without proteinuria, also have an increased risk of future chronic hypertension and cardiovascular disease. This risk appears to be similar to those who had term pre-eclampsia (>37 weeks), but not as great as the risk seen in women who had preterm pre-eclampsia.^{33,25}

PRETERM BIRTH, FETAL GROWTH RESTRICTION AND FUTURE CARDIOVASCULAR DISEASE

Women who have had a pregnancy complicated by preterm birth are at increased risk of death from future cardiovascular disease, RR 2.95 (95%CI 2.12–4.11).^{32,59} Much of this association may be accounted for by iatrogenic preterm birth as part of the management of pre-eclampsia.⁵⁹ However, spontaneous preterm labour (PTL) in the absence of pre-eclampsia is also associated with an increased risk of future maternal IHD.⁵⁹ It is possible that an excessive inflammatory response may link a woman's vulnerability to PTL and future cardiovascular disease.⁶⁰

A pregnancy complicated by FGR also identifies a woman to be at increased risk for future cardiovascular and renal disease.^{32,49} In one population, women who had a baby weighing less than 2500 g had an 11-fold greater risk of death from IHD compared with those who had a baby weighing more than 3500 g.³² These observations highlight the role of the ischaemic placenta, which is evident in women who have growth-restricted babies and also in women with preterm pre-eclampsia, who usually have growth restricted offspring.^{61,62} Indeed, women who had a pregnancy complicated by pre-eclampsia and FGR are at greater risk of future cardiovascular and renal disease than those who had pre-eclampsia alone.^{32,49} Women who had the combination of pre-eclampsia, FGR and PTL have the highest risk of cardiovascular disease in later life (Tables 1 and 2).^{32,34}

Table 1 Summary of relative risk of future disease after pre-eclampsia. Data presented as relative risk and 95% confidence intervals compared with women who had an uneventful pregnancy outcome

	Chronic hypertension	Ischaemic heart disease events	Cerebrovascular disease	Peripheral vascular disease	Deep vein thrombosis	End-stage renal disease	All cancer
All pre-eclampsia	3.70 (2.70–5.05) (Ref. ²⁵)	2.16 (1.86–2.52) (Ref. ²⁵)	1.81 (1.45–2.27) (Ref. ²⁵)	1.87 (0.94–3.73) (Ref. ²⁶)	1.79 (1.37–2.33) (Ref. ²⁵)	4.3 (3.3–5.6) (Ref. ⁶³)	0.96 (0.73–1.27) (Ref. ²⁵)

Table 2 Summary of relative risk of future ischaemic heart disease (IHD) events according to different pregnancy outcomes (PET, pre-eclampsia; FGR, fetal growth restriction; PTL, preterm labour). Data presented as relative risk with 95% confidence intervals compared with women who had an uneventful pregnancy outcome

	All pre-eclampsia	Preterm pre-eclampsia	Mild pre-eclampsia	Severe pre-eclampsia	FGR	PTL	FGR and PTL	FGR, PET and PTL
IHD events	2.16 (1.86–2.52) (Ref. ²⁵)	7.71 (4.40–13.52) (Ref. ²⁵)	1.92 (1.65–2.24), 2.00 (1.83–2.19) (Refs. ^{25,26})	2.86 (2.25–3.65), 5.36 (3.96–7.27) (Refs. ^{25,26})	1.9 (1.5–2.4) (Ref. ³²)	1.58 (1.47–1.71), 1.8 (1.3–2.5) (Refs. ^{32,57})	3.3 (2.2–4.9) (Ref. ³²)	7.03 (3–14.5) (Ref. ³²)

PRE-ECLAMPSIA AND FUTURE KIDNEY DISEASE

Pre-eclampsia is more common in women with chronic kidney disease, especially when associated with chronic hypertension.⁶⁴ Conversely, the prevalence of newly identified renal disease in women who had a pregnancy affected by pre-eclampsia is increased, but relates to how hard and for how long postpartum, you look for it.

More than 30 years ago, hypertensive pregnant women often had a postpartum renal biopsy to investigate for occult renal disease. In one series of mainly black American women, the classic renal histology of pre-eclampsia (glomerular endotheliosis), was associated with other renal disease in approximately 24% of primigravid pre-eclampsia and up to 76% of multiparous pre-eclampsia.³⁷ Currently, very few women who have had pre-eclampsia have a postpartum renal biopsy. It is more likely that persistent postpartum proteinuria will suggest underlying renal disease.⁶⁵ Microalbuminuria is not only common after pre-eclampsia,⁴⁷ but also acts as a marker for cardiovascular disease, the major cause of morbidity in people with renal disease.⁶⁶ Women with proteinuria recognized during pregnancy should therefore be followed-up postpartum, until either the proteinuria disappears, or a reason for their persistent glomerular leak is found.

The most common renal pathology following pre-eclampsia is focal segmental glomerulosclerosis, supportive of the association between pre-eclampsia and chronic hypertension.^{37,67} Given the strong association between pre-eclampsia and renal disease, it is no surprise that end-stage renal disease (ESRD) is more common years after pre-eclampsia. This risk was quantified by combination of large Norwegian registries of pregnancy outcome and renal disease.⁶³ This study found that if pre-eclampsia occurred only in the first pregnancy, the relative risk of future ESRD is 4.7 (95% CI 3.6–6.1).⁶³ This risk of future ESRD increases progressively if a woman has two or even three pregnancies affected by pre-eclampsia. If the pregnancy was also complicated by low birth weight and PTL the relative risk of ESRD increases even further.⁶³ Early identification and treatment of hypertension in women with mild renal disease can prevent or delay the progression to end-stage renal failure.

PRE-ECLAMPSIA AND FUTURE VENOUS THROMBOEMBOLISM

In anticipation of haemorrhage at childbirth, normal pregnancy is characterized by low grade, chronic intravascular coagulation within both the maternal and utero-placental circulation. As a consequence, venous thromboembolism is more common during pregnancy and for up to six weeks postpartum.⁷ Inherited subclinical thrombophilias may manifest as VTE during this hypercoagulable period. Women who have had a deep vein thrombosis (DVT) are at increased risk of recurrence and morbidity in later life, due to post-thrombotic syndrome.⁷

Intravascular coagulation is also part of the syndrome that leads to atherosclerosis and pre-eclampsia.⁴ Some thrombophilias in some populations increase the risk of pre-eclampsia^{14,68} and it is no surprise therefore that the risk of thrombosis following a pre-eclamptic pregnancy, in particular following severe pre-eclampsia, appears to be at least double that of women who have had a normotensive pregnancy.^{69,70} However, despite the elevated relative risk of future thromboembolism, the actual risk of recurrent pre-eclampsia in women with thrombophilia

remains low and to date there has been no conclusive trial to test whether thromboprophylaxis is effective at reducing this risk.

Therefore, thrombophilia screening is not currently justified as routine screening following pre-eclampsia.

PRE-ECLAMPSIA AND DYSLIPIDAEMIA

Dyslipidaemia, in association with insulin resistance, forms part of the metabolic disturbance that is evident during pre-eclampsia.^{11,12} Following pre-eclampsia or eclampsia, dyslipidaemia is still evident, but not usually as strongly as other components of the metabolic syndrome.^{27,33,43,45} The profile of lipids found years after a pre-eclamptic pregnancy is typical of that expected for people at risk of IHD.^{27,43} This includes increased total cholesterol, decreased HDL cholesterol and raised triglycerides.

PRE-ECLAMPSIA, THE METABOLIC SYNDROME AND FUTURE DIABETES MELLITUS

The correlation between pre-eclampsia and maternal BMI,^{11,41} as well as with other features of the metabolic syndrome, places women who have had pre-eclampsia at risk of future type-2 diabetes mellitus.^{11–13,31,45} Several population studies have confirmed an increased incidence of type-2 diabetes following a pregnancy complicated by pre-eclampsia.^{27,44–46} One study from Scotland demonstrated that women who have had pre-eclampsia have an OR 1.40 (95% CI 1.12–1.75) of developing type-2 diabetes, compared with women who had a normotensive pregnancy.⁴⁴ Another from the USA gave a hazard ratio of 1.86 (95% CI 1.22–2.84) following pre-eclampsia, excluding women with gestational diabetes.⁴⁶

The action of sFlt-1 on glomerular capillaries may also be responsible for the observation that pre-eclampsia, but not gestational hypertension, increases the risk of diabetic nephropathy in women with type 1 diabetes mellitus.⁷¹

PRE-ECLAMPSIA AND FUTURE THYROID DISEASE

Women who have had a pregnancy affected by pre-eclampsia are more likely to have an elevated thyroid-stimulating hormone (TSH) level, suggestive of hypothyroidism.⁵⁵ Compared with women who had a normotensive pregnancy, the OR of an elevated TSH after pre-eclampsia is 1.7 (95% CI 1.1–1.7).⁵⁵ This association is stronger for women who have pre-eclampsia in both of their first two pregnancies OR 2.1 (0.9–7.5), in the absence of thyroid peroxidase (TPO) antibodies OR 2.6 (1.3–5.0) and in particular, if pre-eclampsia occurs in two pregnancies as well as in the absence of TPO antibodies OR 5.8 (1.3–25.5).⁵⁵ Such an observation suggests a non-autoimmune pathology is responsible for the association between pre-eclampsia and future hypothyroidism. It is suggested that elevated sFlt-1 levels, found in pre-eclampsia, may reduce thyroid vascularity and function by inhibiting vascular endothelial growth factor (VEGF) expressed on the fenestrated endothelium of thyroid capillaries.

ECLAMPSIA

Eclampsia is the term used to describe seizures in association with pre-eclampsia. It is a rare event, affecting 1–2% of women with pre-eclampsia, depending on the country of origin.⁷² Owing to the heterogeneous nature of pre-eclampsia, it was originally thought that eclampsia in a primiparous woman was a pure form of the condition, which would provide uniform answers on pathophysiology.²⁴ Eclampsia is usually associated with the most severe forms of pre-eclampsia, but can occur in women who have normal blood pressure. In this respect, eclampsia may simply reflect another element in the clinical constellation of the syndrome of pre-eclampsia.

The fenestrated endothelium of the choroid plexus in the brain expresses VEGF, just like glomerular and thyroid capillaries.⁷³ It is possible that inhibition of VEGF by circulating sFlt-1 in pre-eclampsia, impairs this fenestration leading to fluid shifts in the blood–brain barrier that lower the seizure threshold (Karamanchi SA, personal communication).

Diligent follow-up of women who have had eclampsia has shown that when it occurs during a first pregnancy there is no subsequent increased risk of future hypertension, unless the woman is of black African origin.^{24,38,39} If the subsequent pregnancy is complicated by pre-eclampsia then the incidence of chronic hypertension more than seven years later has been estimated at 25%, compared with only 2% for women who had a normotensive pregnancy following their eclamptic pregnancy.³⁸

Future maternal cardiovascular health is also predicted by the gestation of onset of eclampsia.³⁸ Women who had eclampsia before 30 weeks gestation were more than threefold more likely to develop chronic hypertension compared with those who had eclampsia after 37 weeks.³⁸ These observations reflect the importance of recurrent, severe, early-onset pre-eclampsia as a major risk factor for future cardiovascular disease, compared with primiparous pre-eclampsia.

PRE-ECLAMPSIA AND FUTURE MENTAL HEALTH

Three to eight months postpartum, women who have had severe pre-eclampsia have a measurably impaired memory.⁷⁴ This is unrelated to scores of depression, anxiety or attention.⁷⁴ It is possible that women who have had severe pre-eclampsia or eclampsia have permanent white matter damage, or their memory is impaired by the emotional trauma of a severe illness.⁷⁴ Whether this is a ubiquitous finding for all women who had pre-eclampsia, or just those who had severe pre-eclampsia, needs to be studied in a larger population of women. Further work is needed to clarify the cause of cognitive impairment in women with a history of severe pre-eclampsia/eclampsia, in order to improve their clinical outcome.

PRE-ECLAMPSIA, SMOKING AND FUTURE CANCER

Women who smoke have a lower incidence of pre-eclampsia.⁷⁵ This robust observation contradicts all other observations that cardiovascular risk factors predispose to pre-eclampsia. As women who smoke are less likely to develop pre-eclampsia, it has been suggested that women who had pre-eclampsia are less likely to develop cancer.⁷⁶ Systematic review and meta-analysis shows that this does not appear to be true.²⁵

Cigarette smoke may protect from pre-eclampsia through the action of carbon monoxide on the haemeoxygenase system, which in turn has been shown to lower production of sFlt-1 and sEng from endothelial cells and placental trophoblast.⁷⁷ The disadvantages of smoking in pregnancy include FGR, placental abruption, preterm rupture of membranes, placenta praevia and ectopic pregnancy and outweigh the benefit of a reduced risk of pre-eclampsia.⁷⁵ Women who have had pre-eclampsia in their first pregnancy should not therefore be encouraged to take up smoking!

LONG-TERM HEALTH OF OFFSPRING FOLLOWING PRE-ECLAMPSIA

Although beyond the scope of this study, it is worth mentioning that children born of pre-eclamptic pregnancies have increased disease vulnerability in later life. Children of mothers who had pre-eclampsia are often growth restricted and premature, which puts them at risk of future cardiovascular disease and insulin-resistance syndromes.⁷⁸ However, one large population-based cohort found no greater risk of future cardiovascular disease or insulin resistance in offspring of pre-eclamptic pregnancies when matched for birth weight and gestation compared with offspring of non-pre-eclamptic pregnancies.⁷⁹ Children born to pre-eclamptic pregnancies, especially those born at term, appear to be predisposed to inflammatory, endocrine and metabolic conditions, as well as being protected against cerebral palsy.⁷⁹ Whether these offspring share the same vulnerability to disease, which leads to pre-eclampsia in their mothers, or whether such conditions are derived from adaptations to a pre-eclamptic intrauterine environment still needs to be investigated.

PREVENTION OF LONG-TERM DISEASE

The consistent finding that pre-eclampsia, preterm birth and FGR identifies women at risk of cardio-reno-vascular disease, provides a timely opportunity for these relatively young women to adapt their lifestyle to minimize this risk. Monitoring and controlling body weight, hypertension, lipid levels and thyroid function would reduce long-term maternal morbidity and mortality. It is the role of the obstetrician to highlight the consequences of pregnancy outcome, in particular pre-eclampsia, to the primary care physician as well as the mother herself, in order that primary prevention might improve long-term health.

CONCLUSION

Pre-eclampsia is a pregnancy-specific syndrome with a broad clinical presentation. Women with recurrent, early-onset pre-eclampsia resulting in growth-restricted offspring have the highest risk of future cardio-reno-vascular disease and diabetes. These women need to be aware of this increased risk of future disease in order to adapt their life-style or to take prophylaxis that will reduce future morbidity.

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