

Pre-eclampsia: a lifelong disorder

Some women with pre-eclampsia develop hypertension and cardiovascular disease in later life

PRE-ECLAMPSIA AWARENESS WEEK (August 17–23) is an opportune time to reflect on what we know about this malady. Why does it develop? Can it be predicted or, more importantly, prevented? What will happen to affected women and their babies with further pregnancy? And, finally, does pre-eclampsia have long-term health effects?

About one in 10 pregnancies is complicated by hypertension: about 3%–4% have pre-eclampsia, a similar proportion have gestational hypertension and 1%–2% have pre-existing chronic hypertension. The latter is apparent when hypertension is present in the first half of pregnancy, whereas pre-eclampsia and gestational hypertension usually occur later. Despite pre-eclampsia being a placental disease, the mother rather than the fetus may bear the brunt, with, commonly, increased blood pressure, abnormal kidney (proteinuria or renal insufficiency) or liver function (elevated transaminases or severe right upper quadrant or epigastric pain), neurological disturbances including convulsions (eclampsia), and thrombocytopenia or disseminated intravascular coagulation. The fetus may be affected by growth

restriction (about one in four cases), and about 20 per 1000 cases die either *in utero* or as a result of prematurity.

Why does pre-eclampsia occur?

There appears to be an ill-defined genetic predisposition to pre-eclampsia, with some studies suggesting an autosomal recessive inheritance. However, discordance for pre-eclampsia among monozygotic twins questions some of the genetic postulates. Paternal influence on fetomaternal genetic mismatch is important, and being born of a pre-eclamptic pregnancy increases the likelihood for males of fathering an infant whose gestation will also be complicated by pre-eclampsia.

Immune theories abound, largely arising from epidemiological observations that pre-eclampsia is more common in a first pregnancy, and that changing partners for a subsequent pregnancy increases the risk of pre-eclampsia in women with a previous normal pregnancy and decreases the risk in women with previous pre-eclampsia.¹ Prolonged sexual cohabitation before pregnancy appears to protect against

pre-eclampsia, the implication being that this allows development of greater maternal “tolerance” to paternal antigens present in sperm or seminal fluid.²

Shallow trophoblast invasion of the placental spiral arteries is common in pre-eclampsia, leaving blood vessels that cannot deliver the same placental blood supply as in normal pregnancies. Although this is a common finding, it also occurs in idiopathic fetal growth restriction in which there are no maternal abnormalities. Thus, the factor (or factors) linking placental underperfusion or relative hypoxia to the multisystem effects of pre-eclampsia is yet to be established. Maynard et al³ have recently reported increased placental production of the soluble fms-like tyrosine kinase 1 (sFlt1) receptor, which mops up circulating vascular endothelium growth factor (VEGF) and placental growth factor. sFlt1 given to pregnant rats caused proteinuria, hypertension and glomerular endotheliosis, all features of human pre-eclampsia.³ Whether this factor proves to be significant in humans remains to be seen.

Whatever the factor(s) causing pre-eclampsia, it is best understood as a vasoconstrictive process associated with capillary leak and subsequent reduction in perfusion of maternal kidneys, liver, and brain, as well as the placenta.

Can pre-eclampsia be predicted?

It follows that without a precise understanding of the aetiology of pre-eclampsia there is little we can do to prevent its occurrence. Nonetheless, it now appears that endothelial dysfunction predates the clinical appearance of pre-eclampsia,⁴ and we know a range of situations in which pre-eclampsia is more likely. These include primipaternity, essential hypertension, renal disease, multiple pregnancies, donor sperm or donor oocyte pregnancy, history of previous pre-eclampsia or maternal or paternal family history of pre-eclampsia, obesity, diabetes and (probably) thrombophilias, such as Factor V Leiden or prothrombin gene mutations. This allows us to screen such women more often during pregnancy for the emergence of hypertension or fetal growth restriction, although this is not a fail-safe method of detecting all such cases. Taking aspirin 60–150 mg/day from about 14 weeks' gestation until late pregnancy offers a 15% reduction in the likelihood of developing pre-eclampsia, but about 90 women need to be treated to prevent one such case, and it is difficult to select these women.⁵

Management of pre-eclampsia

The development of day assessment units has changed our approach to management of hypertension in pregnancy in Australia. Women with hypertension in the second half of pregnancy previously spent weeks in hospital having their blood pressure controlled. This is now almost always done on an outpatient basis; this applies to women with gestational hypertension (about 25% of whom will develop pre-eclampsia at a later stage) and to a selected number of women with mild pre-eclampsia who have initially been observed in hospital.

The Magpie trial⁶ has shown the benefits of magnesium sulfate for convulsion prophylaxis, but most units in Aus-

tralia have such low rates of eclampsia (convulsions) that use of magnesium sulfate in all women with pre-eclampsia hardly seems justified. Antihypertensive drugs have been shown to reduce the likelihood of episodes of severe maternal hypertension and fetal respiratory distress syndrome, and several antihypertensive drugs, including oxprenolol, methyldopa, clonidine, hydralazine, and nifedipine, are widely used for this purpose.

The most important aspect of managing women with pre-eclampsia is timing of the delivery. This means determining when the woman's condition is deteriorating or when the fetus is at high risk of intrauterine death. Clearly, such management should be undertaken by highly specialised groups, with a team approach of obstetrician, physician, perinatologist and midwife.

What happens after pre-eclampsia?

The most common question asked by women who have had pre-eclampsia is whether it will occur in subsequent pregnancies. Estimates of recurrence vary enormously — anywhere from 5%–8% in late onset cases to 25% in early onset cases — but there is a gap in our knowledge about recurrence rates in Australian women. To help prevent pre-eclampsia, the Australasian Society for the Study of Hypertension in Pregnancy recommends low-dose aspirin. Women should take aspirin from early in their pregnancy, if, in the previous (pre-eclamptic) pregnancy, delivery was necessary before 32 weeks' gestation or fetal death occurred.⁷

Perhaps the more important question is what effect pre-eclampsia has on long-term health. The traditional view was that having pre-eclampsia imposed no greater long-term cardiovascular risk than a normal pregnancy. However, a recent large study from Norway has shown that developing pre-eclampsia before 37 weeks' gestation imposes an eight-fold increased risk of cardiovascular death over a median follow-up of 13 years.⁸ Given the young age of women with pre-eclampsia, this is quite a significant finding. Further, a study from Scotland has found that both pre-eclampsia and gestational hypertension increase the risk of hypertension in later life, with women who have had pre-eclampsia having an increased risk of death from stroke.⁹ Based on these findings, it is reasonable to recommend that all women who have had pre-eclampsia should have their cardiovascular risks assessed regularly (ie, annual blood pressure measurement, assessment of fasting lipids and blood sugar every few years) and should be encouraged to maintain a healthy lifestyle to reduce these long-term risks.

Conclusion

In Pre-eclampsia Awareness Week, we know that, for most women with pre-eclampsia in Australia, the outcome is a healthy mother and baby. However, pre-eclampsia should now be thought of as a lifelong disorder, with some women destined in later life to develop hypertension, and cardiovascular and cerebrovascular disease. Indeed, it is this recognition of the long-term health consequences for women with

pre-eclampsia that is the more recent important achievement in this field.

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