Cardiovascular risk in women after metabolic complications in pregnancy

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Hypertensive pregnancy disorders complicate 10% of all pregnancies. In this article we discuss the spectrum of hypertensive conditions that may occur during pregnancy. Recent studies have consistently shown that hypertensive disorders in pregnancy implicate a two-fold higher risk for the development of hypertension and cardiovascular disease later in life. To optimise preventive management of cardiovascular disease in women with previous complicated pregnancies, we therefore recommend monitoring of hypertension and other cardiac risk factors at an early stage in life. Furthermore, the obstetric history should be routinely incorporated in cardiovascular risk assessment in women who seek medical attention for hypertension and/or cardiac symptoms. (*Neth Heart J* 2007;15:415-7.)

Keywords: hypertension, pregnancy, risk assessment, women

Many physiological changes occur in pregnancy, beginning early in gestation. These changes can interact with an inherited predisposition for cardiovascular disorders that is unmasked by pregnancy-induced metabolic changes. The most important metabolic changes during pregnancy are an increase in plasma volume of 50% in the third trimester with an activation of the renin-angiotensin system, an increase in insulin resistance and changes in the haemostatic and procoagulant systems.¹ Hypertensive disorders complicate 10% of all pregnancies and cover a spectrum of conditions such as gestational hyper-

tension, chronic hypertension and preeclampsia. In a large retrospective cohort study in more than one million women in Canada it was shown that the risk of premature cardiovascular disease (CVD) is strongly related to the severity of metabolic disturbances that have occurred during pregnancy.² Women with a placental syndrome in combination with poor foetal growth or intrauterine death were found to be at greatest risk. The future risk of (premature) CVD was also higher in women with the traditional cardiac risk factors and the metabolic syndrome. In a matched cohort study, with a follow-up duration of 30 to 50 years, it was found that women with gestational hypertension or preeclampsia had a significantly higher risk for the development of hypertension later in life and the occurrence of hypertensive-related diseases.³

Despite the large amount of data that are available on the association between metabolic complications in pregnancy and future heart disease risk, the obstetric history is not yet incorporated in our daily practice and in the most recent guidelines for CVD prevention in women.⁴ Most of the aetiological research on CVD in women has thus far been focused on risk factors that are shared by men. The characteristics of pregnancy-related disorders, however, provide a unique opportunity for a better cardiovascular risk assessment in women, such as earlier detection of hypertension and diabetes.^{1,5} Furthermore, the relatively high age of pregnant women in our Western countries nowadays may facilitate the detection and treatment of these cardiac risk factors.

Spectrum of hypertensive disorders in pregnancy

Gestational hypertension

Gestational hypertension is defined as repeated measures of a diastolic blood pressure ≥ 90 mmHg, in the second part of pregnancy without signs of proteinuria, in previously normotensive women. Blood pressure returns to normal values by 12 weeks postpartum.

Hypertension that is diagnosed for the first time during pregnancy and that does not resolve postpartum is classified as chronic hypertension. Almost 10% of all pregnancies, especially the first, are considered to be

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associated with hypertensive complications.⁶ In a recent study it was shown that 50% of women with a history of hypertension in pregnancy had high blood pressure by the age of 52.⁷

Preeclampsia

Occurring in 3 to 5% of pregnancies, preeclampsia usually starts after 20 weeks of pregnancy and is defined as a gestational blood pressure elevation ($>140/90$ mmHg), combined with proteinuria (>300 mg/24 h, or a positive dipstick 30 mg/dl). Compared with gestational hypertension, preeclampsia is a more systemic syndrome involving oxidative stress and inflammatory responses. Characteristic clinical features of preeclampsia are vasospasm, pathological vascular lesions in multiple organ systems, increased platelet activation with platelet consumption and subsequent activation of the coagulation system. In the more severe forms signs of haemolysis, elevated liver enzymes and thrombopenia can be present (HELLP syndrome), with a high foetal and maternal death rate.

Early-onset hypertension in pregnancy is relatively often associated with severe preeclampsia. Both gestational hypertension and preeclampsia are important causes of complications during pregnancy, such as premature delivery, foetal growth retardation, abruptio placentae and foetal death.⁸ Mothers with these complications have a greater risk of maternal morbidity and mortality and they are at increased risk to develop CVD later in life.^{2,9,10} Preeclampsia occurs less frequently in second pregnancies than in first pregnancies, but the risk of recurrence remains high in women with previous early-onset preeclampsia (30-60%).^{8,11}

Aetiology of hypertensive disorders in pregnancy

In normal pregnancy several components of the metabolic syndrome are temporarily elevated, such as insulin resistance, lipid levels, and coagulation and inflammatory factors. It is hypothesised that normal pregnancy itself stimulates an inflammatory response, which is exaggerated in preeclampsia, and involves dysfunction of the endothelium in the uterine circulation.^{8,12} The ultimate source of the inflammatory stimulus is presumably the placenta itself.¹³ Utero-placental arterial insufficiency may cause the release of inflammatory stimuli (cytokines) into the maternal circulation, leading to vasoconstriction and activation of the coagulation system.¹²⁻¹⁴ Women with a past history of preeclampsia have increased plasma concentrations of the endothelial inflammatory markers and evidence of insulin resistance, up to 15 to 25 years after pregnancy, compared with women with a history of normal pregnancy.^{15,16} While hypertensive disorders early in pregnancy lead to low-weight babies, women who develop hypertension or preeclampsia late in pregnancy (after 37 weeks) tend to have larger babies. The pathophysiology of early and late-onset preeclampsia may therefore be different.¹⁷

Another important association of hypertensive disorders in pregnancy may be related to maternal constitutional factors that indicate a genetic susceptibility to inflammatory responses. Women who develop pregnancy-related disorders have a significantly elevated risk of familial hypertension and/or CVD.¹⁸ Furthermore, impaired endothelium-dependent vasodilatation has been demonstrated in women who have previously had preeclampsia.^{19,20} The specific vascular lesions of preeclampsia, also called acute 'atherosis' in the placental bed, are similar to those observed in atherosclerosis.²¹ Placental renin production and maternal angiotensinogen may have an additive role in the development of preeclampsia.²²

Insulin resistance and diabetes in pregnancy

Insulin resistance and dyslipidaemia, with a rise in triglycerides and small low-density lipoprotein particles, occurs after 20 weeks in every normal pregnancy. This is mediated by several hormonal changes, such as oestradiol, progesterone, cortisol and human placental lactogen.²³ In women with hypertensive disorders in pregnancy, the insulin resistance is more exaggerated, with concomitant metabolic changes that precede the subsequent development to preeclampsia.²⁴ Insulin resistance in pregnancy therefore shares many common features with the metabolic syndrome.^{1,21,23}

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) emerges in the second half of pregnancy in those women who have some degree of pre-existing insulin resistance. Women at higher risk are those with marked obesity, diabetes in a first-degree relative, and a previous infant with macrosomia (elevated birth weight). The risk for later development of diabetes mellitus 5 to 15 years after diabetes mellitus in pregnancy is 15-50%, especially in those women who needed insulin therapy.^{25,26} It is therefore recommended to check glucose tolerance in all women who have had GDM at six weeks postpartum and every three years afterwards.

Obstetric history as a CVD risk marker

Signs of subclinical atherosclerosis were recently found in a case-control study in 22 women within one year after preeclampsia during pregnancy.²⁷ Intima-media thickness measurements in the common carotid artery and femoral artery were significantly higher in women with previous pre-eclampsia compared with women with uncomplicated pregnancies. In another study in 491 healthy postmenopausal women it was shown that women with a history of high blood pressure during pregnancy are at increased risk (OR 1.57, 95% CI 1.04-2.37) of having coronary calcium at multislice computed tomography compared with women with uncomplicated pregnancies.²⁸ This increase in coronary calcification is in line with the population-based data and can be considered as a significant predictor of future CVD.^{2,3,29}

Conclusion

Pregnancy is a cardiovascular challenge test with the development of gestational hypertension or preeclampsia as a marker of increased risk to develop future hypertension and atherosclerosis. Many risk factors for hypertensive disorders in pregnancy overlap with cardiac risk factors. Women with hypertensive disorders in pregnancy should therefore be monitored more closely for the future development of hypertension and the presence of other cardiac risk factors. Furthermore, the obstetric history may be an important additive tool in the cardiovascular risk evaluation in women with hypertension and/or chest pain syndromes. ■

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