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Title:
Biochemical and Epidemiological Studies of Early-Onset and Late-Onset Pre-Eclampsia.

Abstract:
Biochemical and epidemiological aspects of pre-eclampsia were investigated, with the main focus on possible pathophysiological differences between early-onset and late-onset disease.

In pre-eclamptic women poor correlation was found between albumin-creatinine ratio (ACR) in a random urine sample and total amount of albumin in a 24-hour urine collection. *(Paper I)*

In a cohort of women giving birth in Sweden in 1973-82 we estimated the adjusted incidence rate ratio (IRR) for ischaemic heart disease (IHD) during the years 1987–2001. The adjusted IRR for development of IHD was 1.6-2.8 in woman exposed to gestational hypertensive disease during her pregnancy compared with unexposed women. The higher risk represents more severe or recurrent hypertensive disease. *(Paper II)*

Before delivery, in early-onset pre-eclampsia (24-32 weeks) there were pronounced alterations in plasma concentrations of soluble fms-like tyrosine kinase 1 (sFlt1) and placental growth factor (PlGF), and also a higher placental 8-iso-$PGF_{2\alpha}$ concentration and an elevated serum ratio of plasminogen-activator inhibitor (PAI)-1 to PAI-2 compared with early controls. In late-onset pre-eclampsia (35-42 weeks) there were only moderate alterations in sFlt1 and PlGF concentrations, and the placental 8-iso-$PGF_{2\alpha}$ concentration and PAI-1/ PAI-2 ratio were similar to those in late controls. *(Papers III, V)* There was a rapid postpartum decrease in sFlt1 concentration in all groups. One week postpartum the sFlt1 concentration was persistently higher, however, in women with early-onset pre-eclampsia compared with early controls. *(Paper IV)*

In conclusion: random ACR cannot replace 24-hour urine collections for quantification of albuminuria in pre-eclamptic women; gestational hypertensive disease, especially severe or recurrent, increases the risk for later IHD; early-onset, but not late-onset pre-eclampsia is associated with pronounced alterations of angiogenesis-related markers and only early-onset pre-eclampsia is associated with placental oxidative stress and an increased PAI-1/ PAI-2 ratio, all suggesting a stronger link between early-onset than late-onset pre-eclampsia and a dysfunctional placenta.

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