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Preeclampsia and scleroderma: a prospective nation-wide analysis

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Abstract

In a preliminary case-control study, women with scleroderma more frequently reported having had hypertensive complications during pregnancy compared with healthy women. To prospectively investigate this possible association, we conducted a nation-wide cohort analysis of a major hypertensive complication during pregnancy, namely preeclampsia, and later scleroderma. Analyses were based on Danish register-based birth and hospital contact data on preeclampsia and scleroderma. We followed 778,758 women from time of giving birth between 1978 and 2010 to end of follow-up, emigration, death, or scleroderma diagnosis, whichever occurred first. The association was evaluated by incidence rate ratios, obtained in Poisson regression models. We report that preeclampsia is associated with a 69% significantly increased risk of later developing scleroderma. Though these findings do not impact clinical care directly, the association of preeclampsia with scleroderma underscores the significant relationship of preeclampsia and other adverse pregnancy outcomes with later disease in women and should be included in patient counseling and education.

Keywords

Preeclampsia; scleroderma; systemic sclerosis; epidemiology; Denmark

Introduction

Preeclampsia is a pregnancy related syndrome characterized by elevated blood pressure and protein excretion in the urine, affecting 3–7% of pregnancies and potentially causing mild or more severe organ system damage (1, 2). Scleroderma constitutes a group of autoimmune diseases the hallmark feature of which is skin thickening and, depending on the disease subtype, extends to multiple internal organs. The frequency of scleroderma is low, and risk

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factors are poorly described(3). Interestingly, in a preliminary case-control study van Wyk et al. report a significant association between preeclampsia and scleroderma(4). In their retrospective study, women who later developed scleroderma reportedly had twice the odds of having had a pregnancy complicated by a hypertensive disorder compared with healthy women. The study did not report associations in disease subgroups. The current brief report uses a prospective design to assess the association between preeclampsia and scleroderma proposed by van Wyk et al., but also extends the work by studying the role of preeclampsia subsets in overall scleroderma, as well as the role of overall preeclampsia in a subset of systemic sclerosis. Person identifiable data were derived from nationwide Danish registers on hospital contacts, birth characteristics, migrations and deaths.

Material and methods

Register linkage was performed based on the unique 10-digit Danish identity number found in all the applied registers. In the Danish Medical Birth Registry (5) we identified all women who gave birth in Denmark during 1 January 1978 through 31 December 2010. We excluded births with implausible(6) or missing size for gestational age from analyses. Similarly, we excluded multiple gestations and births with missing information on offspring sex. In the Danish National Patient Register (DNPR)(7) we identified maternal hospital contacts with preeclampsia occurring during pregnancy. In DNPR hospital contacts are coded according to the International Classification of Diseases 8th revision (ICD-8) during 1978–1993 and 10th revision (ICD-10) during 1994–2010. We used the ICD-8 codes 637.03, 637.04, 637.09, 637.19, 637.99 and 661.3, and the ICD-10 codes O14 and O15 to identify preeclampsia hospital contacts. We subdivided preeclampsia according to severity based on ICD codes (mild: 637.03, 637.99, O14.0 and O14.9 vs. severe: all other) and onset measured in completed pregnancy weeks (early: 22–33 vs. late 34–44). Also in the DNPR, we identified women diagnosed with scleroderma by ICD-8 codes 701.0 and 734.0 and ICD-10 codes L94.0, L94.1, L94.2, L94.3, M34.0, M34.1, M34.8, and M34.9. Within this group we identified a subset of systemic sclerosis(9, 10) by ICD- codes 734.0, M34.0, M34.1, M34.8 and M34.9. Date of migration and death was obtained for all women from the Danish Civil Registration System (11). We evaluated the association between preeclampsia and scleroderma by calculating incidence rate ratios and 95% confidence intervals (95% CI), obtained by Poisson regression. Person-years at risk were calculated from the date of giving birth to end of follow-up, emigration, death, or scleroderma diagnosis, whichever occurred first. We created preeclampsia exposure and covariates as time-dependent variables. All analyses were adjusted for attained age (5-year groups), calendar period (5-year periods), parity (1, 2, ≥3) and age at most recent birth (5-year groups). The study was approved by the Danish Data Protection Agency (2010-41-5082). According to Danish legislation solely register-based research does not need approval from the National Committee on Health Research Ethics.

Results

We studied a total of 1,537,747 pregnancies in 778,758 women. Hospital contact for preeclampsia was registered in 20,797 (1.4%) pregnancies. Most preeclampsia diagnoses were mild and diagnosed late in pregnancy. Women were followed for a total of 12,480,228

risk-years of follow-up during which 338 women were registered with an incident scleroderma hospital contact, translating to a scleroderma incidence of 27.1 (95% CI 24.3–30.1) per 1,000,000 risk-years. Of the 338 scleroderma hospital contacts 217 (64.2%) were due to systemic sclerosis. Mean age at diagnosis was 40.1 and 40.9 years for scleroderma and systemic sclerosis, respectively. Table 1 shows associations between preeclampsia and scleroderma, and in the subset of systemic disease. Preeclampsia was associated with a 69% significantly increased risk of later scleroderma overall (incidence rate ratios 1.69 (95% CI 1.02–2.80)). In the subset of systemic sclerosis we found preeclampsia to increase the risk of disease by 46%, however this finding did not reach statistical significance (incidence rate ratios 1.46 (95% CI 0.75–2.85)).

Discussion

Our observations confirm and extend on an earlier retrospectively designed study(4). We find a significantly 69% increased risk of later scleroderma among women with preeclampsia. Regrettably we were not able to disentangle the association in subsets of morphea, linear, diffuse and limited forms of scleroderma based on the available ICD-codes. However, in a subset of systemic sclerosis we report a somewhat weaker association. While the explanation behind the association is unknown, persistent fetal origin microchimerism is a plausible candidate.

During pregnancy cells routinely transfer between woman and fetus. In many women cells of fetal origin persist, presumably lifelong(12). The presence of two or more genetically distinct cell populations in one individual is termed chimerism. In parous women cells of fetal origin are often present at low concentrations, and hence this phenomenon is known as fetal origin microchimerism. Fetal origin microchimerism is observed at increased rates during preeclampsia(13). Some hypothesize that the increased fetal origin microchimerism seen in preeclampsia may contribute to known associations of this pregnancy complication with later-life health, including increased risks of cardiovascular(14) and autoimmune diseases(15) and reduced risk of some cancers(16). An association between fetal origin microchimerism and the autoimmune disease scleroderma was first investigated in 1998, based on a female predominance, disease peaks in post reproductive years, and similarities with graft-versus-host disease(17). This study reported higher quantities of fetal origin microchimerism in women with scleroderma compared with healthy women(18). The study by van Wyk et al.(4), and now also the present brief report indirectly supports the notion that fetal origin cells increase the risk of scleroderma by documenting increased risk of scleroderma after preeclampsia.

Both the quantity and type of cells acquired during pregnancy as well as other factors could impact later maternal health(18). Since the original description of microchimerism in scleroderma, differences of microchimerism and of maternal-fetal HLA relationships have been reported to vary according to clinical disease subtype(19). The two subtypes of systemic sclerosis, diffuse and limited differ substantially for clinical characteristics, autoantibodies and prognosis. While the scleroderma incidence in our study was similar to previous reports(3), the preeclampsia prevalence was somewhat lower(1). The latter is due to the use of hospital contact data which captures only the most severe cases. A validation

study of preeclampsia diagnoses in DNPR showed that out of 88 women with preeclampsia as defined following a gold standard from the American College of Obstetricians and Gynecologists, 61 (69%) were recorded with a preeclampsia diagnosis in the register(20). The authors of the validation study conclude that for the purpose of etiologic studies the preeclampsia diagnosis in DNPR has acceptable validity. Scleroderma diagnoses in DNPR have not been validated. In our dataset most women with scleroderma were treated in outpatient clinics (75% for systemic sclerosis and 97% for localized scleroderma). Registered scleroderma hospital contacts may represent severe disease, and we may thus have missed milder cases. However, because the scleroderma incidence in our study was at an expected level we do not regard this a problem.

While our findings do not impact clinical care directly, the association of preeclampsia with scleroderma underscores the significant relationship re of preeclampsia and other adverse pregnancy outcomes with later disease in women (14–16) and should be included in patient counseling and education. We speculate that one plausible pathway is through trafficking of fetal cells from the fetus, with subsequent persistence in the woman. Additional studies are needed that incorporate comprehensive analysis of prior pregnancy outcomes and maternal complications. In addition, further investigation is needed to characterize the phenotype and functionality of persistent fetal origin cells in women with scleroderma compared with healthy women.

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Abbreviations

DNPR	Danish National Patient Register
ICD	International Classification of Diseases
CI	confidence interval

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Key message

Preeclampsia is associated with statistically significant increased risk of developing scleroderma.

Table 1

Association between preeclampsia and scleroderma, and a subset of systemic sclerosis, respectively.

	Scleroderma		Systemic sclerosis	
Preeclampsia	***Events***	***IRR (95% CI)***	***Events***	***IRR (95% CI)***
- Yes	16	1.69 (1.02–2.80)	9	1.46 (0.75–2.85)
- No	322	1 (ref.)	208	1 (ref.)

IRR, incidence rate ratios; CI, confidence interval.