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Abstract**—**Maternal predisposition to vascular and metabolic disease may underlie both vascular-related pregnancy complications, such as preeclampsia and intrauterine growth restriction, as well as future maternal cardiovascular disease. We aimed to substantiate this hypothesis with biochemical and anthropometric evidence by conducting an intergenerational case-control study in a Dutch isolated population including 106 women after preeclampsia or intrauterine growth restriction (median follow-up: 7.1 years) and their fathers (n=43) and mothers (n=64), as well as 106 control subjects after uncomplicated pregnancies with their fathers (n=51) and mothers (n=68). Cardiovascular risk profiles were assessed, including fasting glucose, lipids, anthropometrics, blood pressure, intima-media thickness, and metabolic syndrome. We found significantly higher fasting glucose levels, larger waist circumferences, and a 5-fold increased prevalence of hypertension in women with a history of preeclampsia as compared with control subjects ($P<0.001$). Likewise, their parents had higher glucose levels than control parents ($P<0.05$). Their mothers had larger waist circumferences and higher blood pressures ($P<0.05$). Also, women after pregnancies complicated by intrauterine growth restriction had higher glucose levels and increased prevalence of hypertension ($P<0.01$). Their fathers showed higher glucose levels as well ($P<0.05$). Mean carotid intima-media thickness was increased in a subset of women after preeclampsia diagnosed with chronic hypertension as compared with those without hypertension ($P<0.01$). Metabolic syndrome was more prevalent both in women with a history of preeclampsia and their mothers ($P<0.05$). We demonstrated intergenerational similarities in cardiovascular risk profiles between women after preeclampsia or intrauterine growth restriction and their parents. These findings suggest shared constitutional risks for vascular-related pregnancy complications and future cardiovascular disease. **(*Hypertension*. 2008;51:1-8.)**

Key Words: preeclampsia ■ intrauterine growth restriction ■ cardiovascular disease ■ familial aggregation ■ intergenerational study

Preeclampsia and intrauterine growth restriction (IUGR) are common vascular-related pregnancy disorders. Preeclampsia is characterized by de novo hypertension and proteinuria and is a major cause of maternal and fetal morbidity and mortality worldwide.[1] It has been suggested that preeclampsia and IUGR share a common pathogenesis involving shallow trophoblast invasion with subsequent maternal endothelial cell dysfunction,[2,3] although this is questioned by others.[4]

Epidemiological studies suggest an association between pregnancies complicated by preeclampsia and IUGR and an increased risk of future cardiovascular disease.[5–8] Common risk factors, such as obesity, hyperlipidemia, hypertension, and insulin resistance, are shared by these pregnancy disorders, as well as cardiovascular disease.[9–12] Moreover, a positive family history of cardiovascular disease in women with preeclampsia has been reported[13]. In addition, endothelial dysfunction provides a link between the pathogenesis of these pregnancy disorders and future cardiovascular disease in that it predisposes to both placental dysfunction and atherosclerosis.[14]

The similarities in risk factors, familial predisposition, and pathogenesis between preeclampsia, IUGR, and cardiovascular disease have led to the hypothesis that it is maternal constitution, ie, a predisposition to vascular and metabolic disease, that underlies both preeclampsia and IUGR, as well as future cardiovascular disease,[15] rather than that preeclampsia or IUGR is a cause of cardiovascular disease. The ability

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to identify young women, through pregnancy complications, at increased risk for future cardiovascular disease may enable unique programs of secondary prevention.

This study aims to provide biochemical and anthropometric evidence to substantiate the hypothesis that cardiovascular risk factors are constitutional in women with a history of pregnancies complicated by preeclampsia or IUGR. For that purpose, we chose a novel approach in that an intergenerational study was conducted, assessing cardiovascular risk profiles of women with a history of pregnancies complicated by preeclampsia, IUGR, or uncomplicated pregnancies, as well as of their parents. Assuming that constitution is at least partly genetically determined, we hypothesized that intergenerational similarities in risk profiles substantiate the constitutional origin of vascular risk factors in women with a history of pregnancies complicated by preeclampsia or IUGR.

Methods

Population

The study was conducted in a genetically isolated population in the southwest of the Netherlands and is part of a larger research program called Genetic Research in Isolated Populations, which aims to identify genetic factors in the development of complex disorders.[16] All of the participants were of white origin.

Participants

Women with a history of preeclampsia or a pregnancy complicated by IUGR and their parents were selected from the Genetic Research in Isolated Populations population. Women with a history of pregnancies complicated by preeclampsia or IUGR are referred to as the "index generation" and their parents as "mothers or fathers of the index generation." The scientific protocol of Genetic Research in Isolated Populations was approved by the medical ethics committee of the University Medical Center Rotterdam. All of the participants provided written informed consent. Preeclampsia was defined as de novo hypertension (systolic: ≥140 mm Hg; diastolic: ≥90 mm Hg) and proteinuria as ≥300 mg/24 hours or ≥1+ on semiquantitative analysis.[17] The guidelines recommend 24-hour urinary collection, but when dipstick is the only test available, 1+ is accepted, because it is associated with ≥300 mg/24 hours of proteinuria. In our cohort, only 4 women were diagnosed with preeclampsia by using dipstick analysis. For all of the remaining women, 24-hour urine collection data were available. Superimposed preeclampsia was defined as new-onset proteinuria after 20 weeks of gestation in women with chronic hypertension.[17] Preeclampsia was considered as "early onset" when it was diagnosed before 34 weeks of gestation and as "late-onset" when diagnosed after a gestational age of 34 weeks. IUGR was defined as birth weight of newborns equal to or below the fifth percentile, according to the Dutch fetal growth charts of Kloosterman.[18] If preeclampsia and IUGR co-occurred (n=8), women were categorized in the preeclampsia group. Women of the index generation, who gave birth to children with congenital anomalies, were excluded from the study group. Only singleton pregnancies were included. Women with a history of preeclampsia or IUGR were identified from National Birth Registration Records dating from 1983 to 2004. The records reported 93 women with preeclamptic pregnancies and 104 with IUGR-complicated pregnancies living in this community at time of delivery (Figure 1). In 57 cases, either the patients' identities were unknown or medical charts could not be retrieved. Of the remaining 140 cases, the diagnoses were confirmed by the research physician after reviewing the medical charts. These women were invited to participate in the study by their general practitioner or obstetrician. A total of 106 women with a history of preeclampsia or IUGR (47 with preeclampsia, 3 with superimposed preeclampsia, and 56 with IUGR) agreed on participation. Subsequently, these women were asked to invite their parents for participation. Thirty-five mothers and 23 fathers of women with a history of preeclampsia and 29 mothers and 20 fathers of women with pregnancies complicated by IUGR agreed on participation. Parents refrained from participation because of various reasons, including long travel distance, no contact with family, or bad health.

Control subjects and their parents were recruited from participants of the Erasmus Rucphen Family[19] Study, a study that is also embedded in the Genetic Research in Isolated Populations program. Women who reported no history of hypertensive complications during pregnancy were identified. Their obstetric records were obtained from the midwife's practice within the community and reviewed by the research physician. From all of the women with a history of uncomplicated pregnancies with term deliveries and children with normal birth weight, 106 control subjects (equal to the total number of women with a history of preeclampsia or IUGR) were randomly selected. Sixty-eight mothers and 51 fathers of control subjects participated in the study (Figure 1).

Data Collection

Participants were invited for examination at our research center located within the community. Fasting blood samples were drawn for measurements of lipids and glucose levels according to a standardized procedure.[20,21]

All of the participants were interviewed about their medical history, medication use, and lifestyle. Participants were classified as nonsmokers or current smokers (≥1 cigarette per day). Alcohol consumption was defined as regular use of alcoholic drinks (≥1 U/week).

Educational level was categorized into low (primary school or lower vocational training), intermediate (secondary school or intermediate vocational training), and high education (higher vocational training or university). Blood pressure measurements and anthropometrics were limited to female participants.

Blood pressure was measured twice in the sitting position at the right upper arm using an automated device (OMRON 711, automatic IS). The mean of these 2 measurements was used in the analyses. Hypertension was defined as diastolic blood pressure ≥90 mm Hg, and/or a systolic blood pressure ≥140 mm Hg, and/or use of antihypertensive medication (grades 1, 2, and 3 of the World Health Organization criteria[22]) for the index generation and a diastolic blood pressure ≥100 mm Hg, and/or a systolic blood pressure ≥160 mm Hg, and/or use of antihypertensive medication (grades 2 and 3 of the World Health Organization criteria[22]) for the mothers of the index generation. Height and weight were measured with the participant dressed in light underclothing. Waist circumference was measured on uncovered skin using a tape measure with the participant in the upright position, halfway between the rib cage and the pelvic bone.

Intima-media thickness (IMT), as well as the prevalence of metabolic syndrome, were assessed in the index generation and in mothers of the index generation. IMT of the common carotid artery was assessed by duplex scan ultrasonography using a 7.5-MHz linear-array transducer (ATL Ultra-Mark IV). IMT was measured offline from frozen images recorded on videotape[23] over an average distance of 10 mm of the common carotid arteries. The mean was calculated of the maximum IMT of the near and far wall measurements of both left and right arteries. In presence of a plaque at the 10-mm site, IMT was measured in the region adjacent to the plaque. The reproducibility of IMT measurements, performed in our department, has been described previously.[24]

Metabolic syndrome was retrospectively defined according to the consensus statement from the International Diabetes Federation.[25] According to this definition, for a woman to be defined as having metabolic syndrome, she must have central obesity (waist circumference ≥80 cm) plus any 2 of 4 additional factors; raised triglycerides (≥1.7 mmol/L), reduced high-density lipoprotein cholesterol (<1.29mmol/L or treatment for lipid abnormalities), raised blood pressure (systolic blood pressure ≥130 or diastolic blood pressure ≥85 mm Hg or treatment of previously diagnosed hypertension), or raised fasting glucose (≥5.6 mmol/L or previously diagnosed type 2 diabetes).

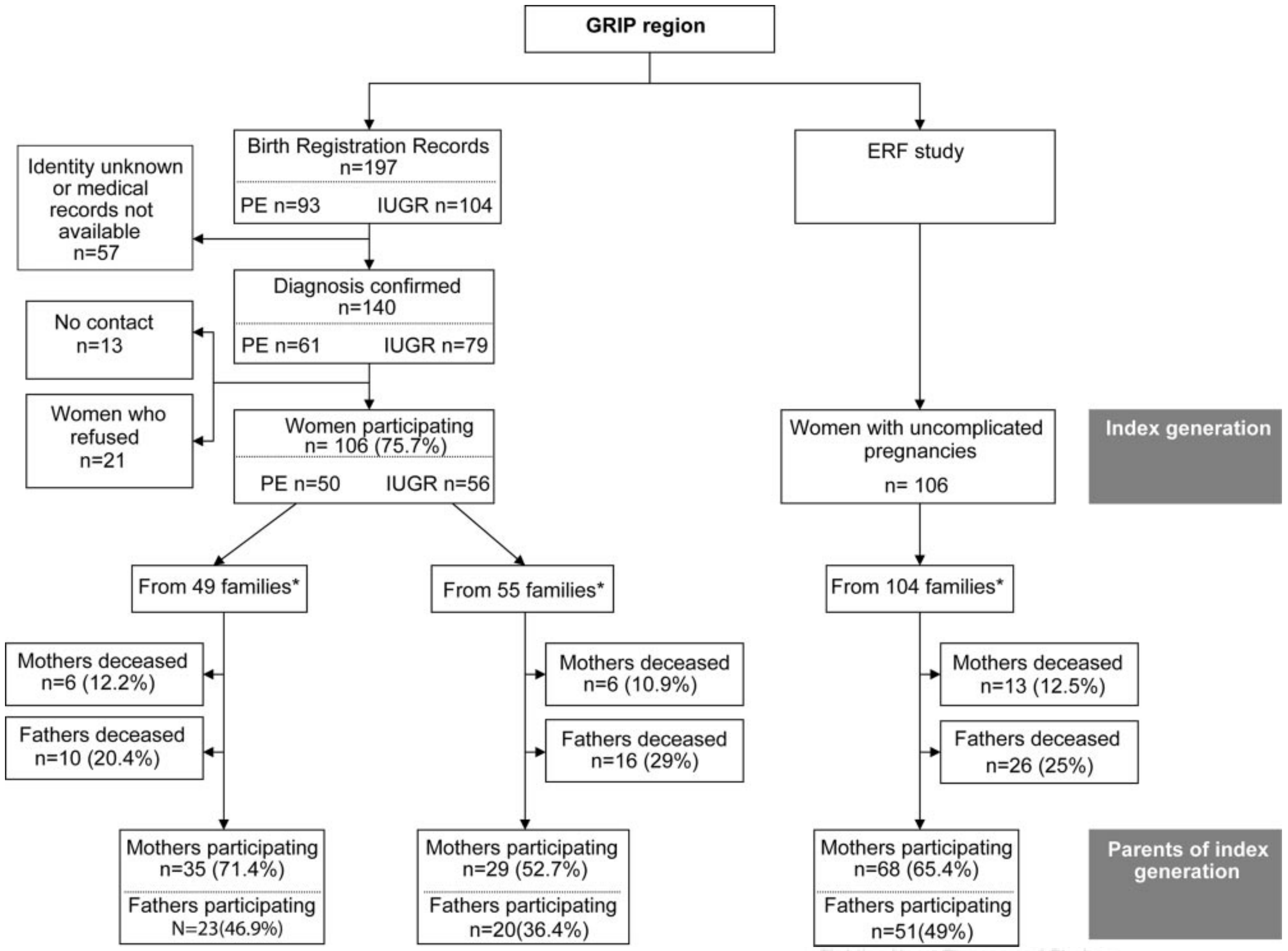

Figure 1. Flow diagram for recruitment of participants. PE indicates preeclampsia. *Differences between the number of families and number of participating women in index generation are explained by the fact that some of the women in the index generation are sisters.

Population for Analysis

For a description of baseline characteristics, all of the subjects were included. For subsequent analyses on anthropometrics, lipids, glucose levels, blood pressure measurements, and IMT, the following exclusion criteria were applied. Pregnant women and postmenopausal women were excluded from the "index generation" to create a more homogenous subgroup of premenopausal women only. Analogously, we excluded premenopausal women from the "mothers of the index generation," resulting in a group of postmenopausal women only. Subjects with diabetes mellitus or using lipid-lowering or antihypertensive medication were excluded from analyses on fasting glucose, lipids, and blood pressure, respectively. In the analyses on metabolic syndrome, all of the (nonpregnant) participants were included. Measurement of 1 blood sample in the preeclampsia group in the index generation failed. IMT measurements were available for a limited number of subjects, including 86 control subjects and 100 patients (n=48 for preeclampsia; n=52 for IUGR) in the index generation and for 107 mothers of the index generation (n=29 for preeclampsia; n=24 for IUGR; and n=54 for control subjects).

Statistical Analyses

Comparisons between groups were performed for women of the index generation, mothers, and fathers separately. General characteristics were compared using *t* test, χ^2 statistics, and Fisher's exact test where appropriate. Differences in cardiovascular risk factors were analyzed using univariate ANOVA. Risk estimates were assessed by cross-tabulations. For all of the statistical analyses we used SPSS for Windows, version 11.0.1.

Variables with skewed distribution were normalized using (natural) logarithm transformation. The analyses on anthropometrics were adjusted for age and time interval between delivery and pregnancy in the index generation and for age only in the parents of the index generation. Additional adjustments were made in the analyses on lipids and glucose levels for body mass index, smoking, use of antihypertensive medication, educational level, and hormone replacement therapy (only in mothers of the index generation). Similar adjustments, with the exception of antihypertensive medication, were made in the analyses on blood pressure. Analyses on IMT measurements were adjusted for age and time intervals between delivery and study.

Results

General Characteristics

General characteristics of case and control subjects of the index generation and their parents are depicted in Table 1.

Cardiovascular Risk Factors

Index Generation

Women with a history of preeclampsia had a significantly greater body mass index and larger waist circumference as compared with control subjects. After adjustment for body mass index, fasting glucose levels were significantly higher in

Table 1. General Characteristics of Index Generation and Parents of Index Generation

Characteristic	Preeclampsia	IUGR	Control Subjects
Index generation, n	50	56	106
Index pregnancy			
Age, mean (±SD), y	29.2 (±3.8)*	29.7 (±3.6)*	26.2 (±4.3)
Birth weight, mean (±SD), g	2559 (±886)*	2223 (±547)*	3345 (±379)
Gestational age, mean (±SD), k	37 (±3.4)*	38.6 (±2.8)†	39.9 (±1.4)
Early preeclampsia, n (%)	16 (32)	NA	NA
Current study			
Age, mean (±SD), y	36.2 (±5.8)†	39 (±5.3)	39.2 (±5.6)
Time interval delivery study, mean (±SD), y	7 (±5.6)*	9.3 (±4.6)*	13.1 (±5.7)
Educational level, n (%)			
Low	19 (38)*	39 (69.6)	77 (72.6)
Intermediate	24 (48)†	11 (19.6)	27 (25.5)
High	7 (14)†	6 (10.7)‡	2 (1.9)
Premenopausal status	48 (96)	52 (94.6)	101 (95.3)
No.	47§	56	106
Antihypertensive drugs, n (%)	9 (19.1)*	8 (14.3)†	1 (0.9)
Lipid-lowering drugs, n (%)	1 (2.1)	1 (1.8)	1 (0.9)
Diabetes mellitus, n (%)	2 (4.3)	2 (3.6)	0
Current smoking, n (%)	11 (22)†	31 (55.4)	52 (49.1)
Alcohol consumption, n (%)	16 (32)	15 (26.8)	33 (31.1)
Mothers of index generation, n	35	29	68
Age, mean (±SD), y	60.6 (±8.9)	61.9 (±6.4)	61.3 (±7.3)
Time interval delivery study, mean (±SD), y	35.2 (±5.1)	36.8 (±4.4)	36.9 (±5.8)
Hypertensive pregnancy complication, n (%)	13 (37.1)†	6 (20.7)	8 (11.8)
Educational level, n (%)			
Low	32 (91.4)	27 (93.1)	64 (94.1)
Intermediate	3 (8.6)	2 (6.9)	4 (5.9)
High	0	0	0
Postmenopausal status, n (%)	32 (91.4)	29 (100)	62 (91.2)
Hormone replacement therapy, n (%)	2 (5.7)	5 (17.2)	6 (8.8)
Anti hypertensive drugs, n (%)	15 (42.9)	14 (48.3)	21 (30.9)
Lipid lowering therapy, n (%)	8 (22.9)	8 (27.6)	17 (25)
Diabetes mellitus, n (%)	5 (14.3)	2 (6.9)	6 (8.8)
Current smoking, n (%)	12 (34.3)	11 (37.9)	34 (50)
Alcohol consumption, n (%)	17 (48.6)‡	6 (20.7)	16 (23.5)
Fathers of index generation, n	23	20	51
Age, mean (±SD), y	62.7 (±8.8)	63 (±5.0)	62.8 (±6.9)
Educational level, n (%)			
Low	17 (73.9)†	14 (70)†	50 (98)
Intermediate	6 (26.1)†	6 (30)†	1 (2)
High	0	0	0
Antihypertensive drugs, n (%)	9 (39.1)	7 (35)	20 (39.2)
Lipid lowering therapy, n (%)	4 (17.4)	6 (30)	13 (25.5)
Diabetes mellitus, n (%)	2 (8.7)	0	5 (9.8)
Current smoking, n (%)	5 (21.7)	7 (35)	19 (37.3)
Alcohol consumption, n (%)	18 (78.3)	14 (70)	32 (62.7)

Each comparison was performed between the case group (preeclampsia or IUGR) and the control group, using *t* test, χ^2, or Fisher's exact test. NA indicates not applicable.

*$P<0.001$.

†$P<0.01$.

‡$P<0.05$.

§Pregnant women (n=3) were excluded.

both formerly preeclamptic women and women with pregnancies complicated by IUGR than in women with uncomplicated pregnancies. Similar levels of total serum cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were found in all of the groups. Elevated systolic and diastolic blood pressures were observed in women with a history of preeclampsia (Table 2). Diagnosis of hypertension was 5 times more common in formerly preeclamptic women compared with control subjects (46.7% versus 8.9%; $P<0.001$) and 3 times in women with IUGR-complicated pregnancies (26.9% versus 8.9%; $P<0.01$). Intima-media thickness of the common carotid artery was not significantly different between case subjects (median, interquartile range, for preeclampsia: 0.66 mm, 0.58 to 0.73 mm; for IUGR: 0.65 mm, 0.6 to 0.74 mm) and control subjects (0.68 mm, 0.62 to 0.74 mm). However, after stratification for hypertension, we found increased IMT in women with hypertension compared with women without the diagnosis of hypertension in the preeclampsia group (0.72 mm, 0.6 to 0.78 mm versus 0.65 mm, 0.58 to 0.69 mm, respectively; $P<0.01$) and the IUGR group (0.72 mm, 0.67 to 0.88 mm versus 0.64 mm, 0.59 to 0.71 mm, respectively; $P=0.08$). No differences were found after stratification in the control group (0.7 mm, 0.63 to 0.77 mm versus 0.68 mm, 0.62 to 0.74; $P=0.9$).

Early Versus Late-Onset Preeclampsia

Diastolic blood pressure was higher in women with early onset preeclampsia compared with those with late-onset disease (median, interquartile range: 88 mm Hg, 77 to 93 mm Hg for early onset; 81 mm Hg, 72 to 88 mm Hg for late onset; $P=0.04$). Diagnosis of hypertension was more common in the early onset than the late-onset group (66.7% for early onset and 34.4% for late onset; $P=0.04$). No significant differences were found in the remaining risk factors.

Mothers of Index Generation

Fasting glucose levels, waist circumferences, and systolic blood pressures were significantly higher in mothers of preeclamptic women but not in mothers of women with pregnancies complicated by IUGR compared with control mothers (Table 2). Hypertension was more frequent in mothers of women with a history of preeclampsia, although not significantly (59.4% in mothers of preeclamptic women; 63% in mothers of IUGR women; and 42.6% in control mothers; $P=0.1$ and $P=0.08$, respectively). IMT of the common carotid artery was not significantly different between mothers of case subjects (median, interquartile range, for preeclampsia: 0.86 mm, 0.78 to 1.1 mm; for IUGR: 0.93 mm, 0.88 to 1.0 mm) and mothers of control subjects (0.95 mm, 0.85 to 1.0 mm). After stratification for hypertension, mothers with the diagnosis of hypertension in the preeclampsia (0.98 mm, 0.8 to 1.1 mm versus 0.83 mm, 0.76 to 0.94 mm; $P=0.3$), IUGR (0.94 mm, 0.87 to 1.1 mm versus 0.92 mm, 0.87 to 0.95 mm; $P=0.5$), and the control group (0.99 mm, 0.94 to 1.2 mm versus 0.9 mm, 0.8 to 0.99 mm; $P=0.2$) tend to have increased IMT compared with mothers without hypertension, although not significant. Exclusion of mothers who reported an obstetric history with preeclampsia or pregnancy-induced hypertension (n=13 in the group of mothers of preeclampsia women; n=5 in the mothers of IUGR women; and n=8 in the control mothers) did not significantly change the results.

Fathers of Index Generation

Fasting glucose levels were significantly higher in fathers of formerly preeclamptic women and women with pregnancies complicated by IUGR compared with control subjects. Fathers of preeclamptic women showed lower concentrations of cholesterol and low-density lipoprotein cholesterol compared with fathers of women with pregnancies complicated by IUGR and control subjects (Table 2).

Metabolic Syndrome

The prevalence of metabolic syndrome in the index generation was 3-fold higher in women with a history of preeclampsia compared with control subjects (Figure 2). No significant difference in the prevalence of metabolic syndrome was found between women with IUGR and control subjects. A similar pattern was observed with regard to comparisons between mothers (Figure 2). Mothers of women with a history of preeclampsia had a 1.6-increased risk (relative risk; 95% CI: 1.1 to 2.2) of having metabolic syndrome as estimated by the relative risk. For mothers of women with pregnancies complicated by IUGR, this risk was also increased, but the association was not significant (relative risk: 1.5; CI 95%: 1.0 to 2.2).

Discussion

In the present study, women with pregnancies complicated by preeclampsia or IUGR and their mothers have unfavorable cardiovascular risk profiles marked by higher glucose levels, prevalence of hypertension, and larger waist circumferences compared with women with uncomplicated pregnancies and their mothers. Our findings suggest shared constitutional risks for vascular-related pregnancy complications and future cardiovascular disease.

This study is the first that we are aware of that assessed biochemical and anthropometric risk factors of cardiovascular disease not solely in women with a history of preeclampsia and IUGR but also in their parents. We hypothesized that intergenerational similarities in risk profiles substantiate the hypothesis that a predisposition to cardiovascular disease underlies preeclampsia and IUGR.

The most marked similarity in risk profiles of women with a history of preeclampsia and their mothers and fathers was the finding of higher fasting glucose levels. These findings could not be explained by differences in body mass index. These results are in line with the results of studies describing an association with hyperinsulinemia and higher HbA1C levels in women 15 to 25 years after preeclampsia.[26,27] The higher glucose levels, although still in the reference range, are predictive for an increased risk of cardiovascular disease and type 2 diabetes.[28] Women with a history of preeclampsia had previously been suggested to be at increased risk of developing type 2 diabetes.[29] Also in women with IUGR-complicated pregnancies and their fathers we found higher fasting glucose levels. This is in accordance with a previous cross-sectional

Table 2. Cardiovascular Risk Factors of Index Generation and Parents of Index Generation

Risk factor	Preeclampsia	IUGR	Control Subjects
Index generation, n	45*	52*	101*
Body mass index, median (interquartile range), kg/m^2	27.2 (23.9 to 33.1)†	23.6 (21.6 to 25.9)	24.4 (21.8 to 27.5)
Waist circumference, median (interquartile range), cm	90 (76.8 to 103.8)†	79.9 (71.5 to 85)	77.6 (71.5 to 83)
No.	42‡	50‡	101‡
Fasting glucose, median (interquartile range), mmol/L	4.8 (4.4 to 5.2)†	4.7 (4.2 to 4.9)†	4.2 (3.8 to 4.5)
No.	43§	51§	100§
Cholesterol, median (interquartile range), mmol/L	4.8 (4.4 to 5.8)	5.3 (4.7 to 6.0)	5.4 (4.6 to 6.2)
LDL cholesterol, median (interquartile range), mmol/L	3.0 (2.6 to 3.8)	3.6 (2.9 to 4.3)	3.6 (2.9 to 4.1)
HDL cholesterol, median (interquartile range), mmol/L	1.3 (1.1 to 1.6)	1.3 (1.1 to 1.5)	1.3 (1.1 to 1.6)
Ratio cholesterol/HDL, median (interquartile range)	3.8 (3.1 to 4.6)	4.2 (3.3 to 4.8)	3.9 (3.3 to 4.7)
Triglycerides, median (interquartile range), mmol/L	1.0 (0.7 to 1.6)	0.9 (0.7 to 1.3)	1.0 (0.7 to 1.3)
No.	36‖	44‖	100‖
Systolic blood pressure, median (interquartile range), mm Hg	126 (120 to 144)¶	121 (113 to 135)	121 (115 to 130)
Diastolic blood pressure, median (interquartile range), mm Hg	81 (72 to 89)#	76 (70 to 84)	75 (69 to 79)
Mothers of index generation, n	32**	29**	62**
Body mass index, median (interquartile range), kg/m^2	28.1 (26.3 to 32.6)	27.8 (24.6 to 30.9)	28.2 (25.9 to 31.4)
Waist circumference, median (interquartile range), cm	96 (88.9 to 105.6)#	92 (81.9 to 102.8)	90.3 (82.0 to 97.3)
No.	27‡	27‡	56‡
Fasting glucose, median (interquartile range), mmol/L	5.2 (4.6 to 5.6)#	4.8 (4.4 to 5.1)	4.6 (4.2 to 5.0)
No.	25§	21§	45§
Cholesterol, median (interquartile range), mmol/L	5.9 (5.0 to 6.6)	6.0 (5.3 to 6.4)	6.4 (5.8 to 7.1)
LDL cholesterol, median (interquartile range), mmol/L	3.8 (2.9 to 4.5)	4.0 (3.5 to 4.6)	4.4 (3.8 to 5.0)
HDL cholesterol, median (interquartile range), mmol/L	1.3 (1.2 to 1.7)	1.3 (1.2 to 1.7)	1.4 (1.2 to 1.6)
Ratio cholesterol/HDL, median (interquartile range)	4.4 (3.3 to 5.5)	4.5 (3.8 to 5.3)	4.6 (3.9 to 5.5)
Triglycerides, median (interquartile range), mmol/L	1.3 (1.0 to 1.9)	1.3 (1.1 to 1.6)	1.4 (1.0 to 1.9)
No.	17‖	15‖	43‖
Systolic blood pressure, median (interquartile range), mm Hg	152 (140 to 177)¶	139 (129 to 163)	140 (129 to 153)
Diastolic blood pressure, median (interquartile range), mm Hg	85 (77 to 93)	81 (74 to 85)	80 (74 to 86)
Fathers of index generation, n	23	20	51
Body mass index, median (interquartile range), kg/m^2	26.9 (24.4 to 30.3)	26.2 (24.5 to 28.2)	27.1 (24.4 to 29.4)
No.	21‡	20‡	45‡
Fasting glucose, median (interquartile range), mmol/L	5.2 (5.0 to 5.7)¶	5.1 (4.8 to 5.8)¶	4.8 (4.3 to 5.3)
No.	19§	14§	38§
Cholesterol, median (interquartile range), mmol/L	4.7 (4.1 to 5.3)#	5.3 (4.3 to 5.8)	5.6 (5.1 to 6.2)
LDL cholesterol, median (interquartile range), mmol/L	3.1 (2.6 to 3.6)#	3.4 (2.8 to 3.8)	3.8 (3.4 to 4.5)
HDL cholesterol, median (interquartile range), mmol/L	1.1 (0.7 to 1.4)	1.1 (0.9 to 1.2)	1.0 (0.9 to 1.2)
Ratio cholesterol/HDL, median (interquartile range)	4.3 (3.2 to 5.3)	5.2 (3.9 to 6.0)	5.6 (4.5 to 6.5)
Triglycerides, median (interquartile range), mmol/L	1.2 (0.8 to 1.6)	1.6 (1.0 to 1.9)	1.6 (1.1 to 2.4)

Each comparison was performed between the case group (preeclampsia or IUGR) and the control group, using ANOVA. LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

*Pregnant women and postmenopausal women were excluded.

†$P<0.001$.

‡Subjects with diabetes mellitus were excluded.

§Subjects using lipid-lowering medication were excluded.

‖Subjects using antihypertensive medication were excluded.

¶$P<0.05$.

#$P<0.01$.

**Premenopausal women were excluded.

study showing an association between insulin resistance in women at older age and low birth weight offspring.[30]

Intergenerational similarities were also found for hypertension. Previous preeclamptic women, at a relative young age, as well as their mothers, have a higher prevalence of chronic hypertension, with hypertension being even more prevalent after early onset than late-onset preeclampsia. Similarly, women with a history of a pregnancy complicated by IUGR

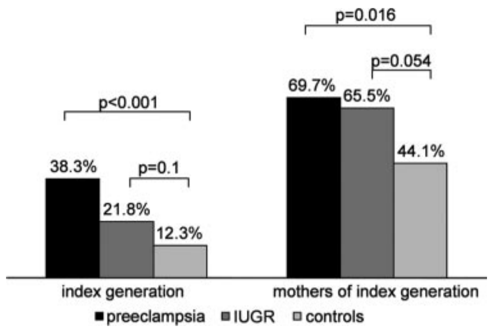

Figure 2. Prevalence of metabolic syndrome in index generation and mothers of index generation. All of the participants were included except for 3 pregnant women in the preeclampsia group.

and their mothers were diagnosed with chronic hypertension more often than control subjects but less frequently than previously preeclamptic women. These findings correspond with previous studies[27,31] and are consistent with the observation that preeclamptic women more frequently have a family history of hypertension.[10,13] Carotid IMT, which is used as a marker of subclinical atherosclerosis,[23,32] was increased in this specific subset of women who were diagnosed with chronic hypertension as compared with those without hypertension.

In addition, we found that women with a history of preeclampsia have larger waist circumferences, as well as their mothers, when compared with control subjects. Likewise, women with pregnancies complicated by IUGR, as well as their mothers, tend to have larger waist circumferences than control subjects, although not significantly. This points at an unfavorable, that is, abdominal, fat distribution in women with preeclampsia, which is known to be strongly associated with the metabolic syndrome[25] and, thus, with increased risk of future cardiovascular disease. Indeed, metabolic syndrome was more prevalent in women with a history of preeclampsia compared with control subjects. Consistent with studies describing a familial history of cardiovascular disease in women with preeclampsia,[13] we found that metabolic syndrome was also more prevalent in mothers of women with a history of preeclampsia.

Hyperglycemia, hypertension, and (abdominal) obesity[14,33] are associated with impaired endothelial function. Therefore, our data fit the hypothesis of Ness and Sibai[2] in which they propose that both women with preeclampsia and IUGR-complicated pregnancies enter pregnancy with some degree of endothelial dysfunction predisposing to poor placentation. Abnormal placentation occurring in women with concurrent metabolic syndrome would result in preeclampsia, whereas in the absence of metabolic syndrome, IUGR would develop. Accordingly, we found that metabolic syndrome, as compared with control subjects, was more prevalent in women with a history of preeclampsia.

The strength of this study is the intergenerational study design that provides the opportunity to explore the constitutional origin of the risk factors. We consciously use the term "constitutional" to indicate that (subclinical) risk factors were likely to be present in women before pregnancy without making any assumptions on their genetic and/or environmental origin. The similarities in risk profiles, particularly for fasting glucose levels, are suggestive for familial aggregation of these traits in families with preeclampsia and IUGR. Previous studies demonstrated genetic influence for familial clustering of features of the metabolic syndrome.[34,35] Whether familial aggregation in our study is because of shared environmental and/or genetic factors cannot be concluded. Nonetheless, our data suggest a potential role for the glucose metabolism in the pathogenesis of both pregnancy disorders. Another interpretation of our data could be that higher levels of fasting glucose are one of the first features marking an unfavorable metabolic and/or vascular phenotype, as described by Haffner et al,[36] who found in a prospective study that elevations of insulin concentrations precede numerous metabolic disorders.

A limitation of this study is the low response rate of the parents, particularly of women with a history of IUGR. However, we have no strong evidence for a selection bias, because the prevalence of hypertension in participating and nonparticipating parents, based on statements of women in the index generation about their parents' health, was not significantly different. Yet, because these comparisons were based on small numbers, selection bias cannot be definitively excluded.

Aside from the etiologic implications, our study has important clinical implications. More than 40%, and ≈30% of women in our study with pregnancies complicated by preeclampsia or IUGR, within a decade after the index pregnancy, are diagnosed with chronic hypertension. For metabolic syndrome, these numbers are ≈40% and 20%, respectively. Identification and follow-up of these women in clinical practice are of major importance, because long-term consequences may be reduced or avoided by preventive strategies. The subset of women with hypertension should be especially recognized and followed up on, because we demonstrated that these women, despite their relative young age, already have subclinical atherosclerosis.

Perspectives

Women with pregnancies complicated by preeclampsia or IUGR have a constitutionally determined, unfavorable vascular and metabolic profile. Given the high prevalence of cardiovascular disease, it is essential that clinicians consider preeclampsia or pregnancies complicated by IUGR as novel, distinct risk indicators of cardiovascular disease.

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Disclosures

None.

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