

Maternal and fetal genetic risk for pre-eclampsia impact fetal growth trajectories throughout pregnancy

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Objectives

To evaluate the effect of genetic variants associated with pre-eclampsia (PE) on fetal growth and blood flow throughout pregnancy. We aimed to assess the effect of both maternal and fetal genetic variants.

Methods

We used data from the prospective Roskilde pregnancy cohort, comprising 1,179 women enrolled at 12–13 weeks of gestation and followed with ultrasound assessments of fetal growth and blood flow at 20, 25 and 32 weeks. Birth weight and placental weight were recorded at birth. Fetal growth trajectories were modelled using mixed linear regression adjusted for maternal age, BMI and fetal gender. Genotypes were available in 1165 mothers and 655 newborns. A genetic risk score (GRS) of GWAS-identified variants associated with PE were calculated to assess the effects on fetal growth, blood flow and placental weight. A genetic risk above 95% centile was considered high. We evaluated effects of transmission of a high GRS from mother to child.

Results

Fetal PE GRS was associated with altered growth trajectory of the femoral bone length (p=0.04) and decreased placental weight (p=0.034). In addition, the fetal PE GRS showed a trend towards association with fetal growth restriction (FGR) at birth (p=0.07) but not with overall fetal growth trajectories. Maternal PE GRS was associated with occurrence of decreased placental weight (p=0.026), suggesting that the effect of fetal and maternal PE GRS is primarily mediated through effects on placenta. Interestingly, when a high genetic PE risk was present in both mother and child, we found significant association with overall fetal growth trajectories from week 20 to birth (p<0.001). The effect on fetal growth trajectories was primarily driven by decreased abdominal circumference (p<0.001). In addition, we found a strong association with altered umbilical artery pulsatility index (PI) and middle cerebral artery PI (p=0.001).

Conclusions

Genetic variants associated with PE have substantial effects on fetal growth and blood flow.

Variable	Median (1 st ; 3 rd quartile)/ n(%)
Maternal age	31 (27;34)
Parity	
0	404 (35.8%)
1	422 (37.4%)
2	165 (14.6%)
3	25 (2.2%)
4	6 (0.5%)
unknown	90 (9.5%)
BMI	23.5 (21.4; 27.1)
Smoking	92 (8.2%)
Preeclampsia in pregnancy	9 (0.8%)
Hypertension in pregnancy	46 (4.1%)
SGA (-15%-21%)	49 (4.3%)
FGR (<-22%)	21(1.9%)
Gestational age at birth (days)	280 (273; 286)
Birth weight	3550 (3250; 3870)

Table 1: Demographic description of cohort (n=1129)

Variable	PE GRS Effect size (95% CI)	p-value
Growth from week 20 to birth	3.65 x 10 ⁻³ (1.67 x 10 ⁻³ - 5.64 x 10 ⁻³)	1.94 x 10 ^{-5*}
Growth from week 20-32	2.38 x 10 ⁻³ (1.09 x 10 ⁻³ - 3.68 x 10 ⁻³)	7.33 x 10 ^{-5*}
OFD	6.29 x 10 ⁻⁵ (-2.64 x 10 ⁻⁶ - 1.28 x 10 ⁻⁴)	0.062
BPD	4.71 x 10 ⁻⁶ (-1.73 x 10 ⁻⁵ - 1.11 x 10 ⁻⁴)	0.708
AC	2.21 x 10 ⁻⁴ (9.87 x 10 ⁻⁵ - 3.44 x 10 ⁻⁴)	4.87 x 10 ^{-5*}
FL	1.80 x 10 ⁻⁵ (-1.73 x 10 ⁻⁵ - 5.34 x 10 ⁻⁵)	0.400
UA	-0.12 (-0.20-0.038)	6.04 x 10 ^{-3*}
MCA	-0.75 (-1.22-0.27)	0.001*
UtA	-0.01 (-0.21- 0.19)	0.908
Birth weight	578.9 (-52.11- 1209.92)	0.081
Placental weight	84.76 (-6.24- 175.76)	0.068
FGR	-0.21 (-0.47- 0.05)	0.115

Table 3: The effect of transmission of a high PE GRS from mother to child