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Development

Early-pregnancy origins of low birth weight

Low birth weight is a significant cause of morbidity and mortality among newborns, and may result from impaired placental function during the first trimester of pregnancy[1]. Here we show that the risk of delivering a low-birth-weight baby at term after an uncomplicated pregnancy varies with maternal circulating concentrations of a placental protein, pregnancy-associated plasma protein-A (PAPP-A) in the first 10 weeks after conception. Poor fetal growth may therefore already have been determined by the time obstetric monitoring begins after completion of the first trimester.

PAPP-A acts as a protease on the binding proteins of insulin-like growth factor (IGF)[2,3] and may therefore increase the known stimulatory effects of placental IGFs[4]. Circulating concentrations of PAPP-A increase during the first three months of pregnancy, and this protein is highly expressed in trophoblasts[5]. We therefore investigated a possible link between the birth weight of a baby at term and maternal levels of PAPP-A during the first trimester. We determined the specificity of associations with PAPP-A by comparing it with the free β-subunit of human chorionic gonadotrophin (β-CG), another trophoblast-derived protein whose circulating levels change in the first trimester[6] but which is functionally unrelated to the IGF system.

As part of a prospective, multicentre, non-interventional cohort study, we obtained serum from 4,288 women at 8–12 weeks of gestation (dated by ultrasound, equivalent to 6–10 weeks after conception), who ultimately had uncomplicated singleton pregnancies and delivered normal, live babies at full term. We had complete data for these women on maternal age, parity, height, body-mass index, race and smoking status.

Serum levels of PAPP-A and free β-CG were measured using a Kryptor immunoassay analyser (Brahms Diagnostica) and converted to multiples of the appropriate gestational median (MOM), corrected for smoking status[7] and maternal weight[8].

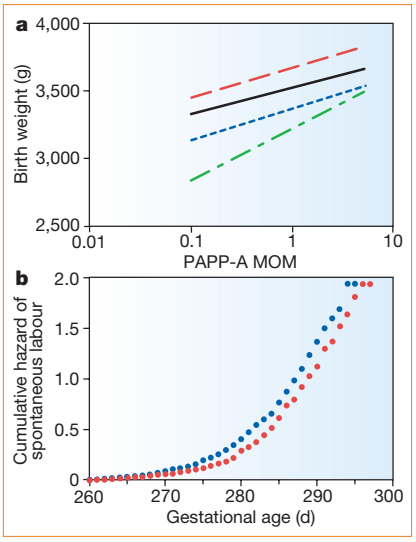

Figure 1 Association between pregnancy-associated plasma protein-A (PAPP-A), birth weight at 38–41 weeks of gestation and timing of labour at full term. **a,** Eventual birth weight plotted against PAPP-A multiples of the median (MOM; on a $\log_{10}$ scale) from a linear regression analysis. Curves (from bottom to top) represent gestational ages of 38, 39, 40 and 41 weeks. Coefficients (95% CI) for change in birth weight associated with a one $\log_{10}$ unit change in PAPP-A MOM: 38 weeks, 380 (209–552); 39 weeks, 231 (113–349); 40 weeks, 196 (104–289); 41 weeks, 221 (112–331); $P < 0.0001$ in each case. Coefficients were virtually unchanged after adjusting for age, parity, body-mass index, height, smoking status and race. **b,** Cumulative hazard (Nelson–Aelen cumulative hazard function[10]) of spontaneous labour on each day of gestation at full term, comparing the lowest (top curve) and highest (bottom curve) quintiles of first-trimester PAPP-A MOMs. Univariate comparison, $P = 0.0003$ (log rank test).

There was a greater proportion of low-birth-weight infants (under 2,500 g) delivered to women with a first-trimester PAPP-A concentration in the lowest 5% (9 out of 201, 4.5%) compared with other women (65 out of 4,087, 1.6%; $P = 0.002$). Using multivariate logistic regression (adjusting for maternal height, race, body-mass index, smoking status and elective delivery), a one $\log_{10}$ unit increase in first trimester PAPP-A MOM (roughly equivalent to the range from the 1st to the 99th percentile) was associated with an 80% reduction in the risk of a low-birth-weight baby (adjusted odds ratio, 0.2; 95% CI, 0.1–0.6; $P = 0.002$). In contrast, there was no significant independent relationship in the case of free β-CG (adjusted odds ratio, 0.6; 95% CI, 0.2–1.3; $P = 0.17$).

The factors that determine variation in birth weight are fetal growth and the duration of pregnancy. We examined the relationship between PAPP-A concentration and fetal growth using multiple linear-regression analysis, and identified a strong, positive correlation between first-trimester levels of PAPP-A and eventual birth weight at 38–41 weeks of gestation (Fig. 1a). There was no strong association between free β-CG levels and birth weight at the same gestational age.

The relationship between first-trimester concentrations of PAPP-A or free β-CG and the timing of labour at full term was determined using time-to-event analysis[9]. Vaginal delivery after non-induced labour was taken as the event and all other modes of delivery were treated as censored. Lower concentrations of PAPP-A during the first trimester were associated with an earlier onset of spontaneous labour at full term (Fig. 1b).

In a multivariate proportional hazards model, there was a strongly additive and inverse relationship between levels of PAPP-A and free β-CG, and the likelihood of spontaneous labour on any given day of gestation at full term (adjusted hazard ratio for a one $\log_{10}$ unit change in MOM (95% CI): PAPP-A, 0.81 (0.69–0.96), $P = 0.003$; free β-CG, 0.79 (0.69–0.91), $P < 0.001$).

The association between PAPP-A levels, fetal growth and the timing of labour is biologically plausible, as PAPP-A is highly expressed in first-trimester trophoblasts[5] and may be responsible for activation of IGFs. Our results indicate that the risk of delivering a low-birth-weight baby at full term may be determined by the placental activity of IGFs in very early pregnancy.

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