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Early retinol-binding protein levels are associated with growth changes in infants born to diabetic mothers

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Summary

Background: Biochemical predictors of infants' growth changes are not available.

Objectives: We tested whether retinol-binding protein (RBP), docosahexaenoic acid and insulin (I) measured within 72 h from birth are associated with growth changes in infants born to mothers with gestational diabetes mellitus (GDM).

Methods: Fifty-six children, 32 born to diabetic mothers treated with insulin (GDM-I) and 24 born to diabetic mothers treated with diet (GDM-D), were evaluated at 0, 1, 3, 6 and 12 months of life.

Results: At multivariable regression performed using generalized estimating equations, early RBP levels and maternal body mass index were associated to average weight changes and early RBP and insulin levels to average length changes, respectively. There was no difference between GDM-I and GDM-D infants.

Conclusions: This exploratory study suggests that early RBP levels may be a predictor of growth changes.

Keywords: Docosahexaenoic acid, gestational diabetes, growth, retinol-binding protein.

Metabolic and nutritional adaptations to the intrauterine and early post-natal environment may cause metabolic derangements leading to obesity, type 2 diabetes mellitus and cardiovascular disease (1). Metabolic programming is the phenomenon whereby a nutritional stress applied during critical periods of early development permanently alters host metabolism, with consequences to be observed later in life. In particular, accelerated growth rates in the early stages of life may increase the risk of adult overweight (2). Gestational diabetes mellitus (GDM) is associated with a higher risk of later metabolic disease for the offspring. Infants born to diabetic mothers have also a higher risk of early weight gain (3). Differently from anthropometric indicators, no data are available on the ability of biochemical markers to identify infants at risk of growth acceleration. We performed an exploratory study to test whether selected anabolic markers, i.e. retinol-binding protein (RBP), docosahexaenoic acid (DHA) and insulin (I), are associated with growth changes in infants born to diabetic mothers. RBP is a marker of short-term nitrogen incorporation into proteins (4) while DHA is a polyunsaturated fatty acid with a permissive role on anabolism and insulin action (5).

Fifty-six infants were consecutively enrolled into the study. GDM was diagnosed using an oral glucose tolerance test following current guidelines. Gestational age <30 weeks, congenital malformations, hypoxic-ischaemic encephalopathy,

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cardiorespiratory instability, early infections, multiple gestations, assisted reproduction, drug usage, alcohol abuse and intrauterine growth restriction, were reasons of exclusion from the study. The study was approved by the local ethical committee and the legal guardians of the children gave a written consent. At the time of the Guthrie test, between 48 h and 72 h from birth and from 2 h to 3 h from the last feeding, blood was collected at about 8:00 a.m. for further analysis. RBP (immunonephelometry), DHA (gas chromatography of whole blood after transmethylation) and I electrochemiluminescence immunoassay were measured. Weight and length were measured at 0, 1, 3, 6 and 12 months following standard guidelines. Standard deviations scores (SDS) of weight and length were calculated using World Health Organization (WHO) growth data (Anthro Software 2005, WHO). Maternal body mass index (BMI) was calculated from pre-pregnancy weight and height. No formal sample size calculation was performed as this was an exploratory study.

Continuous variables are reported as median and interquartile range (IQR) because of skewed distributions. IQR was calculated as the difference between the 75th and 25th percentile. Between-group comparisons were performed with the exact Wilcoxon-Mann-Whitney test for continuous variables and with Fisher's exact test for categorical variables. Generalized estimating equations (GEE) were used to evaluate the multivariable association of RBP, DHA and I with average growth changes after correction for potential confounders. GEE give a population-average or marginal model, i.e. they quantify how much the average response would change across the population for a 1-unit increase of the covariate (6). The outcome variables of GEE models were weight SDS (continuous) and length SDS (continuous) and the predictors were (i) time (continuous), (ii) early RBP (continuous), (iii) early DHA (continuous), (iv) early insulin (continuous), (v) gender (0 = female; 1 = male), (vi) gestational week (continuous), (vii) maternal BMI (continuous) and (viii) treatment of GDM with insulin (0 = no; 1 = yes). The within-subject correlation matrix of GEE was set as exchangeable and robust 95% confidence intervals were calculated. GEE can handle missing data under the assumption of missingness completely at random (MCAR). Multivariable fractional polynomials were used to account for non-linear associations between outcomes and continuous predictors (7).

Fifty-six infants were consecutively enrolled, 32 born from GDM-I and 24 from GDM-D mothers. Nine (28%) of GDM-I and seven (29%) of GDM-D infants were preterm. 80% of children had both parents born in Italy while 20% had at least one parent born outside Italy. Gender distribution (56% vs. 54% males, exact $P = 1.0$) and gestational age (38 [4] vs. 38 [3] weeks, median (IQR), exact $P = 0.6$)were similar in GDM-I and GDM-D infants. Data from infants with missing data (≤20%) at 1, 3, 6 and 12 months were not discarded but modelled using GEE under the MCAR assumption.

Early RBP levels and maternal BMI were associated to average weight changes and early RBP and insulin levels to average length changes (Fig. 1). Being a GDM-I or GDM-D infant did not contribute to average changes of weight and length. RBP was associated with a negative SDS of weight change, i.e. an SDS < 0, up to values of 10 μg/dL, with a maximal association at 5 μg/dL. The effect of maternal BMI on the same outcome ranged from –1.0 SDS at 17.8 kg m^{-2} to +1.0 SDS at 40.0 kg m^{-2} and above. RBP was associated with a negative SDS of length change up to values of 10 μg/dL, with a maximal association at 5 μg/dL. The effect of insulin on the same outcome ranged from +1.0 SDS at 5 μU mL^{-1} to +1.5 SDS at 40 μU mL^{-1} and above.

Our exploratory study shows that early RBP has the potential to serve as surrogate marker of growth development up to 1 year of age in infants born to women with GDM. RBP levels are quite sensitive to nutritional interventions (8). Cord serum RBP-4 and insulin levels were associated with birth weight in fetuses at the top and bottom quartiles of birth weight, suggesting a possible regulatory role for RBP in fetal growth (9). To what extent the associations that we found between RBP and average changes of weight and length may be due to nutritional programming may be just a matter of speculation. As for the other predictors, maternal BMI had an independent association with average weight changes, and the anabolic hormone insulin with average length changes. A high pre-pregnancy maternal BMI is associated with acceleration of infant weight progression (10) and early insulin levels exert permissive roles on length accretion in the first year of life (11). These predictors may have different long-term effects because, on average, an early weight gain tends to be associated with the metabolic syndrome and an early length gain with health benefits (12). Recent reports have shown associations between RBP-4, BMI and insulin resistance in children and adolescents (13), but the programming effect of early RBP levels on later RBP synthesis is presently unknown. In the case of other anabolic compounds, i.e. insulin growth factor I, an inverse relation was found between early and later levels (14). DHA blood levels were not associated with average weight or length changes, but the exploratory

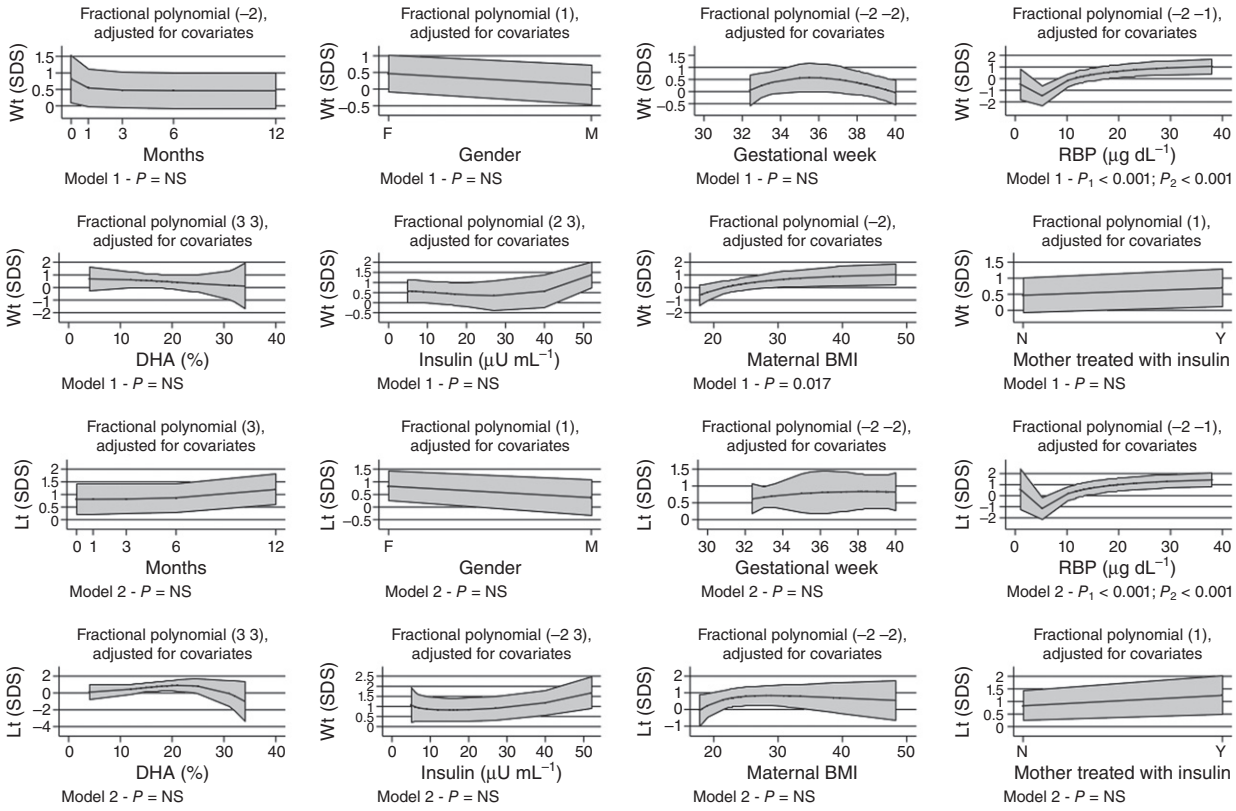

Figure 1 Association between RBP at birth, DHA at birth and insulin at birth and standard deviation scores (SDS) of average weight change (Wt, model 1) and average length change (Lt, model 2) after correction for time, gender, gestational week, maternal BMI and maternal treatment. Grey bands are robust 95% confidence intervals. NS, not significant. A degree 1 fractional (FP) polynomial has one term between parentheses (–2 = $1/X^2$; 1 = X (linear); 3 = X^3) while a degree 2 fractional polynomial has two terms between parentheses (7).

nature of this study does not allow for definitive conclusions. It is at least plausible that potential indicators of later growth could be detected among markers of nitrogen metabolism rather than among compounds exerting permissive roles on insulin action as DHA (5). Our study focused on infants born to diabetic mothers because they are predisposed to rapid early growth, especially weight acceleration. However, 28% of our infants were premature and no nutritional data were available for all infants. The RBP growth association identified by the present study should be further examined in infants born to healthy mothers, especially those small and large for gestational age. If the RBP growth association is confirmed in larger and external sample populations, it may useful to predict the later risk of disease and to devise early preventive strategies (15,16).

Authors' contribution

Gaia Francescato, Massimo Agosti and Elena Pastò were responsible for the study design and data collection. GianVico Melzi d'Eril, Alessandra Barassi and Patrizia Risè performed the laboratory measurements. Giorgio Bedogni performed the statistical analysis. Carlo Agostoni contributed to the study design and wrote the final draft.

Conflict of Interest Statement

Nothing to declare.

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