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Cord blood triglycerides are associated with IGF-I levels and contribute to the identification of growth-restricted neonates

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ABSTRACT

Objective: The aim of this study was to investigate whether readily available laboratory tests may aid in the identification of growth-restricted neonates.
Design: Cord serum levels of 15 chemical analytes, including insulin-like growth factor I (IGF-I) and insulin-like growth factor binding protein 3 (IGFBP-3) were measured in newborns ≥36 weeks gestational age (GA). Based on the number of anthropometric indices (out of four) with values ≤25th centile for GA, the babies were allocated into three groups, i.e., $Group_{25}0$, $Group_{25}1$ and $Group_{25}2$ corresponding to neonates with 0, 1 and 2 or more indices, respectively, that were ≤25th centile for GA. Furthermore, two composite variables were developed: A25 ($Group_{25}0$ and $Group_{25}1$) and B25 ($Group_{25}0$ and $Group_{25}2$). The data were evaluated by the Mann–Whitney test and multiple regression analyses.
Results: Cord serum triglycerides and total cholesterol levels were significantly higher in $Group_{25}2$ compared to $Group_{25}0$ (p values 0.004 and 0.0009, respectively). The triglycerides almost doubled the power of the variable B25 for predicting IGF-I levels and were found to have a highly significant, negative association with the IGF-I levels ($p<0.0001$). The IGF-I along with the IGFBP-3 levels explained almost one third of the variation of triglycerides.
Conclusion: Cord serum triglycerides can assist in the identification of growth-restricted neonates. The novel finding of the association of triglycerides with IGF-I calls for further research as this can illuminate unknown aspects of the fetal lipid metabolism.

1. Introduction

Numerous studies over the last two decades relate in utero growth-restriction (IUGR) with long-term morbidities, extending late into adulthood. IUGR is a well-known, major contributor to perinatal morbidity and mortality. Growth-restricted newborns are known to be prone to develop hypoglycemia (due to miscellaneous pathophysiological mechanisms including hyperinsulinism), hypocalcemia, hyperviscosity, feeding difficulties, necrotizing enterocolitis, and even sudden infant death syndrome [1]. Therefore, it is of crucial importance that those providing neonatal care possess a reliable and practical instrument for the prompt and accurate identification of the growth-restricted babies.

In daily practice, newborns are classified as growth-restricted based on their birth weight, despite a broad agreement that birth weight per se is a poor diagnostic marker for growth-restriction and an insufficient indicator of fetal growth. Birth weight as a single diagnostic marker misclassifies constitutionally small babies as growth-restricted and fails to detect IUGR newborns, who have birth weights above the specified cut-off level. In utero growth-restriction is a highly complex process with respect to etiology, timing and duration of the adverse intrauterine events. It has been recently suggested that the different etiologies of growth-restriction impact on the fetal and placental gene expression in different ways [2], modifying the propensity to subsequent morbidity accordingly. The complexity of in utero growth restriction indicates that a single diagnostic marker cannot suffice to distinguish accurately between growth-restricted and non-restricted neonates.

Evidence suggests that the combination of simple diagnostic markers of growth-restriction, including birth weight, can define a composite test with a higher validity than the individual markers used in isolation [3,4]. The aim of the present study is to investigate

Abbreviations: AC, abdominal circumference; AGA, appropriate for gestational age; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, birth length; BW, birth weight; CANS, Clinical Assessment of Nutritional Status; CC, chest circumference; CI, confidence interval; CK, creatine kinase; GA, gestational age; GGT, γ-glutamyl-transferase; HC, head circumference; IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor binding protein 3; IUGR, intrauterine growth restriction; LDH, lactic dehydrogenase; LPL, lipoprotein lipase; MAC, mid-arm circumference; PI, ponderal index; SGA, small for gestational age.

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whether readily available laboratory tests can provide additional information that will enhance the diagnostic performance of the composite test. For this investigation three outcome variables were chosen as the most appropriate indicators of growth-restriction: cord serum insulin-like growth factor I (IGF-I), insulin-like growth factor binding protein 3 (IGFBP-3) and the placental weight. The IGF system plays a critical role in fetal growth as it exerts a wide range of metabolic, differentiative and mitogenic actions on the fetal tissues and the placenta [5]. Mutation experiments demonstrated that the IGF-I null mutant mice are growth-restricted. They usually die after birth, and if they survive, they exhibit multiple developmental defects in addition to growth-restriction [6].

2. Materials and methods

2.1. Subjects

The study reported here is part of a larger, prospective study designed to evaluate the power of combining simple diagnostic markers for the identification of growth-restricted neonates. The subjects of this study were singleton babies over 36 weeks of gestational age (GA) that were consecutively delivered by elective cesarean section at the General and Maternity Hospital "Elena Venizelou". Babies with major congenital anomalies and those with known congenital infections were excluded from the study.

The enrollment of the babies was based on their nutritional status, which was reviewed by inspecting them briefly at the time of delivery. During the first post-delivery hours a detailed evaluation of each baby was conducted, which guided the final classification. The evaluation included 1) a clinical assessment of the GA [7], 2) an assessment of subcutaneous fat deposition, by means of the Clinical Assessment of Nutritional Status score (CANS) [8], but adding skin evaluation [9], and 3) an auxological assessment using the following set of anthropometric indices: birth weight (BW), birth length (BL), head circumference (HC), mid-arm circumference (MAC), chest circumference (CC) and abdominal circumference (AC). All measurements were performed carefully following the relevant guidelines [10]. Circumferences were taken by a fiberglass tape measure of 0.9 cm width, to the nearest 0.1 cm. Length was measured on a measuring board (Seca, Infantometer Model 416). Each measurement was performed several times until a consistent reading was obtained. After completing the data selection, the ponderal index (PI), i.e., the ratio of birth weight to birth length in cube, and the MAC-to-HC ratio were calculated. In addition, the raw values of the anthropometric indices were expressed as percentiles for the GA. The reference values were derived from a population of 834 consecutively born newborns with the same range of GA as the study population, who had been specifically recruited for this purpose.

BW, CC, MAC and PI were used as diagnostic markers for the classification of the babies as well-grown and growth-restricted as justified previously [4]. Based on these anthropometric indices three groups were generated: $Group_{25}0$ consisted of babies with values in all four indices exceeding the 25th centile for the GA, serving as the controls. $Group_{25}1$ and $Group_{25}2$ included babies with values in either one or more than one of the four indices, respectively, that were at or below the 25th centile for the GA. Furthermore, $Group_{25}0$ was merged with $Group_{25}1$ to form the composite variable A25 and with $Group_{25}2$ to form the composite variable B25.

2.2. Blood sample collection and analysis

Immediately after the delivery of the placenta, cord venous blood was collected from the placental end of the umbilical cord. The blood samples were chilled to 4 °C for up to 3 h, centrifuged and the serum was stored at −84 °C. This storage procedure is deemed appropriate for ensuring the stability of the analytes [11]. Even so, to preclude any error in the estimation of glucose levels, due to its metabolism by erythrocytes, the blood glucose levels were determined at the time of blood collection, using a commercial glucometer (Precision Xceed, Abbott Laboratories), in addition to the measurement of serum glucose levels under the conditions described below. The blood glucose is hereafter referred to as glucose-B. The placenta weight was also recorded after completing the blood collection and removing the umbilical cord.

The concentration of 13 general chemistry analytes was measured in the cord serum with an automated chemistry analyzer (Architect c8000, Abbott Laboratories). The analytes included alanine aminotransferase (ALT), albumin, aspartate aminotransferase (AST), creatine kinase (CK), creatinine, γ-glutamyltransferase (GGT), glucose (glucose-S), lactic dehydrogenase (LDH), total cholesterol, total protein, triglycerides, urea nitrogen and uric acid. The cord serum levels of IGF-I and IGFBP-3 were assayed using commercially available enzyme-labeled chemiluminescent immunometric assays (Immulite 2000, Siemens Healthcare Diagnostics). All samples were assayed concurrently.

Ethical permission for the study was granted by the Ethical Committee of the General and Maternity Hospital "Elena Venizelou" and informed consent was obtained from the mothers to draw cord blood and to include their babies in the study.

2.3. Statistical analysis

The data are reported as the median-95% Confidence Internal (CI). Differences in the measured continuous parameters between the groups were analyzed using the Mann–Whitney *U*-test. $p<0.05$ was taken as the limit of significance. Stepwise multiple linear regression models were developed to examine the relationships between the outcome and the predictor variables. Wherever indicated, a logarithmic transformation was performed to approximate a normal distribution. Statistical analysis was conducted by MedCalc for Windows, version 12.0 (MedCalc Software, Mariakerke, Belgium).

3. Results

A total of 180 babies were recruited for the study; 95 had values for BW, CC, MAC and PI that were above the 25th centile for the GA ($Group_{25}0$), 29 had three of the four indices exceeding this centile ($Group_{25}1$) and 56 babies had at least two of the four indices at or below the 25th centile for the GA ($Group_{25}2$). The distribution of boys/girls in the three groups was 54/41, 12/17 and 24/32, respectively ($p=0.15$). The median GA in all three groups was 38 weeks ($p=0.10$). A summary of the values of the four anthropometric indices (BW, CC, MAC, PI) in each of the three groups as well as the IGF-I and IGFBP-3 cord blood levels, the placental weight and the CANS scores, is presented in Table 1.

3.1. Biochemical profiles of the babies based on group of classification

The cord serum concentrations of the 13 chemical analytes and glucose-B for each of the three study groups are presented in Table 2. For most of the analytes tested, no significant differences were detected between any two of the three groups. The correlation coefficient (r) for the blood and serum glucose levels was 0.91 (95%CI 0.87 to 0.94, $p<0.0001$), and there were no significant differences between the three groups in either of the two glucose measurements. Cord serum glucose levels below 2.5 mmol/L (45 mg/dL) were present in only 6 newborns, equally distributed among the three groups. The total protein and albumin levels did not differ significantly between groups. The median GGT was 16% lower in $Group_{25}2$ compared to $Group_{25}0$, but this difference was not statistically significant. Moreover, the median uric acid levels were 20% higher