Cord C-peptide and insulin-like growth factor-I, birth weight, and placenta weight among North African and Belgian neonates

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OBJECTIVE: Despite their low socioeconomic status, infants of North African immigrants have been reported to have high birth weights in Belgium. The aim of the study was to further explore potential mechanisms explaining this high birth weight.

STUDY DESIGN: Venous umbilical cord blood samples and perinatal characteristics of live-born infants from mothers of North African and Belgian nationality were collected in 1997 through 1998 at the University Hospital La Citadelle, Liège, Belgium.

RESULTS: The median connecting peptide (C-peptide) concentration was significantly higher among North African than Belgian neonates (0.125 vs 0.110 pmol/mL, $P = .04$). However, the median insulin-like growth factor-I concentrations among North African and Belgian newborn infants were, respectively, 74.0 and 69.6 ng/mL ($P = .45$). Nationality remained significantly associated with C-peptide after adjusting for age and parity. C-peptide, insulin-like growth factor-I correlated positively with birth weight and remained significant factors for birth weight after adjusting for confounders in multiple regression.

CONCLUSION: These results suggest a link between higher C-peptide levels and birth weights among North African neonates in Belgium. (Am J Obstet Gynecol 2003;189:1779-84.)

Key words: Birth weight, C-peptide, insulin-like growth factor-I, placenta, immigrants

It is widely accepted that populations of low socioeconomic status are more likely to have low-birth-weight newborn infants. However, this is not the case for all populations. In the United States, Mexican American mothers show rates of low birth weight that are equivalent to those of non-Hispanic white mothers.[1] In Belgium, despite their low socioeconomic status, infants of North African immigrants have been reported to have high birth weights.[2,3] In the analysis of birth certificates from 1981 to 1988, North African neonates had a smaller rate of low birth weight and also a higher mean birth weight than Belgian neonates.[2] Reduced low birth weights have been observed in North Africa in similar group population.[4] The mechanism explaining the high birth weight of North African neonates is unknown. A high prevalence of glucose abnormality measured during pregnancy and an independent effect of maternal glucose level on birth weight has been reported in a Hispanic population in the United States.[5] A difference in umbilical cord insulin between ethnic groups has been reported in New Zealand as a potential factor to explain higher birth weight among Polynesian infants.[6] Insulin, secreted by fetal pancreatic beta cells during the second half of gestation is known to play an important role in fetal weight gain. Connecting peptide (C-peptide), resulting from the transformation of proinsulin into insulin, reflects endogenous pancreatic capacity to secrete insulin, with a longer half life and higher concentration than insulin. It is believed that maternal hyperglycemia results in fetal hyperglycemia, fetal hyperinsulinemia, and increased birth weight,[7-9] but the stimulus for fetal hyperinsulinemia is not well established. Positive correlations between levels of umbilical cord C-peptide and fetal size at birth have been previously reported.[10-15] Insulin-like growth factors are proinsulin-like polypeptides produced in multiple fetal tissues. They represent potent stimulators of cell division and differentiation and are believed to play a substantial role in fetal growth and weight gain.[16,17] Levels of insulin-like growth factor I - (IGF-I) in umbilical cord serum have been reported to correlate positively with birth weight,[11,19-22] although no, or negative, correlations have been found by some authors.[23,24]

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In this study, some perinatal characteristics of North African and Belgian neonates were studied, and umbilical cord serum C-peptide and IGF-I were measured. We primarily sought to study the relation between nationality and C-peptide and IGF-I. The relationship between C-peptide, IGF-I, nationality, and birth weight was also explored.

Methods

Subjects. The study took place from May 1, 1997, to May 31, 1998, at the University Hospital (Centre Hospitalier Régional [CHR]) La Citadelle, Liège, Belgium. Live-born infants eligible for the study were from mothers who delivered at the hospital during the study period with current North African nationality, and from a comparison group of mothers of current Belgian nationality. Eighty-nine North African neonates were included in the study from a total of 115 infants born during the study period. Exclusion criteria were multiple gestation (n = 3), malformation of the fetus at birth (n = 3), mother known to have diabetes mellitus or diagnosed with gestational diabetes mellitus during the current pregnancy (n = 7), and noncollection of cord blood sample (n = 13). There were 184 infants from Belgian mothers (delivering before and after a North African woman) included in the study, using the same exclusion criteria. In the presence of an exclusion criteria, the next patient or the patient before were selected. A total of 273 infants were included in the study. North Africa was defined as including Algeria, Morocco, and Tunisia. Malformation at birth was defined as any malformation registered at birth in the obstetric computerized file. Information on diabetic status before the pregnancy or history of gestational diabetes mellitus during the current pregnancy was collected from the obstetric computerized file and delivery records. Gestational diabetes was diagnosed by a 100-g oral glucose tolerance test using the standard O'Sullivan criteria,[25] after a positive 1-hour 50-g glucose screening test performed between 24 and 28 weeks of pregnancy on the presence of standardized risk factors.[26] The obstetric computerized file of the department of obstetrics and gynecology provided data on obstetric characteristics. Placenta weight was measured during the study period by the labor ward staff and abstracted from the delivery book. Gestational age at delivery was calculated according to last menstrual period (LMP), corrected if necessary by an ultrasound scan. Low birth weight was defined as a birth weight lower than 2500 g.

Samples. Venous umbilical cord blood samples were collected for all neonates and all blood samples were stored at 4°C and centrifuged within a 12-hour period. The plasma were separated and divided into two aliquots stored at -20°C until the assays. Of 1965 women delivered during that period, a total of 1594 umbilical cord blood samples (81%) were collected, with a similar collection rate (89%) for North African mothers.

Assays. C-peptide was measured by radioimmunoassay (C-PEPsp-RIA-CT, BioSource Europe, Nivelles, Belgium) at the laboratory of the CHR La Citadelle, Liège, Belgium. The minimal detectable dose of C-peptide determined in 10 different assays was 0.03 ± 0.01 pmol/mL (mean ± SD). Intra-assay and interassay variations were between 5.5% and 7.2% (n = 20) and 8% and 10% (n = 13), respectively. IGF-I was measured by radioimmunoassay (SM-C-RIA-CT, BioSource Europe) at the immunology laboratory of endocrinology, CHU, Liège, Belgium. The minimal detectable concentration of IGF-I, determined in 10 different assays, was 0.25 ± 0.10 ng/mL (mean ± SD). Intra-assay and interassay variations were between 4.1% and 6.1% (n = 15) and between 9.3% and 9.9% (n = 10), respectively. Two hundred sixty-nine records for C-peptide and 265 records for IGF-I were available (some cord blood samples did not reach the laboratory wards because of logistical problems; for some cord blood samples, volume allowed only one aliquot, and in that case only C-peptide was measured). The samples were tested in two group runs, in December 1997 and in June 1998.

Ethics. For this study, there were no additional blood samples apart from those routinely performed. The research was approved by the CHR La Citadelle Ethics Committee.

Statistical analysis. Perinatal characteristics were compared among North African and Belgian neonates with *t* tests for continuous variables and χ^2 for discrete variables. C-peptide and IGF-I distributions were explored by normal plots. Both C-peptide and IGF-I were not normally distributed; therefore, univariate correlations between C-peptide, IGF-I and birth weight/placenta weight and gestational age were calculated using nonparametric correlation coefficients (Spearman *r*). Pearson correlation coefficients were computed for continuous variables with normal distributions. Intergroup differences were calculated using nonparametric tests (Mann-Whitney *U*-Wilcoxon rank sum W test). Linear regression analysis was used to determine the independent effect of nationality on C-peptide concentrations. As dependent variable, C-peptide was transformed into logarithmic scale (log base 10) because of nonnormal distribution. Linear regression models were also used to determine the independent effect of nationality on birth weight with C-peptide and IGF-I as intermediate variables and adjusted for potential confounders, which were based on literature. Conditions of application and adequacy of the model were verified by the analysis of residuals and collinearity. *P* values were two tailed and the significance level was .05. Statistical analyses were performed with SPSS for windows 6.1.3 software (SPSS, Chicago, Ill.).

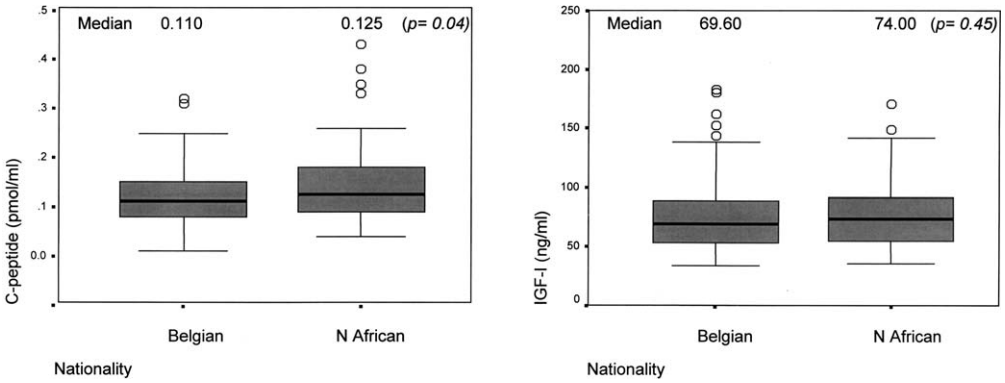

Fig 1. C-peptide and IGF-I cord serum concentrations among Belgian and North African neonates, box plots of distributions. —, Median; *open box,* interquartile range (IQR), 25th and 75th percentiles; *bar,* 25th and 75th percentiles ± 1.5 IQR. *P* values based on Mann-Whitney *U* test.

Table I. Characteristics of Belgian and North African neonates and their mothers

Characteristics	*Belgians (n = 184)*	*North Africans (n = 89)*	*P value**
Age of the mother (mean [SD])	28.7 (4.9)	27.5 (6.0)	.10
Parity of the mother (mean [% primiparous])	0.86 (43.2)	1.11 (41.6)	.77
Gestational age at birth (wk, mean [SD])	38.9 (1.5)	39.2 (1.3)	.14
Sex of the baby			
Male (%)	48.9	43.8	
Female (%)	51.1	56.2	.43
Length of the baby (cm, mean [SD])	49.3 (2.7)	49.6 (2.3)	.44
Skull perimeter (cm, mean [SD])	33.8 (1.6)	34.2 (1.5)	.06
Birth weight (g, mean [SD])	3220 (473.6)	3313 (456.7)	.13
Low birth weight (%)	7.6	4.5	.44
Birth weight >4000 g (%)	4.9	9.0	.19
Weight of placenta (g, mean [SD])	601 (115.4)	639 (133.3)	**.02**
Mode of delivery			
Normal vaginal (%)	83.7	87.6	
Forceps (%)	6.5	5.6	.66
Cesarean-section (%)	9.8	6.7	
Apgar at 1 min, <7 (%)	9.7	5.6	.25

*Based on *t* test for continuous variables and on χ^2 for discrete variables.

Results

North African mothers tended to be slightly younger, of higher parity, and with a longer duration of gestation than Belgian mothers (Table I). Sex, length of the infants, and mean occipitofrontal head circumference were similar in both groups. In our study sample, mean birth weight was 3313 g among North African infants and 3220 g among Belgians, but the difference was not statistically significant. The percentages of low birth weights were 4.5% and 7.6% among North African and Belgian neonates, respectively ($P = .44$). The percentage of infants weighting more than 4000 g was 9.0% among North African neonates and 4.9% among Belgian neonates ($P = .19$). Mean placenta weight was significantly higher among North African infants (639 g) than among Belgian infants (601 g). The proportion of infants with an Apgar score lower than 7 at 1 minute was similar in both groups (Table I).

Relationship between nationality and C-peptide and IGF-I. The median C-peptide concentrations was higher among North African neonates (0.125 vs 0.110 pmol/mL, $P = .04$). Box plots of both distributions are presented in Fig 1. The median IGF-I concentrations among North African and Belgian neonates were, respectively, 74 and 69.6 ng/mL, but the difference was not statistically significant ($P = .45$). C-peptide concentrations were associated with age and parity but not with gestational age at birth (Fig 2). In multiple linear regression, with C-peptide as dependent variable, nationality as an independent variable, and adjusting for age and parity, nationality remained a significant factor ($P = .04$) (Table II).

Relationship between C-peptide, IGF-I, and birth weight and placenta weight. Birth weight correlated positively with C-peptide (Spearman $r = 0.20$, $P = .001$) among Belgian and North African neonates. Birth weight correlated positively with IGF-I (Spearman $r = 0.23$,

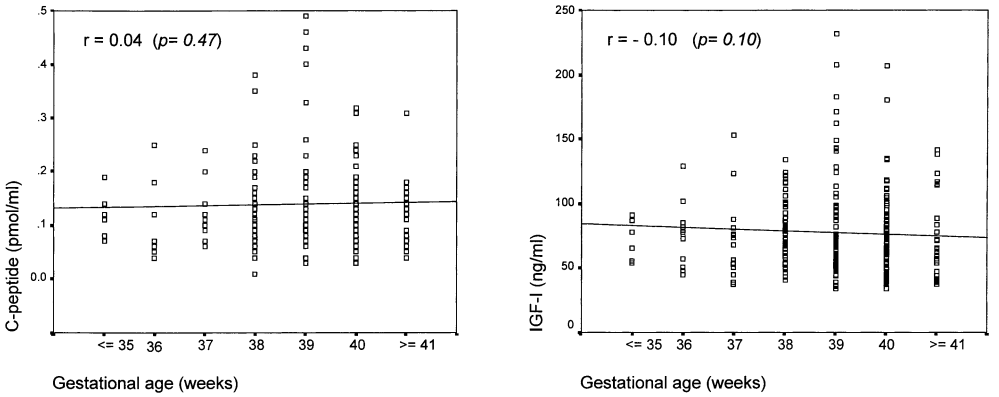

Fig 2. Correlation between C-peptide/IGF-I cord serum and gestational age at birth; *r* = Spearman coefficient.

Table II. Multiple linear regression: Association between nationality and C-peptide, adjusted for parity and age

	*B**	*SE B*	*P value*
Nationality (NA vs B)	0.069	0.034	.044
Parity	0.025	0.015	.103
Age	0.008	0.003	.018
Constant	−1.3	0.1	< .001
R^2	0.061		

NA, North African; *B*, Belgian.
*Regression coefficients, adjusted for all variables above.

$P < .001$). Similarly, placenta weight correlated positively with C-peptide (Spearman $r = 0.21$, $P = .001$) and IGF-I (Spearman $r = 0.17$, $P = .006$). Placenta and birth weights were highly positively correlated (Pearson $r = 0.59$, $P < .001$) among Belgian and North African neonates. There was no correlation between C-peptide and IGF-I (Spearman $r = 0.08$, $P = .187$).

Relationship between C-peptide, IGF-I, and nationality and birth weight. A multiple linear regression analysis with birth weight as the dependent variable, nationality as the independent variable, and adjusting for gestational age at birth, parity, and age of the mother, showed that gestational age at birth was the highest predictor for birth weight (Table III). When C-peptide and IGF-I were included in the model, nationality, age, and parity did not remain significant factors, whereas C-peptide and IGF-I remained independently associated with birth weight.

Comment

In this study, the characteristics of the Belgian and North African mothers are in line with previous reports.[2,3] Among North African neonates, the mean birth weight was higher and the percentage of low birth weight lower than among Belgian neonates, but that was not statistically significantly, probably because of the limited sample size. However, placenta weight was significantly higher among North African neonates in our study sample.

Table III. Multiple linear regression: Association between nationality, C-peptide, IGF-I and birth weight, adjusted for gestational age, parity, age

	*B**	*SE B*	*P value*
Nationality (NA vs B)	14.4	54.1	.790
Gestational age at birth	163.2	16.9	< .001
Parity	27.8	24.7	.394
Age	2.5	5.1	.622
C-peptide	513.8	242.5	.035
IGF-I	2.6	0.7	< .001
Constant	−3491.9	669.27	< .001
R^2	0.309		

NA, North African; *B*, Belgian.
*Regression coefficients, adjusted for all variables above.

Interestingly, a significant difference between concentrations of C-peptide among Belgian and North African neonates was found in this study, even when adjusting for parity and age. This was not the case for IGF-I levels. This suggests a higher insulinemia among North African than Belgian neonates. In New Zealand, a difference in cord insulin but not in IGF-I levels was found between Polynesians, Indians (at high risk of diabetes mellitus), and European neonates.[6,20] Because of the long-recognized association between fetal hypersinsulinemia and somatic overgrowth, these results might be a potential source of explanation for higher birth weight among North African newborn infants. Fetal hyperinsulinemia might increase morbidity among neonates by increasing neonatal hypoglycemia, but also through macrosomia, which increases the risk of birth injuries such as shoulder dystocia. Thus, a high mean birth weight, in a given population, might not be per se associated with better neonatal outcomes, and birth weight distributions are worth being analyzed carefully. Clinical and experimental studies support the concept that maternal hyperglycemia leads to fetal hyperinsulinemia. However, the degree(s) of maternal hyperglycemia associated with poor fetal outcome, and particularly with macrosomia, is

still unclear. Attempts at maintaining strict euglycemia in diabetic mothers have not consistently prevented fetal macrosomia or neonatal hypoglycemia.[27] Apart from maternal hyperglycemia, there may be additional explanations to increased fetal insulin secretion and anabolism that still need to be further explored.[27]

It has been shown that intrauterine growth restriction is associated with cardiovascular diseases and diabetes later in life.[28] The implications of fetal hyperinsulinemia on health later in life are not clear.[29] In Cap Bon, Tunisia, excessive carbohydrate intake among Tunisian mothers has been reported to be associated to neonatal obesity.[30]

In our study hospital, the diagnosis of gestational diabetes mellitus (GDM) was made on standardized risk factors (ie, a 50-g glucose screening test was not systematically administrated to all pregnant women). This is a limitation to our study because some women with GDM might have been missed (and therefore included in our study group). A bias of overestimating the difference between both groups would occur if more North African than Belgian women were missed as a result of, for instance, less intensive prenatal care. Although the fact that a higher percentage of North African women received a diagnosis of GDM in our study (6/89 [6.7%] vs 5/184 [2.7%]) is not in favor of such a bias, we cannot exclude it.

We found that C-peptide and IGF-I were positively correlated with birth weight, as reported earlier in normal pregnancies,[10-13,18,19,22] although the correlations in our study were weaker. In this study, positive correlations of placenta weight with C-peptide and IGF-I were also found. Positive correlations of placenta weight with IGF-I have been reported in normal and diabetic pregnancies,[6,21] but, to our knowledge, not with C-peptide. Our study confirms the strong correlation between placenta weight and birth weight. The placenta has a pivotal function in maternofetal nutrient and metabolic transfer and its role in fetal growth regulation is worth being further studied. No correlation between C-peptide and IGF-I was found in our study. This is not in agreement with some results showing correlation coefficients up to 0.32 (Spearman r) in normal pregnancies[11,20] and therefore does not provide additional evidence that the IGF-I production might be regulated by insulin. The variations of the two markers according to gestational age are consistent with earlier reports, with C-peptide concentrations rather stable, whereas IGF-I concentrations tend to decrease slightly toward the end of pregnancy.

In this study, after adjusting for potential confounders, gestational age at birth was the most important factor associated with birth weight. C-peptide and IGF-I remained significant factors for birth weight, whereas nationality, age, and parity did not. Other potential factors such as occupation of the mother, smoking status, prepregnancy weight, and nutritional habits might be involved in the higher birth weights of North African newborn infants. We could not control for these factors in this study.

Although the differences found are not highly significant, our results suggest a higher C-peptide level among North African neonates living in Belgium. This potential higher insulinemia might be a source of explanation for their higher birth weights and needs to be further investigated.

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