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Original Article

Int J Clin Pediatr. 2014;3(1):5-11

Biochemical Profiling Study in Umbilical Cord Blood as Predictors of Neonatal Damage

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Abstract

Background: During pregnancy inflammatory, metabolic and immunologic disorders that affect differently the fetus, are known. These could be early disorders: abortion, intrauterine growth retardation, low birth weight and neonatal death; or late disorders: cardiovascular and metabolic disease in adults. The objective was to analyze different biochemical parameters in maternal venous blood and newborn's umbilical cord blood (UCB) from healthy and pathological mothers for early detection of future perinatal complications.

Methods: Maternal venous blood (283) and UCB (283) were analyzed. The patients were consecutively, prospectively and transversally studied. Delivery: cesarean section. Mothers and newborns were classified: control group (C) (n = 99) and pathological group (P) (n = 184). Glucose, urea, creatinine, uric acid (UA), bilirubin (Bi), proteins (PT), albumin (Alb), transaminases (ALT/AST), alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), creatinkinasa (CK), lactate dehydrogenase (LDH), iron, calcium, phosphorus, magnesium, sodium, potassium (K), chlorine, cholesterol (Chol), triglycerides (TG) and hsCRP were determined by recommended methods. Student's t and Mann-Whitney tests were applied, $P < 0.05$.

Results: P newborns from P mothers showed significant decrease: in gestation weeks (GW) and newborn weight (NW) with respect to C newborns from C mothers ($P < 0.001$); significant increases in Chol, TG, UA, K, Bi, AST and GGT (P: 0.01, < 0.001, 0.03, < 0.001, 0.04, < 0.001, < 0.001, respectively) and significant decreases in CK, PT and Alb ($P < 0.001$). P mothers showed significant increase in UA, ALT, AST, GGT (P: 0.04, 0.02, 0.04, < 0.001, respectively) with respect to C mothers.

Conclusions: The decrease in GW and NW in P newborns with respect to C would be related to intrauterine growth restriction (IUGR) accompanying these disorders; increases in Chol, TG, UA, K, Bi, AST and GGT would be related to cellular destruction associated to maternal disorders and deficit in pulmonary development by IUGR respectively, whereas decreases in CK, PT and Alb to IUGR. Increase in UA, ALT, AST and GGT from P mothers with respect to C would be associated to inflammatory process with liver alterations. A future study including greater number of samples and analysis of each maternal disorder is proposed to obtain early markers of neonatal damage and to prevent future perinatal complications.

Keywords: Biochemical profiling study; Predictors; Umbilical cord blood; Neonatal damage

Introduction

Various complex disorders which can impact on the fetus at variable degrees are known to affect pregnant women. In some cases, the etiology of these disorders is already well known whereas in some other cases it is still under study. Poor or inadequate nutrition, smoking, alcohol abuse, lower genital tract infections, anemia, hypertension, gestational or non-gestational diabetes, obesity, metabolic and antiphospholipid syndromes, among others, are some of the maternal conditions that may have an effect on fetal growth [1-8]. These maternal disorders affect the environment where the fetus is developing and may produce metabolic, immune, vascular, hemodynamic and renal alterations [9-12]. These alterations can have early manifestations, either during intrauterine life or at birth, such as abortion, intrauterine growth restriction (IUGR), low birth weight, neonatal mortality; or they may occur later causing a greater impact on adult life. As a result, different diseases such as poor glucose homeostasis, insulin resistance, type 2 diabetes [13-15], the metabolic syndrome, obesity, hypertension [16-18], osteoporosis

Manuscript accepted for publication January 28, 2014

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doi: http://dx.doi.org/10.14740/ijcp140e

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[19-20], cardiovascular disease, endothelial dysfunction and coronary heart disease may be a consequence of these alterations [1, 21-23]. On the other hand, slow fetal growth *in utero* may be associated with an increase in the accumulation of nutrients to the adipose tissue during fetal development which could later result in accelerated weight gain during childhood [24, 25], and possibly, in a greater risk of coronary heart disease, hypertension and type 2 diabetes. Furthermore, there is a continuous relation between birth weight and future risk [26]. Moreover, prematurity itself, regardless of the size for gestational age, has been associated with insulin resistance and glucose intolerance in prepuberal children [27], which could later impact on young adults and may be accompanied by elevated blood pressure [28]. Therefore, what happens during the fetal development *in utero* seems to condition some diseases occurring in adult life through different mechanisms.

On the other hand, all these maternal conditions are mostly related to inflammatory processes [29-31]. During these processes, a series of characteristic events are triggered, starting with the participation of polymorphonuclear neutrophils (PMN) and ending with damage to the affected tissue [32, 33]. This inflammation has consequences at molecular, cellular, tissular and systemic levels. Consequently, inflammation has not only been associated with infectious processes but also with hypertension [34], preeclampsia [35], diabetes and the metabolic syndrome [36].

However, there is scant information in the literature with respect to C-reactive protein (CRP) and proinflammatory interleukin levels as well as practically no reference to the levels of metabolites and enzymes in newborns' umbilical cord blood (UCB) from mothers with these conditions.

The objective of this work was to analyze different biochemical parameters (BPs) in maternal venous blood and healthy newborns' UCB from healthy mothers, as well as in newborns' UCB from mothers with underlying conditions and diseases associated with gestation, with the aim of evaluating the possible role of some of them as early predictive markers of perinatal damage such as reduced fetal growth (low weight, IUGR, fetal distress and/or premature birth), in order to prevent future maternal and perinatological complications.

Material and Methods

Patients

Two hundred and eighty-three (283) venous blood samples from mothers admitted for delivery at the Obstetrics Division in the Hospital de Clinicas of the University of Buenos Aires and 283 samples from the UCB of their respective newborns were collected from January 2010 to January 2012. The patients were consecutive, prospective and transversally studied, and all the mothers and their respective neonates were included in this study.

In all cases, delivery was via cesarean section. The mothers and their newborns were classified into two groups: the control group (n = 99), healthy mothers without underlying or gestational disorders; and the pathological group (n = 184). The underlying maternal diseases included: diabetes, hypertension, antiphospholipid syndrome, hyper/hypotiroidism, intrahepatic cholestasis and genital infections, whereas the disorders in the newborns were: IUGR and/or fetal distress.

This study was approved by the Hospital Ethics Committee. All women in the study gave their informed consent to participate.

Methods and statistical analysis

Twenty-three biochemical markers were studied as numerical continuous variables. These were measured by internationally recommended methods, in COBAS Auto-analyzer 6000, C-501 Module-Roche Diagnostics, Germany: glucose (Glu) (hexokinase-enzymatic method), urea (U) (UV-kinetic method), creatinine (Cr) (rate blanked and compensated Jaffe-Kinetic method), uric acid (UA) (enzimatic-colorimetric method), total bilirubin (TB) (colorimetric method), total proteins (TP) (Biuret-colorimetric method), albumin (Alb) (colorimetric bromocresol green method), alanine aminotransferase (ALT) (IFCC- kinetic method), aspartate aminotransferase (AST) (IFCC-kinetic method), alkaline phosphatase (ALP) (DGKC kinetic method), gamma-glutamyl transpeptidase (GGT) (IFCC-kinetic method), creatine kinase (CK) (IFCC-kinetic method), lactate dehydrogenase (LDH) (DGKC-kinetic method), ferremia (Fe) (colorimetric method), calcium (Ca) (colorimetric-endpoint method), phosphorus (P) (colorimetric-endpoint method), magnesium (Mg) (colorimetric-endpoint method), sodio (Na) (potentiometric method-selective ion), potassium (K) (potentiometric method-selective ion), chlorine (Cl) (potentiometric method-selective ion), cholesterol (Cho) (CHOD/PAP-enzymatic method), triglycerides (TG) (GPO/Px-enzymatic method) and high sensitivity C reactive protein (hsCRP) (immunoturbidimetric method).

The statistical analysis of the comparison of gestational weeks, neonatal weight and BPs of both groups was performed by using a parametric test (Student's t) and a non-parametric test (Mann-Whitney), for independent samples. Two tailed tests were used throughout. A P value < 0.05 was considered statistically significant. InfoStat v.2011 (National University of Cordoba, Argentina) software was used.

Results

Maternal age and gestational weeks, neonatal weight and

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Table 1. Maternal Age and Gestation Weeks, Newborn Weight and Biochemical Parameters in Maternal Venous Blood and Umbilical Cord Blood in Control and Pathological Groups Expressed as the Mean and Their Respective Standard Deviation Values

	Maternal venous blood			Umbilical cord blood		
	Controls (99)	Pathological (184)	P	Controls (99)	Pathological (184)	P
Mothers age (years)	27 ± 7	28 ± 8	ns			
Gestation weeks	38.8 ± 1.5	37.1 ± 2.8	< 0.001*			
Newborn weight (g)				3,394 ± 371	2,936 ± 784	< 0.001*
Glucose (mg/dL)	77 ± 29	81 ± 52	ns	58 ± 29	55 ± 31	ns
Urea (mg/dL)	22 ± 7	22 ± 9	ns	20 ± 5	20 ± 6	ns
Cholesterol (mg/dL)	236 ± 54	230 ± 58	ns	68 ± 27	74 ± 33	0.01*
Triglycerides (mg/dL)	208 ± 71	218 ± 102	ns	32 ± 13	37 ± 48	< 0.001*
Uric acid (mg/dL)	4.5 ± 1.2	4.7 ± 1.3	0.04*	4.4 ± 1.2	4.7 ± 1.4	0.03*
Creatinine (mg/dL)	0.6 ± 0.1	0.6 ± 0.4	ns	0.5 ± 0.2	0.5 ± 0.2	ns
Calcium (mg/dL)	8.7 ± 0.6	8.7 ± 0.7	ns	10.0 ± 1.3	10.1 ± 1.0	ns
Phosphorus (mg/dL)	4.1 ± 1.2	4.2 ± 1.3	ns	6.1 ± 2.1	6.3 ± 2.2	ns
Magnesium (mg/dL)	1.8 ± 0.2	1.8 ± 0.2	ns	1.9 ± 0.3	2.0 ± 0.4	ns
Sodium (mEq/L)	138 ± 13	140 ± 5	ns	138 ± 8	139 ± 8	ns
Potassium (mEq/L)	4.3 ± 0.6	4.4 ± 1.4	ns	5.7 ± 1.3	6.3 ± 1.8	< 0.001*
Chlorine (mEq/L)	106 ± 5	106 ± 5	ns	105 ± 7	106 ± 7	ns
Iron (µg/dL)	66 ± 47	65 ± 49	ns	151 ± 38	146 ± 49	ns
Total bilirubin (mg/dL)	0.3 ± 0.2	0.3 ± 0.2	ns	1.5 ± 0.9	1.7 ± 1.3	0.04*
ALT (IU/L)	11 ± 8	18 ± 41	0.02*	8 ± 4	8 ± 6	ns
AST (IU/L)	24 ± 8	29 ± 35	0.04*	35 ± 11	38 ± 20	< 0.001*
ALP (IU/L)	304 ± 160	315 ± 190	ns	337 ± 208	328 ± 181	ns
LDH (IU/L)	443 ± 133	452 ± 136	ns	804 ± 353	848 ± 336	ns
CK (IU/L)	229 ± 174	198 ± 203	ns	312 ± 190	275 ± 121	< 0.001*
GGT (IU/L)	12 ± 7	20 ± 26	< 0.001*	96 ± 56	118 ± 77	< 0.001*
hsCRP (mg(L)	53 ± 67	59 ± 68	ns	0.4 ± 0.8	0.2 ± 0.3	ns
Albumin (g/dL)	3.2 ± 0.5	3.1 ± 0.3	ns	3.8 ± 0.3	3.6 ± 0.5	< 0.001*
Protein (g/dL)	5.8 ± 0.7	5.8 ± 0.6	ns	5.6 ± 0.6	5.3 ± 0.8	< 0.001*

ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; CK: creatine kinase; LDH: lactate dehydrogenase; hsCRP: high sensitivity C-reactive protein. *Statistically significant difference; ns: non-significant difference.

all BPs of maternal venous blood and UCB from both the pathological and control groups were expressed as the mean and the respective standard deviation values (Table 1).

Pathological neonates (n = 184) from pathological mothers (n = 184) showed a significant decrease in maternal gestation weeks and in newborn weight with respect to control newborns (n = 99) from control mothers (n = 99) ($P < 0.001$), as well as significant increases in Cho, TG, UA, K, TB, AST and GGT values in UCB (P: 0.01, < 0.001, 0.03, < 0.001, 0.04, < 0.001 and < 0.001, respectively) and significant decreases in CK, TP and Alb values ($P < 0.001$). The other biochemical markers did not show significant differences in UCB of pathological newborns with respect to those in the control group (Table 1).

A significant increase in UA, ALT, AST and GGT values was observed in venous blood of pathological mothers with respect to those in control mothers (P: 0.04, 0.02, 0.04 and < 0.001, respectively). There were no significant differences in the other biochemical markers (Table 1).

Discussion

The decrease observed in gestation weeks and newborn weight in pathological newborns from pathological mothers with respect to the control group might be associated with the IUGR related to these disorders.

The observed increase in Cho, TG, UA, K, TB and AST values in UCB in pathological newborns from pathological mothers with respect to those in the control group might be related to cellular destruction associated with the maternal condition, whereas the increase in GGT levels in UCB of these newborns might be due to a deficit in pulmonary development as a result of IUGR. There are few studies in the bibliographical references referring to the normal levels and their alterations, in terms of metabolites and enzymes, in newborns' UCB from mothers with underlying metabolic disorders, infections of the lower genital tract, underlying inflammatory or immunological conditions and diseases associated with gestation and informing about the way these alterations impact on the newborn.

Similarly to what was observed in this study, the increase in the levels of certain metabolites such as cholesterol and triglycerides in maternal blood of patients with preeclampsia has been described as a result of the cellular damage it produces, suggesting a possible role in the pathophysiology of the syndrome [37]. Thus, likewise, the different maternal disorders included in this study, which have in common the presence of cellular damage and inflammation, such as diabetes, hypertension, the antiphospholipid syndrome and genital infections, among others, might impact on the newborn by producing an increase in intracellular ions such as K and intracellular enzymes such as AST and other metabolites such as UA and TB.

Furthermore, the decrease observed in CK, total protein and albumin levels in pathological newborn's UCB with respect to control newborns would be due to IUGR.

Furthermore, the decrease of specific metabolites such as glucose in blood obtained by cordcentesis in fetuses with IUGR has been described, considering that glucose is the main substrate for fetal energy metabolism and its demand increases as growth progresses [38]. This fact could be the result of alterations in the placenta or in fetal glucose metabolism [39, 40]. Moreover, there have been reports of high concentrations of triglycerides and low levels of free fatty acids in fetuses with IUGR, similarly to what was observed in the present study [38]. These alterations are the result of chronic hypoglycemia with compensatory lipolysis and an inability to hydrolize circulating triglycerides allowing a decrease in their use as fat deposits. The decrease in free fatty acids impacts on the fetus since they are major components of the cell membrane and a source of energy for fetal development and growth [41]. In addition, it has been reported that in fetuses with cardiac defects and IUGR, the levels of troponine T in umbilical venous blood are increased by 12% and 20%, respectively [42]. Nevertheless, unlike what has been observed in our study, other authors have reported that AST values in UCB from newborns affected by IUGR were not different from those observed in normal newborns; even lower ALT values have been described in newborns with IUGR with respect to normal newborns, which suggests that the reduced activity may be due to hepatic immaturity of the newborn to produce enzymes [43].

On the other hand, an increase in AU, ALT, AST and GGT levels was observed in venous blood of the pathological mothers with respect to those in the controls, which were probably associated with the inflammatory process related to the studied maternal diseases and hepatic alterations. In this respect, it has been linked to inflammation in the pathogenesis of hypertension [34] and particularly, in preeclampsia [44]. Furthermore, its impact on the development of long-term cardiovascular disease is being evaluated [45]. Recent publications have also considered chronic subclinical inflammation as a pathophysiological factor causing type 2 diabetes, gestational diabetes, the metabolic syndrome, obesity, atherosclerotic cardiovascular disease and myocardial infarction [46]. Even though no significant increases in hsCRP values were observed in maternal blood, this parameter would be a predictor of the development of these disorders [47-50]. However, there are few studies referring to hsCRP levels in UCB as early markers of fetal distress risk associated with severe maternal disorders such as diabetes and the antiphospholipid syndrome and with typical conditions related to gestation such as preeclampsia, spontaneous abortion and premature rupture of fetal membranes. In our study, no differences in hsCRP levels were observed in UCB of pathological newborns with respect to the control group. Although most of the maternal diseases included in this

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study are related to inflammatory processes, such processes were not reflected in hsCRP levels in pathological newborns' UCB. This lack of correlation, also described by other authors, suggests that hsCRP levels in amniotic fluid have fetal origin [51].

Conclusions

In view of the differences observed in UCB from pathological newborns with respect to those in the control group, a future study including a greater number of samples is proposed with the aim of studying each specific maternal disease and obtaining early markers of neonatal damage that could prevent future maternal and perinatological complications.

Acknowledgement

We are very grateful to all the pregnant women who participated in this survey and to the medical residents and nursing staff that helped in the collection of maternal blood and newborns' umbilical cord blood samples.

Financial Support

This work was supported by Universidad de Buenos Aires grant UBACYT 01/K24 project from the Facultad de Farmacia y Bioquimica.

Conflict of Interest

We do no have any conflict of interests.

Ethical Approval

This study was approved by the Hospital Ethics Committee. All women in the study gave their informed consent to participate.

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