

Biochemical Markers in Umbilical Cord Blood as Predictors of Perinatal Complications

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Abstract: Background: Inflammatory, metabolic and immunological disorders affecting the fetus in different ways commonly occur during pregnancy. Disorders such as abortion, intrauterine growth restriction (IUGR), low birth weight and neonatal mortality are known to occur in early life and cardiovascular and metabolic disease could occur in adult life. **Objective:** To analyze different biochemical parameters (BP) for the early detection of perinatal complications in maternal venous blood (MVB) and newborns' umbilical cord blood (UCB) from healthy mothers and mothers with underlying conditions or diseases associated with gestation. **Materials-Methods:** Samples from MVB (173) and UCB (173) were analyzed. Delivery was via cesarean section. Mothers and newborns were classified into two groups: the control group (C-n = 64) and the pathological group (P-n = 109). Maternal diseases: diabetes, hypertension, anti-phospholipid syndrome, hyper/hypotiroidism, intrahepatic-cholestasis and genital infections. Newborn disorders: IUGR and/or fetal distress. BP: Glucose, urea, creatinine, uric acid, total bilirubin, proteins, albumin, transaminases (ALT/AST), alkaline phosphatase, gamma-glutamyltranspeptidase (GGT), creatine kinase, lactate dehydrogenase (LDH), iron, calcium, phosphorus, magnesium, sodium, potassium (K), chlorine, cholesterol, triglycerides, hsCRP were measured by recommended methods-Roche autoanalyzer. Student's and Mann Whitney tests were performed, $p < 0.05$. **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 ($p: 0.001; 0.01$, respectively); significant increases in K, AST, LDH, GGT ($p: 0.005; 0.03; 0.03; 0.02$; respectively). -P mothers showed significant increase in hsCRP ($p: 0.02$) with respect to C mothers. **Conclusions:** In P newborns from P mothers with respect to C, the decrease in GW and NW might be related to IUGR, a typical condition associated with these disorders; increases in K, AST, LDH, GGT would be related to cellular destruction associated to maternal disorders and deficit in pulmonary development as a result of IUGR, respectively. The increase in hsCRP from P mothers with respect to C mothers could be associated to an inflammatory process. A future study with a greater number of samples and analysis of each maternal disease is proposed in order to obtain early markers of neonatal damage.

Key words: Predictive biochemical markers, cord blood, perinatal complications.

1. 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. A 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

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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 [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, independent of 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 from mothers with these conditions.

The objective of this work was to analyze different biochemical parameters in maternal venous blood and healthy newborns' umbilical cord blood from healthy mothers, as well as in newborns' umbilical cord blood 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 perinatal complications.

2. Material and Methods

One hundred and seventy three (173) venous blood samples from mothers admitted for delivery at the Obstetrics Division in the Hospital de Clinicas of the University of Buenos Aires and 173 blood samples from the umbilical cord of their respective newborns were collected from January to December, 2010.

In all cases, delivery was via cesarean section. The mothers and their newborns were classified into two groups: the control group (n: 64) and the pathological group (n: 109). The underlying maternal diseases included were: diabetes, hypertension, anti-phospholipid 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.

Twenty three (23) biochemical markers were measured by internationally recommended methods, in HITACHI Auto Analyzer 917-Roche Diagnostics Germany: Glucose (Glu) (GOD/PAP-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), amylase (Amy) (Blocked PNP-Kinetic method), cholinesterase (Cho) (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 CRP (hsCRP) (immunoturbidimetric method).

The statistical analysis of the comparison of gestational weeks, neonatal weight and biochemical parameters of both groups was performed by using a parametric test (Student) 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- 2009 version (National University of Cordoba, Argentina) was the software used.

3. Results

Maternal age and gestational weeks, neonatal weight and all biochemical parameters of maternal venous blood and umbilical cord blood from both the pathological and control groups were expressed as the mean and the respective standard deviation values (Table 1).

Pathological neonates from pathological mothers showed a significant decrease in maternal gestation weeks and in newborn weight with respect to control newborns from control mothers (*p*: 0.001 and 0.01,

respectively), as well as significant increases in K, AST, LDH and GGT values in umbilical cord blood (*p*: 0.005; 0.03; 0.03 and 0.02 respectively). The other biochemical markers did not show significant differences in the umbilical cord blood of pathological newborns with respect to those in the control group (Table 1).

A significant increase in hsPCR values in the venous blood of pathological mothers with respect to those in control mothers (*p*: 0.02) was observed. There were no significant differences in the other biochemical markers (Table 1).

4. 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 K, AST and LDH values in umbilical cord blood 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 umbilical cord blood 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' umbilical cord blood 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.

In this respect, 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

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 the respective standard deviation values.

	MVB (n=173)			UCB (n=173)		
	Controls	Pathological	<i>P</i>	Controls	Pathological	<i>P</i>
n	64	109		64	109	
Mothers Age (years)	27.5±7.7	27.7±7.6	ns			
Gestation Weeks	38.8±1.4	37.2±2.9	0.0007*			
Newborn Weight (gr)				3319±412	2952±813	0.007*
Glucose (mg/dl)	89±27	91±61	ns	59±29	61±57	ns
Urea (mg/dl)	20±6	21±6	ns	20±5	20±6	ns
Cholesterol (mg/dl)	236±55	224±52	ns	66±20	72±35	ns
Triglycerides (mg/dl)	213±83	214±112	ns	35±26	58±43	ns
Uric acid (mg/dl)	4.5±1.1	4.6±1.3	ns	4.4±1.1	4.6±1.6	ns
Creatinine (mg/dl)	0.54±0.12	0.55±0.13	ns	0.45±0.15	0.47±0.21	ns
Calcium (mg/dl)	8.5±0.6	8.4±0.5	ns	9.9±1.3	9.9±0.8	ns
Phosphorus (mg/dl)	4.2±1.5	4.3±1.8	ns	5.8±1.4	6.0±1.8	ns
Magnesium (mg/dl)	1.8±0.2	1.9±0.5	ns	1.9±0.2	2.0±0.3	ns
Sodium (mEq/l)	138±6	139±6	ns	139±8	138±8	ns
Potassium (mEq/l)	4.1±0.3	4.2±0.5	ns	5.6±1.1	6.4±1.8	0.005*
Chlorine (mEq/l)	106±6	106±5	ns	106±7	107±7	ns
Iron (mg/dl)	70±54	64±50	ns	147±40	143±49	ns
Total Bilirubin (mg/dl)	0.4±0.2	0.4±0.2	ns	1.6±1.1	1.8±1.6	ns
ALT (UI/L)	8±5	17±45	ns	6±4	7±4	ns
AST (UI/L)	23±8	29±40	ns	33±12	39±23	0.03*
FAL (UI/L)	383±121	400±186	ns	443±177	518±467	ns
LDH (UI/L)	412±119	437±141	ns	799±419	892±386	0.03*
CK (UI/L)	212±156	196±198	ns	287±136	266±117	ns
Amy (UI/L)	61±20	60±24	ns	9±8	5±3	ns
Che (UI/L)	5187±924	5005±1124	ns	5802±1507	5291±954	ns
GGT (UI/L)	11±8	16±12	0.009*	94±53	118±74	0.02*
hsCRP(mg/l)	20.9±19.5	54.9±44.2	0.02*	0.11±0.23	0.09±0.26	ns
Albumin (mg/dl)	3.2±0.6	3.1±0.3	ns	3.8±0.3	3.6±0.6	ns
Proteins (mg/dl)	5.7±0.7	5.8±0.6	ns	5.5±0.6	5.3±0.9	ns

Values are expressed as the mean and the respective standard deviation, MVB maternal venous blood, UCB: umbilical cord blood, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, FAL: alkaline phosphatase, GGT: Gamma-glutamyl transpeptidase, CK: Creatine kinase, LDH: Lactate dehydrogenase, Amy: amylase, Che: cholinesterase, hsCRP: high sensitivity C-reactive protein,*Statistically significant differences, ns: non-significant differences.

the syndrome [37]. In other words, the different maternal disorders included in this study, that 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 enzymes linked to inflammatory processes, such as LDH.

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 [38]. These alterations are the result of chronic hypoglycemia with compensatory lipolysis and an inability to hydrolyze circulating triglycerides allowing a decrease in their use as fat deposits. The decrease in free fatty acids impact 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 umbilical cord blood 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 hsCRP values in venous blood of pathological mothers has been observed with respect to those in the control group. This finding could probably be associated with the inflammatory process related to the maternal disorders studied. 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]. Therefore, hsCRP would be a predictor

of the development of these disorders [47–50]. However, there are few studies referring to hsCRP levels in umbilical cord blood 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 the umbilical cord blood of pathological newborns with respect to the control group. Therefore, it is herein shown that no correlation between hsCRP values in the blood of pathological mothers and hsCRP levels of umbilical cord blood in pathological newborns was observed. This lack of correlation, also described by other authors, suggests that the hsCRP of the amniotic fluid has a fetal origin [51].

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

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