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Blood Parameters in Human Fetuses with Congenital Malformations and Normal Karyotype

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1. Introduction

Congenital malformations can be defined as structural anomalies arising during the periods of embryogenesis and organogenesis (Roux, 2001).

However, during the fetal period, various external factors of infectious, vascular or toxic origin can also interfere with the development of previously formed structures (Gallot, 2002).

The causes of malformations are either endogenous (genetic) or exogenous, and there are probably interactions between the genetic and the exogenous factors (Roux, 2001). The precise cause of the malformation process, however, is most often unknown and the underlying physiopathological mechanisms are not elucidated (Brent, 1986).

The biology of fetal blood has been widely described in cases of isolated intra-uterine growth restriction (Cox et al., 1988; Economides et al., 1989; Weiner et al., 1989; Pardi et al., 1989; Roberts et al., 1999) but few studies have been conducted in fetuses with morphological anomalies (Bocconi, 1997; Lallata, 1998), and their biochemical profile remains little known.

We present the results of a study on 53 pregnancies with the complication of congenital malformations of variable expression and severity, and during which a fetal blood sampling was performed for fetal karyotyping. The gestational age ranged from 21 to 38 weeks of amenorrhea (average age: 28.5 ±4.45 WA). The karyotype proved to be normal for all the fetuses in this group.

The acid-base balance (pH, pCO_2, bicarbonate concentration) and the oxygenation level of the fetuses (pO_2, SaO_2) were evaluated on umbilical venous blood (UVB), taken by cordocentesis. At the same time, the glucose, lactate, free fatty acid, aceto-acetate, beta-hydroxybutyrate and cholesterol concentrations were measured, being essential biochemical constituents in relation to the nutritional status.

The aim of the work was to identify cases of fetal suffering and / or malnutrition, and to define the blood chemistry profile of this fetal population.

The results were compared with those of a control group of 73 healthy fetuses, with an average gestational age of 26 ± 5.7 weeks of amenorrhea, the results of which have already been published (Bon et al., 1997, 2007).

2. Materials and methods

2.1 Population studied

The pregnant women had consulted the Obstetrics department of the Hôtel-Dieu Hospital in Lyon, France (Professor D Raudrant). They were informed of the risks of fetal blood sampling and gave their consent.

The study was conducted in accordance with the recommendations of the Helsinki Declaration, paragraph II-6, and was approved by the hospital's Ethics Committee.

The gestational age at the time of blood sampling was calculated from the date of the last menstrual period, and confirmed by early ultrasound examination, carried out between 8 and 12 weeks of gestation.

2.1.1 Pathological group

This comprised 53 fetuses, with an average gestational age of 28.5 ±4.45 weeks of amenorrhea, for which the ultrasound examination had revealed one or more congenital malformations.

The various fetal anomalies found are described in table 1; in all cases, they were confirmed at birth or the end of pregnancy. The fetal blood sampling allowed a karyotype analysis which proved normal for all the fetuses in this group, so a chromosomic anomaly could be ruled out. Fetal growth was assessed in successive ultrasound examinations, by the measurement of three characteristic parameters: the transversal abdominal diameter, the biparietal diameter and the femoral length, the values being compared to those of the department's reference tables based on gestational age. Some fetuses presented growth restriction, associated with the morphological anomaly.

2.1.2 Control group

It is composed of 73 fetuses, with an average gestational age of 26.3 ±5.7 weeks of amenorrhea, in which cordocenteses were carried out for the prenatal diagnosis, due to a risk incurred by the fetus: suspicion of infection (30 cases of toxoplasmosis, 2 cases of rubella, 13 cases of varicella), fetal karyotype check (18 cases), and risk of fetal thrombopenia (10 cases). These fetuses were not affected by the suspected pathologies and had a normal karyotype; they had a normal morphology, growth and vitality for their gestational age.

All the babies were born at full term, had a birth weight above the 10th percentile of the reference curves in the department; their good health was confirmed by pediatric examination. The group studied could be regarded as similar to a reference population.

• Renal malformations	14 cases
• Obstructive uropathy, Prune Belly syndrome	1 case
• Unilateral obstructive uropathy	4 cases
• Bilateral obstructive uropathy	3 cases
• Cystic dysplasia (just 1 cyst)	1 case
• Unilateral multi-cystic renal dysplasia	3 cases
• Bilateral multi-cystic renal dysplasia	2 cases
• Digestive malformations	8 cases
• Stenosis of the small intestine with hydramnios	4 cases
• Stenosis of the oesophagus with hydramnios	2 cases
• Other digestive malformations	2 cases
• Cardiac malformations	5 cases
• Complete atrioventricular canal	1 case
• Interventricular communication	1 case
• Transposition of the major vessels	1 case
• Transposition of the large vessels, interventricular communication, interauricular communication	1 case
• Abnormal pulmonary venous return	1 case
• Malformations of the central nervous system	11 cases
• Hydrocephaly	4 cases
• Hydrocephaly and microcephaly	1 case
• Hydrocephaly and agenesis of the corpus callosum	1 case
• Microcephaly	2 cases
• Porencephalic cyst	1 case
• Spina bifida	2 cases
• Pulmonary malformations	3 cases
• Type 1 cystic adenomatoid malformation	1 case
• Type 2 cystic adenomatoid malformation	1 case
• Pulmonary hypoplasia with amniotic band syndrome	1 case
• Ascites	4 cases
• Isolated fetal ascites	3 cases
• Ascites with fetoplacental anasarca	1 case
• Multicystic hepatic tumour	1 case
• Limb reduction anomaly	1 case
• Anomaly of the extremities (club foot, club hand)	2 cases
• Genital anomaly (left ovarian cyst)	1 case
• Polymalformative syndrome	1 case
• Familial recurrent chylothorax	1 case
• Microphthalmia	1 case

Table 1. Pathological group. Fetal anomalies observed.

2.2 Sampling procedures

Fetal blood was obtained by cordocentesis from the umbilical vein, a technique carried out without maternal premedication, and only under local anesthesia at the puncture site (Daffos, 1983).

Five hundred microlitres of umbilical venous blood were collected in a heparinised syringe for gasometric and acid-base analyses, pH, partial CO_2 pressure (pCO_2), bicarbonate concentration, partial oxygen pressure (pO_2) and oxygen saturation (SaO_2).

The concentrations of ketone bodies (aceto-acetate and beta-hydroxybutyrate), free fatty acids (FFA) and cholesterol were evaluated on the same sample.

Two hundred microlitres of umbilical venous blood were collected on sodium fluoride to measure glucose and lactate, and 200 µl were collected without anticoagulant to measure hCG.

The good quality of the sample was verified, in particular the absence of contamination by maternal blood or amniotic fluid (Forestier, 1988). An immediate check was made by determining the erythrocyte group iI, and then a Kleihauer test, red and white cell count and a leukocyte differential count were carried out.

The serum hCG concentration of fetal blood was also measured, this test being proposed as a sensitive contamination marker due to the low hCG content of fetal serum, compared with that of the maternal blood and / or amniotic fluid (Dommergues et al., 1993).

Fetal blood samples were stored in ice at +4°C and transported to the laboratory immediately. The blood pH and gas measurement and the deproteinisation of the whole blood with perchloric acid for the ketone bodies determination were carried out upon receipt of the samples; the deproteinisation supernatants were decanted and kept at -20°C.

The blood was centrifuged at +4°C for the other analyses. The plasma glucose, lactate, cholesterol and hCG concentrations were determined immediately; the free fatty acid contents were determined subsequently on the plasma kept at -20°C.

The sample storage conditions were verified for the quantitative analysis carried out after freezing.

2.3 Analytical methods

The gasometric and acid-base analyses (pH, pO_2, pCO_2, bicarbonate, SaO_2) were carried out using the ABL 300 analyser (Radiometer, Copenhagen, Denmark).

The glucose and lactate concentrations were determined with the Ektachem 500 automated analyser (Kodak, New York, United States) by an enzymatic method using glucose oxidase (EC 1.1.3.4) and lactate oxidase (EC 1.13.12.4) and a measurement by reflectometry (reference interval in adult blood: 3.6 – 5.8 mmol/l for glucose and 0.7 – 2.1 mmol/l for lactate).

The total free fatty acid concentration was measured by a manual colorimetric enzymatic assay (Okabe et al., 1980), using an acyl-coenzyme A synthetase (EC 6.2.1.3), an acyl-coenzyme A oxidase (EC 1.3.3.6) and a peroxidase (EC 1.11.1.7) (Biomérieux, Marcy l'Etoile, France).

The ketone bodies content was determined by a fluorimetric enzymatic micromethod based on the measurement of NADH fluorescence (Olsen, 1971). Fluorescence was quantified on a spectrofluorimeter, the Kontron SFM (Kontron, Zurich, Switzerland), the excitation and emission wavelengths being 350 and 460 nm respectively. The reagents (lactate dehydrogenase, beta-hydroxybutyrate dehydrogenase, NADH, NAD) were supplied by Boehringer (Mannheim, Germany).

The adult blood reference values with the techniques used are from 0.018 to 0.078 mmol/l for aceto-acetate and 0.050 to 0.100 mmol/l for beta-hydroxybutyrate.

The cholesterol concentrations were measured by an enzymatic assay using a cholesterol esterase (EC 3.1.1.13) and a cholesterol oxidase (EC 1.1.3.6.) (Biomérieux, Marcy l'Etoile, France); the reference interval in adult blood is 3.6 – 7 mmol/l.

The hCG content was determined using the IMx automated analyser (Abbott Diagnostics, Abbott Park, United States), by a microparticle enzyme immunoassay.

2.4 Statistical analysis

The comparative study between the results of the control group and the pathological group was carried out using the Student's t-test (unpaired series) and the Mann-Whitney U test (non-parametric test). The search for a possible relation between different constituents measured in the umbilical venous blood was carried out by calculating the linear correlation coefficient r and the Spearman coefficient rs. The significance of the correlations was evaluated with Fisher's exact test.

In the control group, an analysis by linear regression was used to study any changes in the parameters according to gestational age (expressed as weeks of amenorrhea).

A p value below 0.05 was considered to be statistically significant.

3. Results

The results obtained from fetuses with malformations were compared with those from control fetuses, with normal growth and morphology.

The means and standard deviations were calculated for all 53 fetuses and per sub-group, with a minimum of 3 cases per category of malformation. When a type of anomaly is presented only by one or two fetuses, the results are given individually.

3.1 Gasometric and acid-base parameters in the umbilical venous blood (tables 2 and 3, figure 1)

The results were compared with norms established in the control population for the gestational age considered, as the pH, pO_2 and SaO_2 decrease physiologically in the UVB during gestation, whereas the pCO_2 and the bicarbonate concentration rise (Bon et al., 1997).

The acidemia and hypoxemia statuses were defined by pH and pO_2 values beyond a standard deviation below the mean, and the hypercapnia statuses by pCO_2 values higher by more than one standard deviation to the mean.

Only the pO_2 and the SaO_2 of the entire group (n=53) are significantly reduced when compared to the norms of the control group, whereas the other parameters have not significantly changed.

However, the results are scattered and were analysed by sub-group.

	Controls	Malformations (entire group)	Renal malformations	Digestive malformations	Cardiac malformations	Malformations of the central nervous system	Pulmonary malformations	Ascites
n	73	53	14	8	5	11	3	4
pH	7.31 0.054	7.28 0.090	7.31 0.033	7.31 0.023	7.22** 0.130	7.24** 0.125	7.23 0.049	7.28 0.107
pCO_2 (kPa)	5.99 0.85	6.17 1.27	5.79 0.67	6.02 0.58	7.62** 2.05	6.52 1.60	6.47 0.65	5.65 0.45
HCO_3^- (mmol/l)	22.16 1.90	21.46 2.45	21.73 1.86	22.77 1.44	22.92 3.73	20.04** 2.66	20.23 1.72	19.97 3.42
pO_2 (kPa)	6.02 1.69	4.89*** 1.60	5.53 1.61	4.35** 1.16	4.01** 1.27	4.38** 1.20	5.30 1.92	4.47 2.38
SaO_2	0.71 0.18	0.58*** 0.23	0.67 0.19	0.54** 0.16	0.43** 0.22	0.53** 0.24	0.61 0.24	0.54 0.35

The results are expressed as means and standard deviations.
n = number of samples
** $p < 0.01$
*** $p < 0.001$

Table 2. Gasometric and acid-base parameters in the umbilical venous blood (number of cases ≥ 3).

3.1.1 Renal malformations (n=14)

Four cases of moderate hypoxemia (pO_2 between 3.1 and 4.04 kPa) were found in the following pathologies: one case of Prune Belly syndrome, two cases of bilateral obstructive uropathy, and one case of multicystic renal dysplasia.

The pH is still within normal limits, whereas the pCO_2 is elevated in one case, associated with an increase in the plasma bicarbonate concentration.

The bicarbonate level is reduced in 3 cases, lying between 18 and 20 mmol/l.

3.1.2 Digestive malformations (n=8)

The pO_2 value is low for 3 fetuses, including 2 cases of duodenal stenosis and one case of oesophagus stenosis with hydramnios.

The pH and the pCO_2 remain within normal limits, while the plasma bicarbonate concentration was found to be raised in 2 cases.

3.1.3 Cardiac malformations (n=5)

This sub-group is characterised by a state of acidemia, hypoxemia and hypercapnia in 3 cases out of 5.

The mean pH and pO_2 are significantly decreased and the mean pCO_2 significantly increased, when compared with the control group values.

One case in particular of severe acidosis (pH of 6.99), both gaseous and metabolic, was observed in a fetus presenting a complex cardiopathy, with a complete atrioventricular canal.

The gasometric and acid-base balance was however found to be normal in two fetuses, one of which presented a transposition of the main vessels and the other an abnormal pulmonary venous return.

3.1.4 Malformations of the central nervous system (n=11)

The pH, pO_2, SaO_2, and bicarbonate concentration are on average significantly lower than those of the control group.

A state of acidemia, often gaseous and metabolic, is present in 5 cases, and a state of hypoxemia in 6 cases.

These anomalies are found in fetuses with hydrocephaly or spina bifida.

Also noted is one case of acidemia (pH of 7.18), associated with hypercapnia (pCO_2 of 7.99 kPa), in the presence of microcephaly linked to a cytomegalovirus (CMV) infection.

3.1.5 Pulmonary malformations (n=3)

The pH and the pO_2, and likewise the bicarbonate concentration of the UVB, are lower in a fetus presenting a major cystic adenomatoid malformation of the left lung, type 2, with the start of hydrops and hydramnios.

In the case of type 1 adenomatoid malformation, the biological balance is normal.

The third clinical case (pulmonary hypoplasia with amniotic band syndrome) is associated with acidosis (pH of 7.20) with hypercapnia (pCO_2 of 7.22 kPa); at birth, the infant presented generalised cyanosis and acute respiratory distress.

3.1.6 Ascites (n=4)

This subgroup is characterized by scattered results.

The gasometric and acid-base balance is normal in 3 cases. However, in the presence of ascites with the complication of fetoplacental anasarca, we found acidosis (pH 7.10), which was essentially metabolic (bicarbonate concentration of 14.9 mmol/l), and severe hypoxemia (pO_2 of 1.20 kPa).

3.1.7 Other malformations (isolated cases, n=8)

The gasometric balance shows acidemia, hypoxemia and hypercapnia, in the presence of a multicystic hepatic tumour.

A decrease in pO_2 is observed in the fetus presenting a genital anomaly, whereas the pH, pCO_2, and bicarbonate concentration are within the normal range.

One state of probably gaseous alcalosis, in the presence of a polymalformative syndrome, is found.

The case of chylothorax, with pleural effusion, is complicated by gaseous acidosis with moderate hypoxemia.

	Hepatic tumour	Reductional anomaly of the limbs	Anomaly of the extremities	Genital anomaly	Polymalformative syndrome	Familial recurrent chylothorax	Microphthalmia
n	1	1	2	1	1	1	1
pH	7.19*↘	7.33	7.32 7.36	7.31	7.49*↗	7.25*↘	7.36
pCO_2 (kPa)	8.56*↗	5.33	5.25 6.08	5.57	3.75*↘	7.24*↗	5.01
HCO_3^- (mmol/l)	23.9	21.1	19.9 25.6	20.9	21.5	23	21.3
pO_2 (kPa)	2.74*↘	7.28	7.01 5.91	2.97*↘	5.07	3.79*↘	7.08
SaO_2	0.23*↘	0.85	0.82 0.79	0.33*↘	0.77	0.43*↘	0.86

n = number of samples
* value outside the normality interval for the gestational age
↗ value increased
↘ value decreased

Table 3. Gasometric and acid-base parameters in the umbilical venous blood (number of cases ≤ 2).

3.2 Metabolic parameters in the umbilical venous blood (tables 4 and 5, figure 1)

The results were analysed by type of pathology and compared with the norms established for the gestational age considered.

In the reference population, the umbilical venous concentrations of the parameters studied were found to be stable during gestation, with the exception of lactate which rises physiologically (Bon et al., 2007).

The limit of normal values was set at one standard deviation more or less on either side of the mean value of the control group, except for free fatty acids and ketone bodies for which the limits were set at the 10th and 90th percentiles of the values of this group.

	Controls	Malformations (entire group)	Renal malformations	Digestive malformations	Cardiac malformations	Malformations of the central nervous system	Pulmonary malformations	Ascites
n	73	53	14	8	5	11	3	4
Glucose (mmol/l)	3.48 0.36	3.57 0.90	3.48 0.53	3.57 0.44	3.68 0.44	3.48 0.45	2.36 0.70	3.02 0.96
Lactate (mmol/l)	1.48 0.45	2.15*** 1.12	1.87* 0.64	1.86* 0.59	2.42*** 0.80	2.44*** 1.27	2.6 2.34	2.42 2.35
Free fatty acids (mmol/l)	0.125 0.046	0.138 0.049	0.177*** 0.030	0.124 0.022	0.188** 0.045	0.091* 0.045	0.130 0.032	0.142 0.044
Aceto-acetate (mmol/l)	0.111 0.059	0.126 0.084	0.128 0.093	0.178** 0.120	0.072 0.037	0.139 0.074	0.136 0.073	0.091 0.015
Beta-hydroxy-butyrate (mmol/l)	0.321 0.149	0.345 0.240	0.350 0.296	0.394 0.278	0.173 0.054	0.398 0.272	0.370 0.242	0.350 0.070
Cholesterol (mmol/l)	1.67 0.35	1.59 0.44	1.72 0.40	1.69 0.35	1.76 0.29	1.23** 0.38	1.27 0.47	1.49 0.50

The results are expressed as means and standard deviations.
n = number of samples
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Table 4. Metabolic parameters in the umbilical venous blood (number of cases ≥ 3).

3.2.1 Renal malformations (n=14)

Lactatemia is moderately increased in 4 cases, in relation with a fall in the pO_2.

Glycemia is no different, on average, from that of the control group; however, a low umbilical venous glucose concentration, at 2.8 mmol/l, is found in one case of multicystic renal dysplasia.

An increase in UVB free fatty acids level is also observed.

3.2.2 Digestive malformations (n=8)

Few metabolic anomalies are found, with the exception of an increase in lactatemia in 3 cases, and an increase in ketone bodies, in particular aceto-acetate, in 2 cases.

3.2.3 Cardiac malformations (n=5)

The metabolic balance shows a significant increase in lactatemia, with umbilical venous concentrations lying between 1.4 and 3.1 mmol/l; a small increase in the serum concentration of free fatty acids is also found.

3.2.4 Malformations of the central nervous system (n=11)

Hyperlactatemia is present in 6 cases, associated with a diminution in the pO_2, with lactate concentrations being between 3 and 5.4 mmol/l.

This sub-group is also characterised by a decrease in the average free fatty acid concentration, and by a significant fall in cholesterolemia. UVB cholesterol is found at a lower level than that of the control group in over 50% of cases, the lowest concentration being 0.93 mmol/l.

3.2.5 Pulmonary malformations (n=3)

Umbilical venous glucose and cholesterol concentrations are found to be reduced in the 2 cases of cystic adenomatoid malformations of the lung.

3.2.6 Ascites (n=4)

The results are within the normal range in the three cases of isolated fetal ascites.

The case of ascites with the complication of fetoplacental anasarca shows severe metabolic changes: hyperlactatemia of 5.9 mmol/l, hypoglycemia of 1.7 mmol/l, and hypocholesterolemia of 1.05 mmol/l.

3.2.7 Other malformations (isolated cases, n=8)

Hypoglycemia, hyperlactatemia, and a fall in the venous umbilical ketone bodies concentration are found in the case of multicystic hepatic tumour.

Likewise, in the two fetuses presenting anomalies of the extremities, the following are noted: elevated umbilical venous glycemia of 6.8 and 7.1 mmol/l, with maternal glycemia being 7.0 and 7.8 mmol/l respectively.

Lactatemia is significantly increased in the presence of a genital anomaly (left ovarian cyst).

A moderate rise in the lactate and ketone bodies UVB concentrations is observed in the case of familial recurrent chylothorax.

	Hepatic tumour	Reductional anomaly of the limbs	Anomaly of the extremities	Genital anomaly	Polymalformative syndrome	Familial recurrent chylothorax	Microphthalmia
n	1	1	2	1	1	1	1
Glucose (mmol/l)	2.5*↘	3.5	6.8*↗ 7.1*↗	3.6	3.7	4.0	4.6
Lactate (mmol/l)	2.9*↗	1.2	1.6 1.7	4.3*↗	1.8	2.3*↗	1.5
Free fatty acids (mmol/l)	0.076	0.179	0.068 0.135	0.087	0.117	0.113	0.134
Aceto-acetate (mmol/l)	0.020*↘	0.101	0.090 0.098	/	0.105	0.195*↗	0.110
Beta-hydroxy-butyrate (mmol/l)	0.105*↘	0.236	0.230 0.284	/	0.294	0.640*↗	0.470
Cholesterol (mmol/l)	1.20	1.45	1.92 2.34	1.43	1.82	2.17	2.43

n = number of samples
* value outside the normality interval for the gestational age
↗ value increased
↘ value decreased

Table 5. Metabolic parameters in the umbilical venous blood (n ≤ 2).

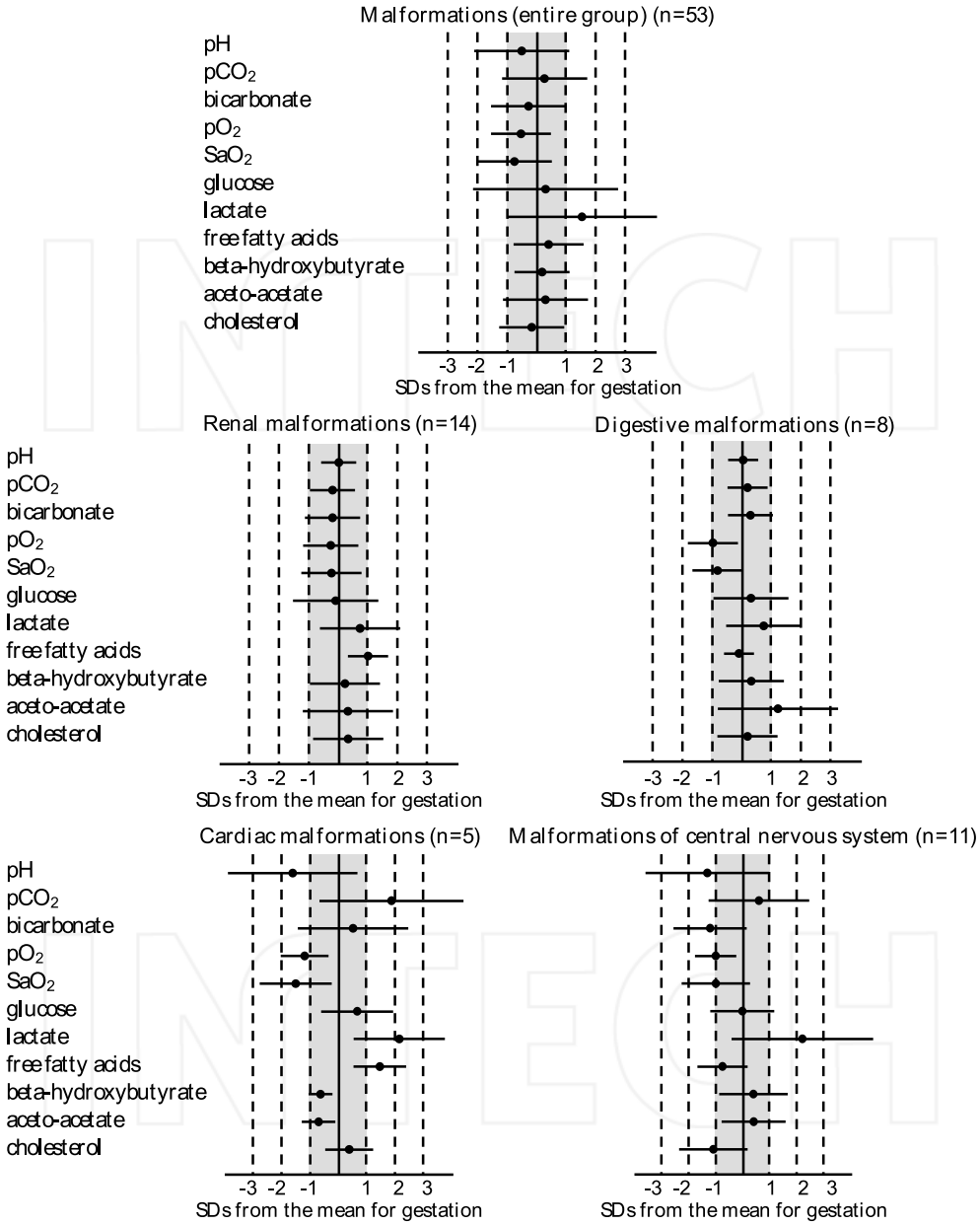

Fig. 1. Means (circles) and standard deviations (bars) of UVB constituents in pathological group and sub-groups (number of samples ≥ 5). Values are expressed as number of standard deviations (SDs) from the mean of control group. Shaded area indicates extent of reference range for the different variables.

4. Discussion

During its intra-uterine life, the conceptus can be exposed to various agents (physical, chemical and infectious) which may interfere with its development. However, they are responsible for only 5% of the congenital malformations observed, as around 5% are attributable to chromosome anomalies, 10 to 20% to hereditary diseases, and 70% due to indeterminate causes (Gallot, 2002). The fetus' response to an aggression depends mainly on its level of maturity.

We have studied 53 pathological pregnancies, for which a fetal blood sampling was performed following confirmation by ultrasound of one or more fetal malformation(s), or a risk of malformation; the population studied is characterised by its heterogeneity, as previously described.

The fetal karyotype was found to be normal in all cases.

In this context, the obstetrical decision as to whether or not to continue the pregnancy, depends principally on the prognosis associated with the malformation.

The acid-base parameters measured allow a state of fetal distress to be diagnosed, the metabolic parameters assessed characterise the level of energy supply to fetus affected by morphological anomalies, some 20% of which also presented growth restriction.

The fetal origin of the umbilical venous blood taken was carefully checked in our study protocol, in particular with the measurement of hCG serum concentration; reference values in the fetal blood were established previously for this parameter (Bon et al., 1999).

4.1 Acid-base balance and gasometric data

The pH is not significantly different, on average, from that of the control group; however, the analysis of results showed a state of acidemia to be present in 12 fetuses, i.e. 22% of the group; this relates mainly to cases of cardiac malformation, central nervous system malformations, pulmonary malformations, one case of effusion with anasarca, and one case of hepatic tumour.

The plot on a Davenport diagram of the pH and total CO_2 shows that acidosis is usually mixed: gaseous and metabolic. However, gaseous acidosis is predominant as the pH is significantly correlated with the pCO_2 ($r = -0.866$, $p < 0.001$), while the correlation between pH and plasma bicarbonate concentration is less significant ($r = 0.402$, $p = 0.003$). The pCO_2 is significantly increased in the event of cardiac malformations.

In the presence of effusion with fetoplacental anasarca and flooding with amniotic fluid, acidosis is of essentially metabolic origin, due to the high level of lactic acid in the amniotic fluid.

The most frequent gasometric anomaly is the fall in the partial oxygen pressure, present in over 40% of observations. The state of hypoxemia is not specific to any pathology; it is found in all types of malformation, with the exception of anomalies of the limbs and extremities.

Strictly fetal causes - anemia or cardiovascular failure - can be the cause of fetal hypoxia, responsible for a deviation in the metabolism towards anaerobia.

Cerebral hypoxia is often associated with a poor neurological prognosis, and depending on its severity, can be the cause of an apoptotic process. A state of hypoxemia frequently accompanies malformations of the central nervous system.

The fall in the umbilical venous pO_2 is associated in 15% of cases, with a rise in the pCO_2, leading to a state of gaseous acidosis. An impaired transplacental diffusion of respiratory gases may be the cause; indeed, placental lesions (infarct and thromboses of the villositary vessels) were indicated in some observations.

The episode of acidosis may be secondary to anomalies in development, as a fetus with malformations probably has limited regulation abilities and insufficient resources to fight against acidosis.

Conversely, a state of hypoxemia and then acidemia was able to favour the occurrence of malformations, due to a greater sensitivity of the fetus to an external, infectious, toxic aggression. An episode of acidosis may facilitate a toxic drug being passed on to the fetus, with the pH gradient between maternal blood and fetal blood influencing the transfer of certain drugs, such as weak acids (Fontaine, 2001).

4.2 Metabolic parameters

Nutritional and metabolic anomalies are less frequent and often less severe than acid-base anomalies.

The umbilical venous glucose concentration, an essential energetic substrate for the fetus, does not differ, on average, from that of the control group, which means that the hormonal factors of glycemic regulation are functional in the pathological group, with the neoglucogenesis abilities being maintained.

However, ten cases of hypoglycemia are noted, often associated with hypoxemia. A fall in blood glucose may be secondary to a fall in the transplacental passage of glucose, in parallel to the reduced diffusion of oxygen, or alternatively to a fetal or placental over-consumption of glucose, associated with an acceleration of anaerobic glycolysis; these mechanisms were mentioned with regard to severe growth retardation (Economides et al., 1989, Nicolini et al., 1989).

Fetal glycemia is low in the presence of a multicystic hepatic tumour; it is accompanied by a fall in ketone bodies and cholesterol concentrations in the umbilical venous blood; these biological results are the consequence of hepatic dysfunction. In the case of effusion with fetoplacental anasarca, the fall in the umbilical venous glycemia is probably the result of dilution by amniotic fluid.

Umbilical venous glucose was found to be elevated in some cases, in particular concentrations of 6.8 and 7.1 mmol/l are associated with maternal venous concentrations of 7.2 and 7.8 mmol/l. At these conditions, these values are the expression of a pre-diabetic or diabetic state in the mother, and this can be implicated in the occurrence of the malformation (Boivin et al., 2002, Gabbe et al., 2003).

Umbilical venous lactatemia is, on average, significantly higher in the pathological group than in the control group. Hyperlactatemia, present in 34% of observations, is secondary to

hypoxia, with a significant negative correlation between pO_2 and lactate in the UVB ($r = -0.420$, $p < 0.02$). The rise in lactate may also be associated with poor lactate clearance by the placenta and is one of the components of metabolic acidosis.

Umbilical venous concentrations of free fatty acids were found to be significantly lowered in the group of fetuses with malformations of the central nervous system.

Few data are available on the maternal-fetal metabolism of free fatty acids during pathological pregnancies.

In a group of 24 patients with a pregnancy complicated by intra-uterine growth restriction (Ortega - Senovilla, 2010), an increase in free fatty acid and retinol concentrations was found in the maternal plasma, in comparison with the results of the control group; the authors put forward the hypothesis of a limitation in the transplacental transfer of retinol and free fatty acids, lower concentrations of which are found in the fetal plasma. A similar mechanism can be mentioned in the case of pregnancies complicated by fetal malformations, or alternatively an accelerated turnover of free fatty acids in the fetal compartment could be implicated.

Umbilical venous concentrations of ketone bodies and in particular beta-hydroxybutyrate are very scattered in the pathological group and do not differ, on average, from those of the control group. However, in some pregnancies, namely around 15% of cases, a moderate increase in ketone bodies concentration was found in the umbilical venous blood: in three cases of renal malformations, two cases of digestive malformations, three cases of malformations of the central nervous system and one case of pulmonary malformation.

Fetal ketone bodies can be supplied by transplacental transfer from the maternal blood (Pere et al., 2003), and there is also probably an intrinsic fetal production (Tannirandorm et al., 1999). The teratogenic action of beta-hydroxybutyrate has been suspected in certain diabetic pregnancies (Jovanovic et al., 1998).

Cholesterol, an essential constituent for embryo development and growth, is found at a reduced umbilical venous concentration in some pathological pregnancies: in the presence of renal malformations (2 cases out of 14), pulmonary malformations (2 cases out of 3), ascites with anasarca (1 case), hepatic tumour (1 case), and malformations of the central nervous system (7 cases out of 11); in this final sub-group, umbilical venous cholesterolemia is, on average, significantly lower than that of the control group.

It should be borne in mind that cholesterol is essential for the development of the central nervous system and cerebral growth (Roux et al., 1997, 2000).

Cholesterol is mainly synthesised in the fetal compartment as maternal cholesterol does not readily pass through the placenta (Carr et al., 1982).

In the pathological pregnancies, the inadequate production of cholesterol by the fetal liver may be associated with hepatic immaturity, or alternatively with defective oxygenation conditions in the fetus; we noted the frequency of cases of hypoxemia in the group of fetuses studied.

The possibility of a fetal liver disorder was reported by Roberts et al. in growth-restricted fetuses.

The decrease in cholesterolemia may be related to growth problems which are often associated with morphological anomalies. The fundamental role of cholesterol in embryo development is well established, and anomalies in cholesterol synthesis are involved in a number of human malformation syndromes (Porter et al., 2003; Guizzetti et al., 2005).

5. Conclusion

We studied a group of 53 fetuses with malformations of varying clinical expression and severity, and measured in the fetal blood essential biochemical parameters which may be associated with fetal well-being; the results obtained were compared with those from a group of 73 fetuses with normal growth and morphology.

The disparity in the populations studied make the interpretation of the results difficult. Around 20% of the pathological pregnancies are accompanied by a state of fetal distress with acid-base balance alterations. Gaseous acidosis is present in the cardiac malformations; acidosis is mixed in the malformations of the central nervous system and pulmonary malformations, and is essentially metabolic in the case of fetoplacental anasarca.

The gasometric anomaly most frequently encountered is hypoxemia, present in around 40% of observations and in almost all types of pathology.

The reduction in the umbilical venous pO_2 probably reflects an impaired transplacental transfer of respiratory gases and placental dysfunction; it may also be related to a maternal cause (such as an episode of hypoxemia), or a properly fetal cause such as fetal anemia.

Metabolic anomalies, often less common, are associated with acid-base anomalies. The decrease in umbilical venous glucose, found in 18% of the pathologies studied, leads to a suspicion of a reduced transplacental passage of glucose, in parallel to the reduced diffusion of oxygen.

Conversely, the umbilical venous hyperglycemia present in some cases, is secondary to a maternal hyperglycemia and probably associated with a diabetic or pre-diabetic state in the mother.

Changes to concentrations of lactate, free fatty acids, ketone bodies and cholesterol are markers of a disrupted fetal metabolism. Hyperlactatemia is associated with impaired oxygenation conditions and inadequate placental clearance.

The reduction in umbilical venous cholesterolemia found in some pregnancies reflects defective metabolic conditions in the fetus. It has possible consequences on fetal growth and is possibly linked to the morphological anomalies found, with cholesterol being an essential constituent for the development of the embryo.

The results obtained are however a reflection of an instantaneous measurement and the biochemical anomalies found may be a consequence of the malformations.

Moreover, in nearly 50% of cases, the blood chemistry and the in utero living conditions of the fetus with congenital malformations are not very disrupted compared with those of the normally constituted fetus.

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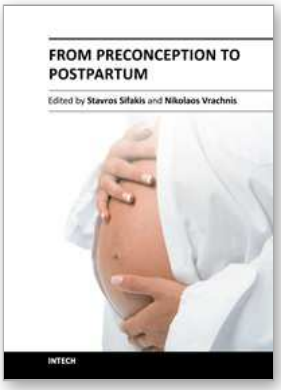

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