Fetal Metabolism

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Abstract

Normal reference ranges for apolipoprotein A-I, apolipoprotein A-II, apolipoprotein B, total triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol + chylomicron, plasma glucose, total protein, albumin and globulin were determined from 25 fetal plasma samples between 21-39 weeks' gestation. Pure fetal blood was obtained by cordocentesis under continuous ultrasound guidance. They were referred to us for advanced maternal age and a previous chromosomal aneuploidy baby. All these biochemical parameters excepts total protein and albumin showed no change with gestational age. These normal values of fetal metabolism will improve our knowledge of physiology and help to determine the specific values of a test in fetal pathology.

Key word : Fetal Blood, Lipid, Glucose, Protein, Reference ranges

Biochemical studies on neonates[1] report some differences compared with adults. It seems that fetal metabolism also differs too. However, past studies on fetal metabolism depended on samples of blood obtained from premature infants or fetuses which had either spontaneously aborted or been delivered by hysterotomy[2,3]. The postnatal sampling techniques could affect physiological status and might have altered normal values[4]. Due to advances in fetal medicine, pure fetal blood can now be easily obtained *in utero* by sampling *via* the umbilical cord, using a needle guided by ultrasound[5], with minimal disturbance to the fetus and the results probably represent physiological levels. To our knowledge there is no report of fetal metabolism in Thailand. A knowledge of normal fetal metabolism during gestation has become indispensable. The normal values are a prerequisite for prenatal diagnoses of congenital biochemical disorders, for a better approach to normal and abnormal behavior, and possibly in the future for fetal monitoring and therapy.

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MATERIAL AND METHOD

Patients

A cross sectional prospective study was undertaken at the Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn Hospital. Written informed consents were undertaken in all cases. Fetal and maternal samples were obtained from 25 normal pregnancies of between 21 and 39 weeks' gestation. The gestational age was determined by calculation from the date of the last menstrual period and confirmed by ultrasonography. All mothers were healthy without any medical complications such as diabetes or hypertension. All babies were confirmed healthy at birth.

Sampling procedures

Fetal blood samples were obtained by direct puncture of the umbilical vein near the cord insertion on the placenta (cordocentesis) as previously described[6]. Pure fetal blood was obtained in all cases, without dilution by amniotic fluid or contamination by maternal blood[6]. The maternal samples were all from the antecubital veins immediately before the fetal blood sampling. For this study, 2 ml of fetal blood and 5 ml of maternal blood were taken into heparinized tubes and then immediately separated, the plasma then being stored at -40°C until analysis.

Biochemical measurements

Lipid metabolism: Total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol + chylomicron, total triglyceride, apolipoprotein A-I, apolipoprotein A-II and apolipoprotein B were determined by spectrophotometry. Standardization of the analysis was compared with the CDC laboratory (Atlanta, U.S.A.), Saint Jan laboratory (Bruggs, Belgium) and WHO CCR (Geneva, Switzerland).

Protein metabolism: Total protein, albumin and globulin were determined by spectrophotometry. Standardization of the analysis was compared with our central laboratory.

Carbohydrate metabolism: Plasma glucose was determined by glucose oxides technique. Standardization of the analysis was compared with our central laboratory.

Statistical analysis

SPSS program was used for statistical analysis. Mean and standard deviation (SD) for each parameter were calculated. Correlation coefficient and regression analysis were calculated by standard formula to compare the correlation between each parameter and gestational age. Comparison between maternal and fetal sample was made by unpaired *t* test or Mann-Whitney test where appropriate.

RESULTS

The results obtained for 25 normal human fetuses and their mothers between the 21st and 39th week of gestation are shown in Table 1. The indications for fetal blood sampling were advanced maternal age (23 cases) and previous aneuploidy baby (2 cases).

Lipid metabolism

The concentrations of apolipoprotein A-I, apolipoprotein A-II, apolipoprotein B, total triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, and VLDL-cholesterol + chylomicron, in both maternal and fetal blood showed no change with gestational age. All parameters except LDL-cholesterol were significantly lower in the fetus than in the mother.

Protein metabolism

Maternal total protein, albumin and globulin concentrations did not change with gestation. The mean concentrations of total protein, albumin and globulin in maternal plasma were 6.86 g/dl (SD = 0.47, range 6.20 - 7.50), 3.75 g/dl (SD = 0.24, range 3.30 - 4.10), and 3.11 g/dl (SD = 0.30, range 2.60 - 3.60), respectively. Total protein and albumin concentrations in fetal plasma increased throughout gestation (Fig. 1 and Fig. 2). The correlation was as follows: Total protein in fetal plasma (g/dl) = -0.01 + 0.134 gestational age (wk), $R = 0.78$, $P < 0.0001$; Albumin in fetal plasma (g/dl) = -0.82 + 0.109 gestational age (wk), $R = 0.76$, $P < 0.0001$. Fetal globulin remained constant throughout gestation with the mean concentration of 1.53 g/dl (SD = 0.43, range 0.09 - 2.5).

Carbohydrate metabolism

Fetal plasma glucose did not change with gestation and the concentration was significantly lower than the maternal value (Table 1).

DISCUSSION

Normal values of biochemical parameters are clearly established for neonates as well as for premature infants. Past studies on the biochemical constituents of fetal blood were taken from fetuses

Table 1. Maternal and fetal biochemical parameters between 21 and 39 weeks of gestation (N = 25).

Parameter	Maternal (mean ± SD) (range)	Fetal (mean ± SD) (range)	P
Apolipoprotein A-I (mg/dl)	154.52 ± 23.77 (108.00 - 197.40)	49.49 ± 7.89 (34.90 - 68.80)	0.001
Apolipoprotein A-II (mg/dl)	42.45 ± 9.67 (27.40 - 67.00)	19.05 ± 7.38 (12.02 - 49.05)	0.001
Apolipoprotein B (mg/dl)	87.89 ± 20.99 (58.90 - 138.00)	18.31 ± 4.36 (12.86 - 29.21)	0.001
Total triglyceride (mmol/L)	2.09 ± 0.66 (1.08 - 3.86)	0.35 ± 0.19 (0.18 - 1.10)	0.001
Total cholesterol (mmol/L)	5.41 ± 1.09 (3.41 - 7.39)	1.73 ± 0.55 (0.94 - 3.49)	0.001
HDL-cholesterol (mmol/L)	1.42 ± 0.27 (1.06 - 1.99)	0.49 ± 0.29 (0.29 - 1.74)	0.001
LDL-cholesterol (mmol/L)	0.76 ± 0.16 (0.01 - 4.06)	0.64 ± 0.28 (0.13 - 1.21)	NS
VLDL-cholesterol + chylomicron (mmol/L)	3.25 ± 1.37 (0.48 - 6.24)	0.68 ± 0.42 (0.23 - 2.19)	0.001
Plasma glucose (mg/dl)	82.39 ± 11.48 (58.00 - 107.00)	69.04 ± 12.93 (41.00 - 91.00)	0.001

NS = not significant

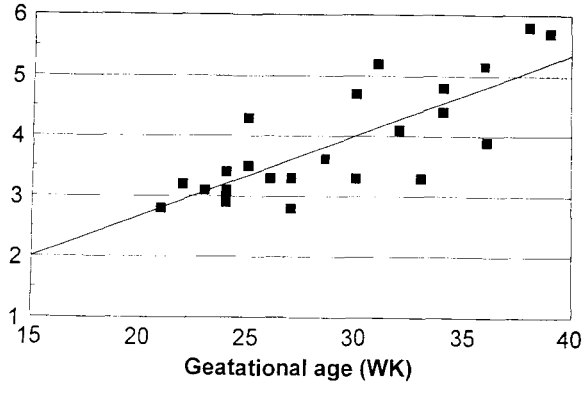

Fig. 1. Total protein in fetal blood.

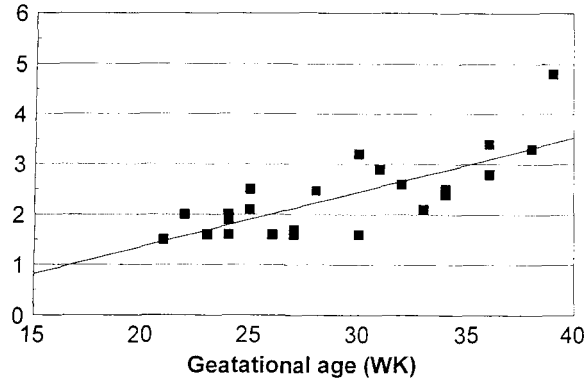

Fig. 2. Albumin in fetal blood.

which had been aborted and were, therefore, restricted to a few parameters. Moniz et al[7] and Forestier et al[8] reported normal reference ranges for fetal biochemical substances in fetal blood in the second trimester of pregnancy, and in the maternal plasma. In our study, the normal values of lipid metabolism, protein metabolism and carbohydrate metabolism were determined in samples obtained by direct puncture under continuous ultrasound guidance from 25 normal human fetuses between the 21st and 39th week of gestation.

All fetal lipid profiles did not change with gestation and were found to be very low, except LDL-cholesterol, when compared to maternal levels. This could reflect a fast utilization in lipid building and a very high lipid turnover during fetal life. Another hypothesis concerns the liver immaturity of fetuses at this stage of development. Both the

developing fetus and the placenta require lipid metabolism for the synthesis of complex lipids necessary for the biogenesis of plasma membranes, intracellular membranes, and organelles; triacylglycerol stores; and secreted products such as lipoproteins, bile, and pulmonary surfactant[9]. Our normal values can be used as the reference values for the prenatal diagnosis of abnormal lipid metabolism *in utero* such as congenital hypercholesterolemia.

In our study, the levels of total protein and albumin were lower during fetal life, compared with maternal levels. Both total protein and albumin concentrations in fetal plasma increased throughout gestation. It has been reported that the levels of total protein and albumin at birth are the same as in adults[10]. The very low fetal plasma protein concentration bears out the hypothesis that the placenta is sparingly permeable to proteins. By 12-16 weeks the fetal liver can synthesize all the plasma proteins except the gammaglobulin[10]. Fetal plasma albumin concentrations begin increasing substantially from 20 weeks. There is suggestive evidence that fetal alpha-fetoprotein synthesis is decreasing at this time and it is likely that albumin synthesis is switched on to become the major plasma protein in the circulation[11].

Fetal glucose values were lower than in the mother. The decrease of glucose levels in the fetuses will involve a reduction of energy supply. Echonomides et al[4] found that maternal blood glucose concentration, not fetal plasma insulin, was the major determinant of fetal blood glucose concentration. The rate of maternal-to-fetal glucose transfer is a function of the transplacental concentration gradient[12].

Comparing our fetal levels of total triglecéride, total cholesterol, total protein, albumin and globumin with those at similar gestation in previous studies[7,8], our results are in general very similar. However, there have been no reports of other fetal lipid profiles *in utero*.

In conclusion, this study reported the normal values of commonly measured fetal metabolism in pure fetal blood from healthy fetuses. These values may be used as the reference ranges for pathophysiological investigations.

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REFERENCES

1. Diaz M, Leal C, Ramon Y, et al. Cord blood lipoprotein-cholesterol: relationship birth weight and gestational age of newborns. Metabolism 1989;38:435-8.
2. Hyvarinen M, Zelter P, Oh W, Stiehm ER. Influence of gestational age on serum levels of alpha-fetoprotein, IgG globulin and albumin in newborn infants. J Pediatr 1973;82:430-7.
3. Thalme B. Potassium, sodium, chloride, total protein, calcium and inorganic phosphorus in plasma of human fetuses and newborn infants. Biol Neonate 1971;18:444-56.
4. Echonomides DL, Proudler A, Nicolaides KH. Plasma insulin in appropriate- and small-for-gestational-age fetuses. Am J Obstet Gynecol 1989; 160:1091-4.
5. Tannirandorn Y. Recent advances in antenatal diagnosis. Chula Med J 1990;34:625-41.
6. Tannirandorn Y, Promchainant C, Romyanan O, Witoonpanich P, Snidvongs W, Phaosavasdi S. Rapid karyotyping in the second and third trimesters for fetuses at risk of chromosomal abnormalities at Chulalngkorn Hospital. J Med Assoc Thai 1991;74:200-4.
7. Moniz CF, Nicolaides KH, Bamforth FJ, Rodeck CH. Normal reference ranges for biochemical substances relating to renal, hepatic, and bone function in fetal and maternal plasma throughout pregnancy. J Clin Pathol 1985;38:468-72.
8. Forestier F, Daffos F, Rainaut M, Bruneau M, Trivin F. Blood chemistry of normal human fetuses at midtrimester of pregnancy. Pediatr Res 1987;21: 579-83.
9. Coleman RA. Placenta metabolism and transport of lipid. Fed Proc 1986;45:2519-23.
10. Dancis J, Brauerman N, Lind J. Plasma protein synthesis in the human fetus and placenta. J Clin Invest 1957;36:398-404.
11. Gitlin D, Pernicells A, Gitlin GM. Synthesis of alpha-fetoprotein by the liver, yolk sac and gestational tract of the human conceptus. Cancer Res 1972;32:979-82.
12. Ingermann RL. Control of placental glucose transfer. Placenta 1987;8:557-71.

เมตาบอลิสมของทารกในครรภ์

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ผู้วิจัยได้รายงานค่าปกติของ Apolipoprotein A-I, Apolipoprotein A-II, Apolipoprotein B, Total triglyceride, Total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol + chylomicron, Plasma glucose, Total protein, Albumin และ Globulin ที่ได้จากการตรวจเลือดทารกในครรภ์จำนวน 25 ราย เมื่ออายุครรภ์ 21-39 สัปดาห์ เลือดทารกได้จากการเจาะเลือดดำของสายสะดือ โดยอาศัยการตรวจคลื่นเสียงความถี่สูงชี้นำปลายเข็ม ทารกในครรภ์ได้ถูกส่งมาปรึกษาเนื่องจากมารดาอายุมากและเคยคลอดบุตรที่มีโครโมโซมผิดปกติ ค่าชีวเคมีปกติที่ได้พบว่า ไม่มีความสัมพันธ์กับอายุครรภ์ ยกเว้นค่า Total protein และ Albumin ค่าชีวเคมีปกติของทารกในครรภ์เหล่านี้ เป็นพื้นฐานสำหรับการวินิจฉัยและรักษาภาวะผิดปกติของเมตาบอลิสมของทารกที่เป็นมาแต่กำเนิด นอกจากนี้ยังช่วยอธิบายให้แพทย์ได้เข้าใจถึงสาเหตุที่ทำให้เกิดความผิดปกติของทารกในครรภ์ได้ดีขึ้น

คำสำคัญ : เลือดทารกในครรภ์, ไขมัน, กลูโคส, โปรตีน, ค่าปกติ

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