Fetal Hematology

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Abstract

The objective of this study was to establish normal fetal hematological parameters throughout gestation.

Samples of pure fetal blood from 35 fetuses of 21-38 weeks' gestation were obtained by fetal blood sampling under continuous ultrasound guidance. The hematological parameters were determined with automated cell counter within 30 minutes after the procedures.

Fetal red blood cell and granulocyte counts rose significantly with advancing gestation, whereas, the mean corpuscular volume fell. There were no significant changes in fetal hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, total white blood cell count, lymphocyte count, mid-cell count, platelet count, mean platelet volume, and platelet distribution width with increasing gestation.

The growing application of fetal blood sampling to the prenatal diagnosis renders mandatory a knowledge of normal fetal blood values. These results may provide useful reference values for prenatal diagnoses of hematological disorders.

Key word : Fetal Hematology, Normal Value

Past studies on fetal hematology depended on samples of blood obtained from fetuses which had either spontaneously aborted or been delivered by hysterotomy[1,2]. The postnatal sampling procedures may have altered hematological values[3]. Moreover, only a few hematological values during gestation have been published[4,5]. Since an easy and safe technique for fetal blood sampling has been developed, it is now possible to obtain fetal blood with minimal disturbance to the fetus and the results probably represent physiological levels[6,7]. To our knowledge there is no report of fetal hematology in

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Thailand. A knowledge of normal fetal hematological parameters during gestation has become indispensable, which are a prerequisite for prenatal diagnoses of congenital hematological disorders.

MATERIALS AND METHOD

We reviewed the case records for all patients (129 cases) who underwent fetal blood sampling between January 1993 and June 1997 at the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University. Fetal blood sampling was performed by ultrasound-guided needle puncture of the umbilical vein at either the placental cord insertion or the fetal intrahepatic portion, as described elsewhere[7,8]. Informed consent was obtained after counseling about the risks and benefits of the procedure. Pure fetal blood was obtained in all cases, without dilution by amniotic fluid or contamination by maternal blood[7,8].

Data for normal hematology were acquired from fetuses whose gestation had been confirmed by last normal menstrual period and ultrasonographic measurement of fetal biometry before 20 weeks. Those with abnormal karyotypes, hydrops fetalis, intrauterine growth retardation, congenital infection and thalassemia either disease or trait were excluded. Thirty-five fetuses satisfied these criteria. Their gestational age (GA) ranged from 21-38 weeks (GA 21-24 wk = 11 cases, GA 25-28 wk = 15 cases, GA 29-32 wk = 6 cases, GA 33-36 wk = 2 cases and GA $\geq$ 37 wk = 1 case). The indications for blood sampling were rapid karyotyping of ultrasonically detected abnormalities in 19, advanced maternal age in 12, and various genetic conditions in 4. All patients were delivered in the hospital.

Fetal blood (1 ml) was collected in heparinized syringe and immediately sent to the central hospital laboratory where hematological parameters were determined with automated cell counter (Cell Dyne 1600). The automated evaluation of hematological data was completed within 30 minutes.

The following parameters were measured in the hospital laboratory after sampling: white blood cell count (WBC), lymphocyte (LYM), mid-cells (MID) (mid-cells include less frequently occurring and rare cells correlating to monocytes, eosinophils, basophils, blasts and other precursor white cells), granulocyte (GRAN), red blood cell count (RBC), hemoglobin (HB), hematrocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentra-

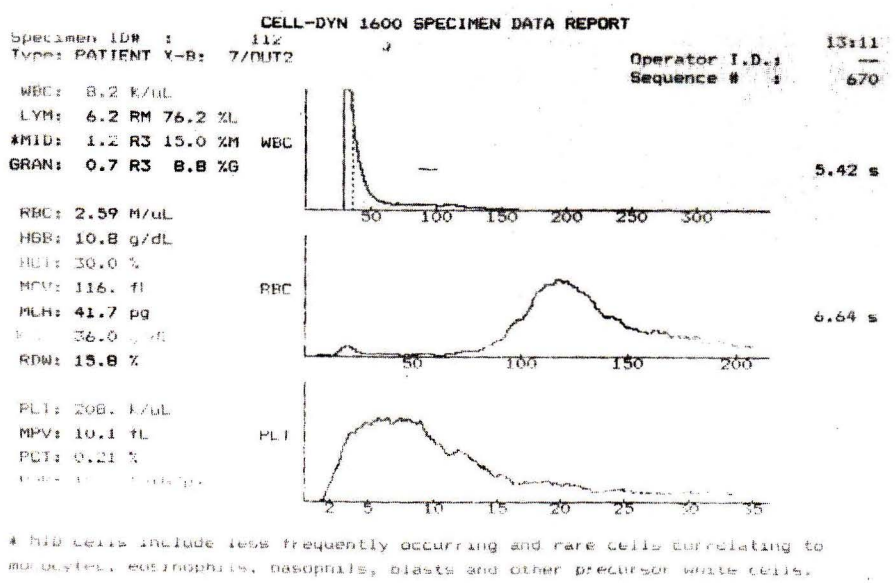

Fig. 1. Graphics terminal which displays histograms of white cell, red cell, platelet distribution curves, and hematological parameters of fetal blood.

Table 1. Hematological parameters from fetuses between 21 and 38 weeks of gestation.

Parameters	(mean ± SD) (N=35)	95% CI
WBC ($x10^3$/uL)	5.94 ± 1.73	5.34 - 6.53
Lymphocytes ($x10^3$/uL)	3.96 ± 1.63	3.39 - 4.53
MID cells ($x10^3$/uL)	0.87 ± 0.46	0.71 - 1.03
Granulocytes ($x10^3$/uL)	1.14 ± 0.87	0.84 - 1.43
RBC ($x10^6$/uL)	3.25 ± 0.68	3.02 - 3.49
HB (g/dL)	12.09 ± 1.57	11.55 - 12.63
HCT (%)	34.91 ± 5.66	32.97 - 36.86
MCV (fL)	110.25 ± 10.67	106.58 - 113.91
MCH (pg)	38.71 ± 6.99	36.31 - 41.11
MCHC (g/dL)	35.06 ± 4.86	33.39 - 36.70
RDW (%)	15.78 ± 1.59	15.23 - 16.32
PLT ($x10^3$/uL)	197.2 ± 44.92	181.77 - 212.63
MPV (fL)	7.69 ± 0.87	7.36 - 8.02
PDW (%)	18.19 ± 1.38	17.56 - 18.82

CI = Confidence interval

tion (MCHC), red cell distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), and platelet distribution width (PDW)

For statistical analysis, SPSS program was used to calculate mean, standard deviation (SD), and 95 per cent confidence interval (CI) for each value. Pearson correlation coefficient was used only when the least-squares method supported a linear relationship. Regression and correlation coefficients were calculated by standard formulas and comparison were made by Student *t* test or Fisher exact test where appropriate.

RESULTS

Typical distribution curves for WBC, RBC, PLT volumes, and hematological values are presented in Fig. 1.

The mean, SD and 95 per cent CI of WBC, LYM, MID, GRAN, RBC, HB, HCT, MCV , MCH, MCHC, RDW ,PLT, MPV , and PDW from 21 to 38 weeks of gestation are shown in Table 1.

Linear regression analysis between each hematological parameter and gestational age was determined by least square fitting. Significant gestational age correlation was observed for some parameters. The most notable of which is depicted in Fig. 2 which illustrated the rise in GRAN, RBC and reciprocal fall in MCV whilst the other hematological parameters remain relatively constant throughout gestation.

DISCUSSION

In the present study, a normal range of fetal hematological indices was determined in samples obtained directly from live fetuses throughout gestations. We utilized automated cell counter, the very accurate instruments and well adapted to small volumes of blood. Among the individual measurements it was observed that the RBC rose significantly with advancing gestation, whereas, the MCV fell. Our findings are in agreement with all previous fetal studies[4,5,9]. Our study showed no significant changes in HB, HCT, MCH, MCHC, and RDW with increasing gestation. These findings are in accordance with the study of Millar et al[5], covering shorter ranges of gestational age. However, in the study of Forestier et al[4], they found that the HCT and HB increased with advancing gestation, whereas, the MCH and RDW decreased. In addition, no correlation was found between MCHC versus gestation age. The increase in fetal RBC throughout gestation may be due to an increase in fetal hematopoietic tissue with advancing gestation[10]. Fetal MCV is known to be considerably higher than maternal MCV[9]. The reasons for this physiologic macrocytosis in fetal life and its ordered decline with gestation are not well understood[11], but are believed to reflect medullary hematopoietic maturation with gestation[5,10]. The high concentrations of late immature erythroid cells in peripheral blood of the second trimester fetus support this concept of accen-

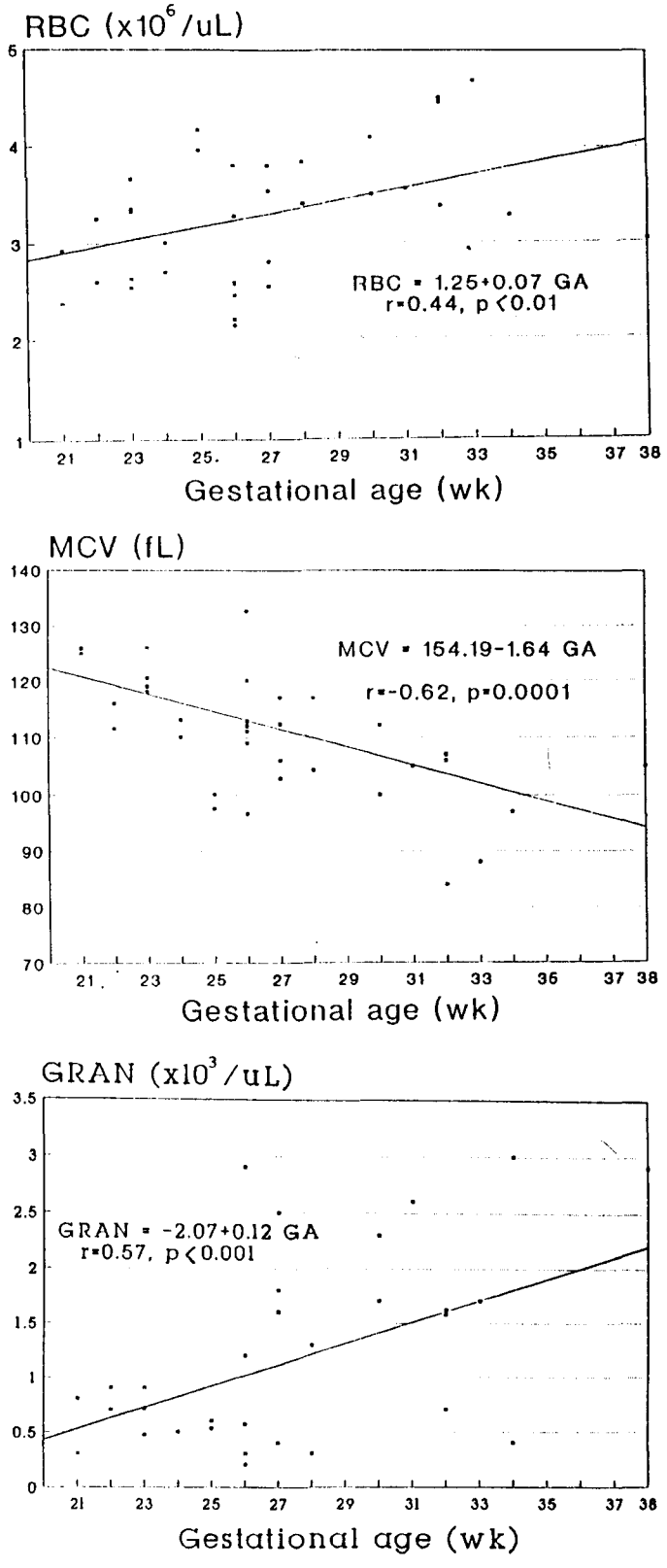

Fig. 2. Relationships between red blood cell count (RBC), mean cell volume (MCV), granulocyte count (GRAN) and the gestational age by means of regression linear analysis.

tuated erythropoiesis, whereby the production of red cell precursors proceeds at a far greater rate than in postnatal life[9]. Another factor is the reduced survival of fetal red cells in comparison with those of the neonate[3], producing a greater proportion of younger and larger cells.

Little is known about white blood cell counts in utero. In our study total WBC, LYM and MID counts did not change during this gestational age. However, we observed that granulocyte count increased during gestation. Our results are in agreement with the findings of Forestier et al[4]. In the neonatal studies[12-14], it has been found that the preterm infant has a slightly lower total white cell count than the term infant. In addition, the prematures tend to have lower granulocyte counts than the term infants[14].

In the first two trimesters of fetal life, granulocyte numbers are less than half of the normal adult value[15]. By term, however, adult values are obtained or even exceeded[15]. The production of granulocytes in the liver and various connective tissues of the body has been observed in very early fetal development, but significant white cell production does take place until the myeloid phase of hematopoiesis[15]. Bone marrow in the clavicle is the first site of white cell production[16].

The production of lymphocytes is able to be demonstrated in the fetal liver and lymphoid plexuses at about 7 weeks of gestation[15]. Almost immediately thereafter, lymphopoiesis is present in the thymus and the equivalent of Payer's patches in their embryonic form. By 10 to 12 weeks of gestation, lymphocytes may be found in the spleen and in the bone marrow. The earliest circulating lymphocytes are detectable in fetal blood at 7 to 8 weeks of gestational age[17].

Although erythroid and myeloid developments have been extensively studied, little is known about platelet development. In our study, no cytological or quantitative changes were observed in platelets during the fetal period studied. This may indicate that mature megakaryocytopoiesis is completed before 18 weeks' gestation and before bone marrow erythropoiesis has begun[18]. Megakaryocyte development and platelet development begin in the yolk sac[15]. Bone marrow megakaryocytopoiesis is established by about 11 weeks' gestation[15].

In conclusion, normal fetal hematological parameters are established from the 21st to the 38th week of gestation. These results may provide useful reference values for prenatal diagnoses of hematological disorders.

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โลหิตวิทยาของทารกในครรภ์

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วัตถุประสงค์ของการศึกษานี้เพื่อหาค่าปกติทางโลหิตวิทยาของทารกในครรภ์ ในอายุครรภ์ต่างๆ

ได้ทำการเจาะเลือดทารกในครรภ์จำนวน 35 ราย ระหว่างอายุครรภ์ 21–38 สัปดาห์โดยอาศัยการเจาะเลือดภายใต้การตรวจด้วยคลื่นเสียงความถี่สูง ค่าทางโลหิตวิทยาได้จากการตรวจ โดยเครื่องนับเม็ดเลือดอัตโนมัติภายในเวลา 30 นาที หลังการเจาะ

ผลการศึกษาพบว่า จำนวนเม็ดเลือดแดง และแกรนูโลไซต์เพิ่มขึ้นตามอายุครรภ์ที่เพิ่มขึ้น ในขณะที่ขนาดของเม็ดเลือดลดลงตามอายุครรภ์ที่เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ สำหรับค่าฮีโมโกลบิน ฮีมาโตคริต ค่าเฉลี่ยฮีโมโกลบินในเม็ดเลือด ค่าเฉลี่ยความเข้มข้นของฮีโมโกลบินในเม็ดเลือด การกระจายความกว้างของเม็ดเลือดแดง จำนวนเม็ดเลือดขาว จำนวนลิมโฟไซต์ จำนวนเซลล์เม็ดเลือดขาวขนาดกลาง จำนวนเกร็ดเลือด ขนาดของเกร็ดเลือด และการกระจายความกว้างของเกร็ดเลือด ไม่มีการเปลี่ยนแปลงตามอายุครรภ์

การนำเอาการเจาะเลือดทารกในครรภ์มาใช้ในการวินิจฉัยทารกก่อนคลอดมากขึ้น ทำให้สามารถหาค่าปกติต่างๆ จากเลือดทารกในครรภ์ ค่าปกติทางโลหิตวิทยาของทารกในครรภ์ อาจจะใช้เป็นค่าอ้างอิงในการวินิจฉัยความผิดปกติทางโลหิตวิทยาในทารกก่อนคลอด

คำสำคัญ : ค่าปกติ, โลหิตวิทยาของทารกในครรภ์

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