Hematological Values of 163 Normal Fetuses between 18 and 30 Weeks of Gestation

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ABSTRACT. Utilizing an easy and safe procedure for fetal blood sampling *in utero* we have studied 409 fetuses for prenatal diagnosis of rubella, toxoplasmosis, hemophilia, and hemoglobinopathies. Retrospectively we selected 163 fetuses confirmed as normal at birth and tested between 18 and 30 wk of gestation to establish normal hematological parameters and to follow the evolution of erythropoiesis, differential counts, hemoglobin synthesis, and hemostasis. Total white blood cell and platelet counts did not change during this period. The lymphocytes represented the main population and we observed a decrease of normoblasts during gestation. The results show a progressive increase of red blood cells and hemoglobin. This evolution is demonstrated by the ratio hemoglobin A to acetylated hemoglobin F. No significant modification of hemostasis was observed over a 12-wk intrauterine gestation. These results provide useful reference values for future investigations. (*Pediatr Res* 20: 342–346, 1986)

Abbreviations

WBC, white blood cell count
RBC, red blood cell count
PLT, platelet count
Hb, hemoglobin
Ht, hematocrit
MCV, mean corpuscular volume
MCH, mean corpuscular Hb
MCHC, mean corpuscular Hb concentration
RDW, red cell distribution width
IEF, isoelectrofocusing

Our knowledge of fetal hematology is limited due to the fact that most earlier studies were performed on aborted fetuses or under sampling conditions which may have altered hematological values. Moreover, only a few hematological values during gestation have been published (1). Having developed an easy and safe technique for fetal blood sampling, we selected retrospectively for this study 163 fetuses born healthy at full term delivery to establish reference fetal hematological values using standardized methods. To date no fetal loss or premature labor has been attributed to these fetal samplings.

MATERIALS AND METHODS

Sampling procedure. The fetal sampling method has been described in detail previously (2, 3). A real time ultrasound scanner (ATL MARK III) was used to locate the umbilical cord insertion on the placenta and to determine the best route of access to it without fetal interposition. The transducer was then maintained immobile while, under aseptic conditions, local anesthesia was performed with 1% xylocaine into the anterior abdominal wall at the chosen puncture site. No β-mimetic drugs or other medication were used prior to the procedure. A 20-gauge spinal needle (10 or 13 cm long), filled with 0.129 M sodium citrate solution and fixed to a 2 ml disposable syringe containing 0.1 ml of this solution, was introduced into the plane of the ultrasound sector near the transducer. The needle tip emitted a clearly visible echo and its progress toward the insertion of the cord was followed on the scope. The vein of the cord was punctured about 1 cm from its insertion.

Immediately after the first drop of blood was obtained, the syringe was replaced by a new one containing no additive. The blood sample was immediately transferred into special tubes containing adequate anticoagulant for biological studies. The duration of the entire procedure was less than 10 min in 90% of the cases, and the automated evaluations of hematological parameters were completed within 30 min.

Patients. We studied 409 pregnancies and 435 fetal blood samplings were carried out (26 repetitive samplings) with the approval of the ethics committee of the hospital, the medical expert panel, and the informed consent of the patients. The fetal samplings were conducted for the prenatal diagnosis of toxoplasmosis (285 cases), rubella (37 cases), or hemophilia (30 cases), for rapid fetal karyotyping (32 cases), or for diagnosis of other miscellaneous conditions (25 cases). Medical abortions of affected fetuses were performed in 51 cases. For this study, aimed at establishing hematological reference values, we obtained data from 163 fetuses born in good health at full term delivery, without intrauterine growth retardation, and sampled between 18 and 30 wk of gestation. Hematological data also were obtained from 63 mothers at the date of the fetal blood sampling; these women were selected because of the absence of iron and folate deficiencies. Their corresponding neonates also were studied (the cord blood was collected at delivery by direct puncture under aseptic conditions).

Biological investigations. Usually we obtained approximately 2 ml of blood and divided it into three aliquots: about 500 μl anticoagulated in lyophilised EDTA K_2 from Sarstedt (ref. 32332); 400 μl collected in 0.129 M sodium citrate solution in an Eppendorf microtube (ref. 72698), ratio 9/1; and about 500 μl drawn into a heparin-lithium dry mixture. The remaining blood was not anticoagulated. Hematological parameters were determined with a Coulter Counter S Plus II.

The following parameters were measured in the hospital laboratory immediately after the sampling: WBC, RBC, PLT, Hb, Ht, MCV, MCH, MCHC, and RDW. The histograms of the volumes of WBC, RBC, and PLT were recorded. The blood smears were stained with the May Grunwald Giemsa method for the differential blood count. From these data and the white cell counts provided by the Coulter, the number of nucleated red cells was determined. The Kleihauer Betke test (4), used to confirm the absence of contamination by maternal blood, was done using the fetal Hb test from Boehringer.

Biochemical measurements. Hb samples consisted of 0.2–0.5 ml of EDTA anticoagulated fetal blood. Standard procedures were used for Hb studies as described by Basset *et al.* (5). The tests used included I.E.F., citrate agar electrophoresis, and scanning of the gels with a densitometer (Cello-System, Sebia, France). The results provided information about the expression of adult Hb related to gestational age and the frequency of Hb F Sardinia (γ75 Thr–136 Ala).

Ferritin was measured in 14 cases using a radioimmunoassay kit (Ferk-CEA, France).

Coagulation tests were performed on 103 frozen plasmas with a single stage method for antihemophilic A and B factors, proaccelerin, prothrombin using KC 10 Dade (AHS). Factor VIII and IX's related antigen activities were measured by ELISA (Stago) and adapted on an Olli C + D (Kone-Westinghouse). All the factor VIII activities were compared to the WHO's reference plasma 80/511 (6).

RESULTS

Typical distribution curves for WBC, RBC, and PLT volumes are presented in Figure 1 for a mother and her fetus at 20 wk of gestation. Only one peak of WBC is observed in the fetal histogram. The mean and SD of the main hematological parameters are summarized for 63 fetuses in Table 1 and compared with the data of 63 newborns (cord samples at birth) and their mothers. The fetal values were obtained at 22–23 wk of gestation. The fetal WBC is low compared to adults (3.92/8.76 × 10⁹/liter; the PLT level is within the normal range and was never below 150 × 10⁹/liter; the RBC count is 3.04 ± 0.07 × 10¹²/liter with a high mean MCV (125.4 ± 1.2 Fl). The hematocrit is 37.9 ± 0.7% and the Hb 12.4 ± 0.24 g/100 ml.

In order to better assess the evolution of the hematological parameters, we selected 163 fetuses confirmed retrospectively as normal at birth. Hematological values from 18 to 30 wk of gestation are presented in Table 2.

We observed a gradual decrease of the MCV and an increase of the hematocrit. Total WBC counts did not change during this period, nor did the platelet counts. The increase of RBC is not substantial ranging from 2.66 to 3.52 × 10¹²/liter.

Linear regression analysis between MCV, MCH, RBC, RDW, Ht, Hb, WBC, PLT, or MCHC and gestational age were determined by least squared fitting. Significant correlations were observed between MCV, MCH, RBC, RDW, Ht, and Hb *versus* the weeks of gestation as shown in Figure 2. No correlation was found between WBC, PLT, and MCHC versus gestation age.

Differential counts are summarized in Table 3. Because acidophilic normoblasts are present in a normal fetal differential and because nuclei of normoblasts are counted as WBC by the Coulter, we thought it was relevant to record their presence in the differential count among 200 cells. The lymphocytes represent the main population and, during gestation, there is a progressive decrease in normoblastic cells from 12 ± 8 to 4 ± 3.5%.

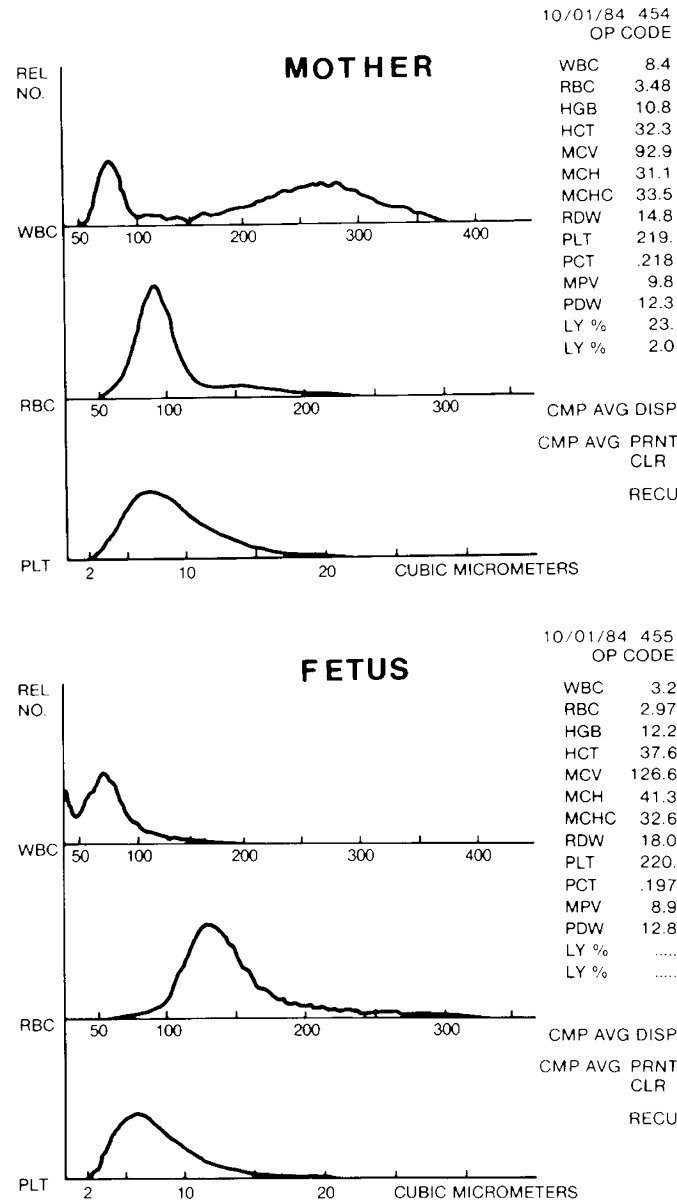Coagulation factors from 103 fetuses are summarized in Table

Fig. 1. Graphics terminal which displays histograms of white cell, red cell, and platelet distribution curves of a mother and her related fetus.

Table 1. *Principal hematological data of 63 blood samples collected from fetuses between 22 and 23 wk of gestation compared to the data of 63 cord blood samples at birth and the corresponding mothers the day of the fetal blood sampling (mean ± SD)*

	Fetuses (22–23 wk)	New borns (cord samples at delivery)	Relative mothers at the day of the blood sampling
WBC (× 10⁹/liter)	3.92 ± 0.17	11.11 ± 4.42	8.76 ± 0.48
RBC (× 10¹²/liter)	3.04 ± 0.07	3.56 ± 0.76	3.86 ± 0.05
Hb (g/100 ml)	12.4 ± 0.24	13.29 ± 1.6	12.1 ± 0.17
Ht (%)	37.9 ± 0.7	41.2 ± 6.02	36 ± 0.5
MCV (Fl)	125.4 ± 1.2	118.81 ± 14	93.9 ± 0.8
MCH (pg)	41 ± 2.27	38.25 ± 9.83	31 ± 0.1
MCHC (g/100 ml)	32.8 ± 1.65	34.99 ± 11.4	33.6 ± 0.2
Red cell distribution width	19.4 ± 1.86	20.53 ± 1.4	13.6 ± 0.8
Platelets (× 10⁹/liter)	241 ± 8	299.5 ± 58.4	244 ± 10

Table 2. *Evolution of hematological values of 163 normal fetuses during pregnancy (mean ± SD) from studies performed with a Coulter model S-PLUS II*

| Wk of gestation	WBC (× 10^9/liter)	Platelets (10^9/liter)	RBC (× 10^12/liter)	Hb (g/100 ml)	Ht (%)	MCV (Fl)	MCH (pg)	MPHC (g/100 ml)	Red cell distribution width
18-20 (n = 25)	4.20 ± 0.83	242.1 ± 34.48	2.66 ± 0.29	11.47 ± 0.78	35.86 ± 3.29	133.92 ± 8.83	43.14 ± 2.71	32 ± 2.38	20.64 ± 2.28
21-22 (n = 55)	4.19 ± 0.84	258.2 ± 53.65	2.96 ± 0.26	12.28 ± 0.89	38.53 ± 3.21	130.06 ± 6.17	41.39 ± 3.32	31.73 ± 2.78	20.15 ± 1.92
23-25 (n = 61)	3.95 ± 0.69	259.43 ± 42.45	3.06 ± 0.26	12.40 ± 0.77	38.59 ± 2.41	126.19 ± 6.23	40.48 ± 2.88	32.14 ± 3.2	19.29 ± 1.62
26-30 (n = 22)	4.44 ± 0.85	253.54 ± 36.6	3.52 ± 0.32	13.35 ± 1.17	41.54 ± 3.31	118.17 ± 5.75	37.94 ± 3.67	32.15 ± 3.55	18.35 ± 1.67
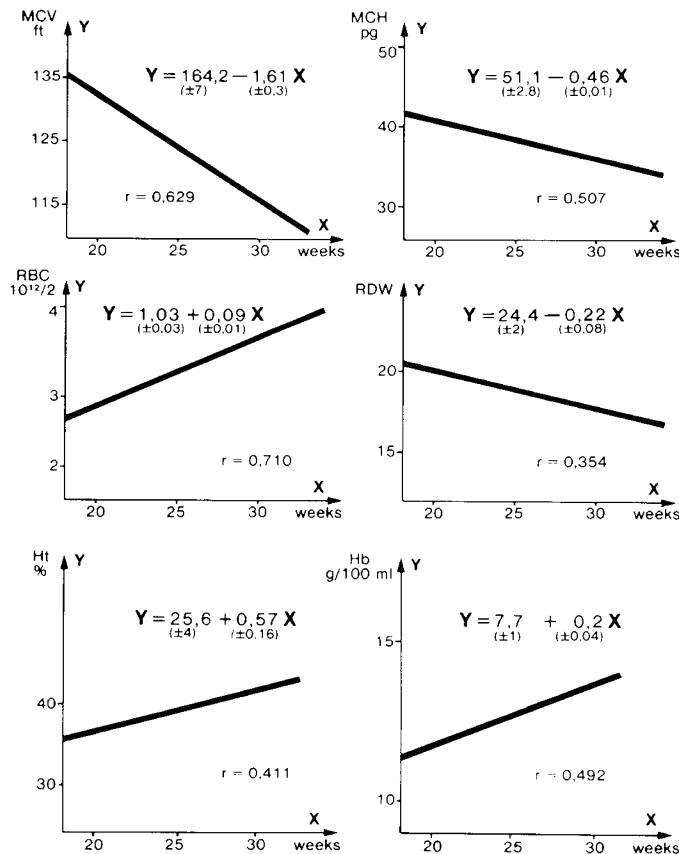
Fig. 2. Relationships between RBC, Hb, Ht, RDW, MCV, MCH values and the gestational age of 163 normal fetuses by means of regression linear analysis.

4: antihemophilic A (coagulant and antigen related activities), antihemophilic B, proaccelerin V, and prothrombin II. The mean value for factor VIIIC was 40% and for factor IX 9% between 19 and 21 wk. Mean factor V and II levels were respectively 39 and 13%, and VIIIRAg 59%. These values remained essentially unchanged through 27 wk. Means and SD values for pregnant women the day of the samplings were: VIIIC 160 ± 80%, VIIIRAg 190 ± 110%, IX 90 ± 20%, V 85 ± 10%, and II 95 ± 15%.

Repetitive samplings were carried out on five pregnant women with the aim of examining the evolution of selected enzyme activities and myoglobin values relating to a possible prenatal diagnosis of muscular dystrophy. Figure 3 illustrates the evolution of the RBC and the MCV values for the five fetuses each

sampled three times or more during gestation. The results show a progressive increase of RBC in all the fetuses in good correlation with our normal hematological values during gestation (see Table 1 and Table 2).

Hb type was characterized in 125 samples: 45 (36%) individuals had carried a fraction of fetal Hb with the IEF pattern of Hb F Sardinia (γ75 Thr-136 Ala) (7); samples with a different chain mutation have been detected. In the complete group, no α variant was found, two cases of sickle cell trait and one case of Hb E were noted. Hb Bart's was suggested in 13 cases, but clearly seen in nine. Unfortunately, sample volumes were too small to allow precise quantitation. In only one case, Hb Bart's elevation was accompanied by a microcytosis as defined in Table 2. Table 5 shows the ratio of Hb A to acetylated Hb F (Hb A/Hb Fac) as a function of the gestational age. Acetylated Hb F is a constant fraction of total Hb F and represents about 8% of Hb F. These values, although overlapping, are proportional to gestational age with the following formula: y = 0.019x + 0.47 (r = 0.4) (y = Hb A/Hb Fac ratio; x = gestational age in weeks). In two cases of suspected β-thalassemia trait, Hb A/Hb Fac ratios were found to be low for the gestational age (20 wk of gestation—ratio 0.45, 22 wk of gestation—ratio 0.2). In one case, we found a low level of Hb Fac, as compared with a normal Hb A fraction for gestational age. Gamma chain variants had a high Hb A/Hb Fac ratio.

Ferritin values measured in 14 cases were between 19 and 98 μg/liter (mean ± SD: 51.07 ± 19.64; wk of gestation: 23.5 ± 4).

DISCUSSION

For the present study we utilized a Coulter S Plus II, a very accurate instrument and well adapted to small volumes of blood and rapid identification of fetal blood by analysis of WBC and RBC volumes. Fetal bone marrow erythropoiesis begins between the 16th and 18th wk of gestation (8) as liver hematopoiesis (9) is challenged by hepatocyte proliferation (10-13). It has been noted that the changes in the number of circulating normoblasts between 10 and 18 wk is associated with a progressive maturation of these cells (10). There is a diminution of the diameter and densification of the nucleus and more acidophilia. In our study, the number of late normoblasts markedly decreased (from 13 ± 6 to 5 ± 4%) during the 12-wk period of gestation studied. Our values are lower than previously reported (14). The normoblasts had almost the same cytological feature throughout this period. In contrast, changes in RBC and Hb levels were rather small. Maturation is demonstrated by a diminution of MCV and RDW, and by the moderate increase in Hb A synthesis. Adult Hb is sufficiently separated from either Hb F or acetylated Hb F by IEF (15). Since acetylated Hb F is a constant fraction of Hb F (16, 17), it is justified to follow the increase in Hb A synthesis by the Hb A/Hb F acetylated ratio (18) using IEF and gel scanning.

Table 3. *Some aspects of fetal differential counts from 18 to 30 wk of gestation of 163 normal fetuses (mean ± SD)*

Wk of gestation	Lymphocytes (%)	Neutrophils (%)	Eosinophils (%)	Monocytes (%)	Normoblasts (%)
18–20 (n = 25)	80 ± 9	5 ± 2	1.5 ± 2.5	1.5 ± 2	12 ± 8
21–22 (n = 55)	81 ± 7	5.5 ± 3.5	1 ± 1	1.5 ± 1.5	11 ± 7
23–25 (n = 61)	82 ± 6	7.5 ± 4.5	2 ± 2	1.5 ± 1.5	7 ± 4
26–30 (n = 22)	84 ± 6	8.5 ± 2.5	2 ± 1	1.5 ± 1	4 ± 3.5

Table 4. *Evolution of coagulation factors of 103 normal fetuses during pregnancy and their relative mothers (mean ± SD)*

Fetuses (wk of gestation)	VIII C (%)	VIII RAg (%)	IX C (%)	V C (%)	II C (%)
19–21 (n = 51)	40 ± 12	59 ± 12.5	9 ± 2.5	39 ± 11	13 ± 4
22–24 (n = 44)	39 ± 13.5	64 ± 13	9 ± 3	40.5 ± 5	14 ± 2
25–27 (n = 44)	42.5 ± 12	63 ± 13	12 ± 4	39 ± 9	14 ± 3.5
Mothers	160 ± 80	190 ± 110	90 ± 20	85 ± 10	95 ± 15

No cytological or quantitative changes were observed in platelets during the fetal period studied. This may indicate that mature megakaryocytopoiesis is completed before 18 wk and before bone marrow erythropoiesis has begun (19). Interestingly, PLT were never below 150 × 10⁹/liter in normal fetuses. Neutrophils were very low and increased slightly from about 0.2 (20th wk) to 0.4 × 10⁹/liter (30th wk). This pattern also is obvious in cases sequentially sampled and contrasts with the neutrophilia observed at birth. About half of the granulocytes are band forms throughout the studied period. This neutropenia also appears in the WBC volume distribution curve (Fig. 1).

It can be interpreted either as a strong margination or, more likely, as the physiological initiation of granulopoiesis in the bone marrow (19). Anatomophysiological data (8, 20) support the latter hypothesis. This observation also further supports the absence of maternal contamination.

Eosinophil and monocyte counts were relatively constant from the 18th to the 30th wk of gestation. Some fetal lymphocytes are larger (but vary considerably in size) with a cytoplasm more basophilic than typical lymphocytes. The absolute counts are relatively stable. These observations disagree with those previously reported (21, 22).

Excluding the prenatal diagnosis of hemoglobinopathies, Hb abnormalities are surprisingly numerous. The geographic origin of the foreign families was about 7% from North Africa, 2% from South East Asia, and 1% from black countries. In this population, two cases of Hb S and one case of Hb E were detected by IEF (5). In two children from β-thalassemic heterozygote mothers, the expression of Hb A was lower than usual with a Hb A/Hb Fac ratio below 0.5. This method already has been used for antenatal and neonatal diagnosis of β-thalassemia (23, 24). If this foreign population is withdrawn, the frequency of heterozygote and homozygote fetuses for Hb F Sardinia is 36% for the French population. This is very close to previous data for Caucasian newborns in the United States (25) and in the Netherlands (26). Hb Bart's was detected in a group of 13 fetuses. A severe microcytosis, (111 Fl at 20 wk compared to our reference value: 134 ± 9) was obvious in only one (a fetus of black African origin) of these cases. Extrapolating from reported
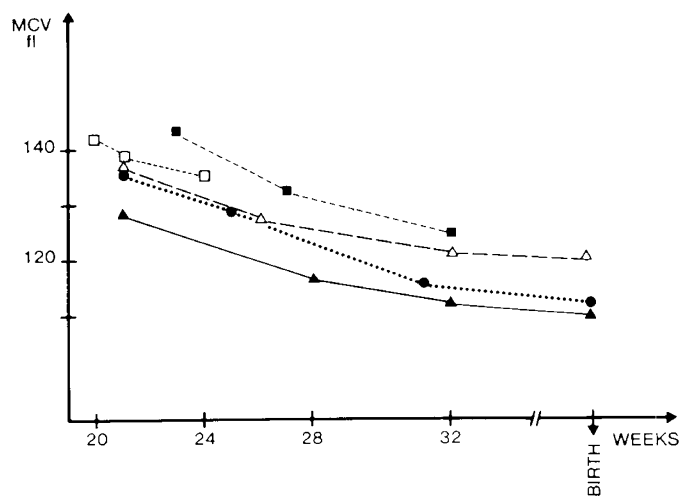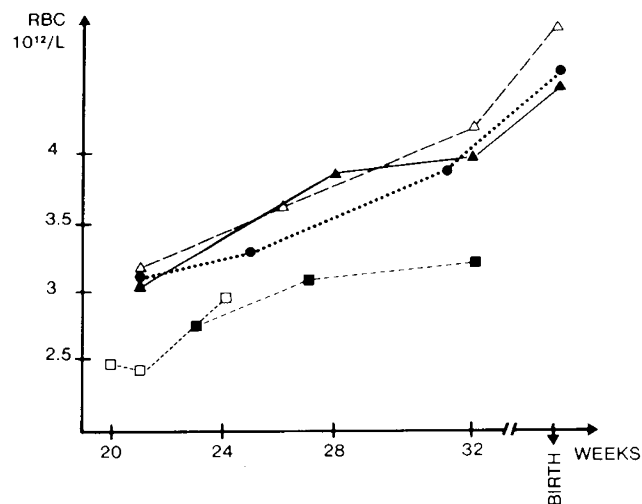

Fig. 3. Evolution of the RBC and the MCV values of five fetuses each sampled three times or more during the gestation.

Table 5. *Evolution of Hb A/Hb Fac ratio between 19 and 36 wk of gestation (mean ± SD)*

Wk of gestation	No. of cases	HbA / HbFac
19–21	34	0.86 ± 0.13
22–24	44	0.92 ± 0.18
25–27	15	0.94 ± 0.21
28–30	7	1.00 ± 0.2
31–36	9	1.19 ± 0.18

findings in black newborns (27), this latter case might be an α-thalassemia trait. A surprising finding was the detection of three different γ chain variants (2.3%). Other recent studies have permitted identification of a large number of such variants, which may be more frequent than previously thought (25).

In the small number of cases in which ferritin was evaluated, no large differences were seen between individuals of varying gestational age. We did not measure ferritin values in mothers the day of the samplings. However, our normal values in the newborn range from 95 to 350 μg/liter and from 5 to 30 in pregnant women at the 3rd trimester of pregnancy.

As indicated in Table 4, blood factors VIII and V are about 40% of the activity between 19 and 27 wk. Factors II and IX (vitamin K dependent) are lower (around 10%). We did not observe any significant increase of these parameters.

These data confirm the results in prenatal diagnosis of hemophilia (which is usually performed at the 18th wk of pregnancy) and the development of hemostasis in the human fetus (28, 29).

In conclusion, it has been possible to establish normal hematological parameters for a large group of 163 fetuses over a 12-wk period (from the 18th to the 30th wk of gestation). In a few cases, we were able to obtain serial measurements of hematological values to assess fetal erythropoiesis. This work suggests that studies of selected aspects of human prenatal biology are possible without significant risk to the fetus from the 18th wk of gestation to birth. We have conducted 435 fetal blood samplings without accident by direct puncture of the umbilical cord under ultrasound. This procedure, already routinely used for prenatal diagnosis of hemophilia (31), rubella (32), and toxoplasmosis (33), could be applied to a wide range of new possibilities (34), including the study of the transplacental passage of drugs (35, 36), the administration of intrauterine therapy (37), and possibly for fetal monitoring.

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