The investigation of many hemostatic defects in the newborn is limited by the lack of normal reference values. This study was designed to determine the postnatal development of the human coagulation system in the healthy full-term infant. Consecutive mothers of healthy full-term infants born at St Joseph's Hospital in the city of Hamilton were approached for consent. One hundred eighteen full-term infants (37 to 42 weeks' gestational age) were entered into the study. Demographic information and a 2-ml blood sample were obtained in the postnatal period on days 1, 5, 30, 90, and 180. Between 40 and 79 full-term infants were studied on each day for each of the coagulation tests. Plasma was fractionated and stored at -70°C for batch assaying of the following tests: prothrombin time, activated partial thromboplastin time, thrombin clotting time, and factor assays (biologic): fibrinogen, II, V, VII, VIII, IX, X, XI, XII, and high-molecular weight kininogen. Factor XIII subunits A and S, von Willebrand factor, and the inhibitors antithrombin III, α2-antiplasmin, α2-macroglobulin, α2-antitrypsin, C1 esterase inhibitor, protein C, and protein S were measured immunologically. Plasminogen, prekallikrein, and heparin cofactor II were measured by using chromogenic substrates. The large number of infants studied at each time point allowed us to determine the following: (a) the range of normal for each test at five time points in the postnatal period; (b) that coagulation tests vary with the postnatal age of the infant; (c) that different coagulation factors show different postnatal patterns of maturation; and (d) that near-adult values are achieved for most components by 6 months of life. In summary, this large cohort of infants studied consecutively in the postnatal period allowed us to determine the normal development of the human coagulation system in the full-term infant.

From the Departments of Pediatrics, Clinical Epidemiology and Biostatistics, and Pathology, McMaster University Medical Centre, Hamilton, Ontario; and the Department of Medicine, Washington University, St Louis.


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Address reprint requests to Maureen Andrew, MD, Department of Pediatrics, McMaster University Health Sciences Centre, Room HSC-3N27, 1200 Main St W, Hamilton, Ontario, Canada L8N 3Z5.

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prepared by immunodepletion of normal plasma (Interhaematol, Burlington, Ontario). Factor V-deficient plasma was prepared in-house by prolonged incubation of normal plasma collected into sodium oxalate. Factor II-deficient plasma was prepared from bovine plasma by adsorption with tricalcium phosphate. Factor X-deficient plasma was purchased from Sigma Chemical Co, St Louis, as VII-, X-, and bovine-deficient plasma. Factor XIII, subunits A and S, was measured by using Laurel immunoelectrophoresis. The antibodies were obtained commercially from Behring (Hoescht, Montreal). The plasma protease inhibitors antithrombin III (AT-III), α₂-antiplasmin (α₂-AP), C₁ esterase inhibitor (C₁E-InH), α₁-macroglobulin (α₁-M), and α₁-antitrypsin (α₁-AT) were all measured immunologically with commercially available rabbit antihuman antibody (Atlantic Antibodies, NCS Diagnostics, Inc, Mississauga, Ontario) by using a radial immunodiffusion that required 3 to 5 μL per assay. Heparin cofactor II (HCII) was measured biologically on 50 μL of plasma by a previously published method. Protein C was measured by using an enzyme-linked immunosorbent assay (ELISA) (Diagnostica Stago, Wellmark Diagnostics, Guelph, Ontario), von Willebrand factor (vWF) was also measured by an ELISA method. Protein S (Interhaematol) was measured by using 50 μL of plasma by a previously published method. The sample size calculation was based on previously published data. The α and β errors were set at 0.05 and 0.1, one-tailed, respectively. The change in time over the postnatal period for each factor level was measured by a one-way analysis of variance. The newborn values at each time were compared with the adult values to determine whether they were statistically indistinguishable by using Dunnett’s test. All P values <.05 were considered significant.

RESULTS

Subjects. Of 359 mothers interviewed, 118 agreed to have their infants join the study. Of these 118 mothers, 93 agreed to return for follow-up appointments. Between 61 and 77 infants returned and were studied at each time point for each assay. Not all infants were studied at each time point, primarily because of failure to return for follow-up, recruitment after day 1 of life, discharge before day 5, and occasionally clotted samples. The infant population was white (98%), with an equal proportion of males (53%) and females (47%). The mode of delivery was vaginal (98%), and all infants had a five-minute Appgar score ≥7. The mean values for the weight, head circumference, and length of the infants in our study population at each time point are given in Table 1 as well as the proportion who were breast-fed at each time point.

<table>
<thead>
<tr>
<th>Test</th>
<th>Day 1 (n)</th>
<th>Day 5 (n)</th>
<th>Day 30 (n)</th>
<th>Day 90 (n)</th>
<th>Day 180 (n)</th>
<th>Adult (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (s)</td>
<td>13.0 ± 1.43 (61)*</td>
<td>12.4 ± 1.46 (77)†</td>
<td>11.8 ± 1.25 (67)‡</td>
<td>11.9 ± 1.15 (62)§</td>
<td>12.3 ± 0.79 (47)*</td>
<td>12.4 ± 0.78 (29)</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>42.9 ± 5.80 (61)</td>
<td>42.6 ± 6.82 (76)</td>
<td>40.4 ± 7.62 (87)</td>
<td>37.1 ± 6.52 (62)</td>
<td>35.5 ± 3.71 (47)</td>
<td>33.5 ± 3.44 (29)</td>
</tr>
<tr>
<td>TCT (s)</td>
<td>23.5 ± 3.86 (68)*</td>
<td>23.1 ± 3.07 (64)</td>
<td>24.3 ± 4.44 (53)</td>
<td>25.1 ± 2.32 (62)</td>
<td>25.3 ± 2.86 (41)</td>
<td>25.0 ± 2.66 (19)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.83 ± 0.58 (61)*</td>
<td>3.12 ± 0.75 (77)</td>
<td>2.70 ± 0.54 (67)</td>
<td>2.43 ± 0.68 (60)</td>
<td>2.51 ± 0.68 (47)</td>
<td>2.78 ± 0.61 (29)</td>
</tr>
<tr>
<td>II (U/mL)</td>
<td>0.48 ± 0.11 (61)</td>
<td>0.63 ± 0.15 (76)</td>
<td>0.68 ± 0.17 (67)</td>
<td>0.75 ± 0.15 (62)</td>
<td>0.68 ± 0.14 (47)</td>
<td>1.08 ± 0.19 (29)</td>
</tr>
<tr>
<td>V (U/Ml)</td>
<td>0.72 ± 0.18 (61)</td>
<td>0.95 ± 0.25 (76)</td>
<td>0.98 ± 0.18 (67)</td>
<td>0.90 ± 0.21 (62)</td>
<td>0.91 ± 0.18 (47)</td>
<td>1.06 ± 0.22 (29)</td>
</tr>
<tr>
<td>VII (U/mL)</td>
<td>0.66 ± 0.19 (60)</td>
<td>0.89 ± 0.27 (75)</td>
<td>0.90 ± 0.24 (67)</td>
<td>0.91 ± 0.26 (62)</td>
<td>0.87 ± 0.20 (47)</td>
<td>1.05 ± 0.19 (29)</td>
</tr>
<tr>
<td>VIII (U/mL)</td>
<td>1.00 ± 0.39 (60)*</td>
<td>0.88 ± 0.05 (75)*</td>
<td>0.91 ± 0.33 (67)*</td>
<td>0.79 ± 0.23 (62)*</td>
<td>0.73 ± 0.18 (47)</td>
<td>0.99 ± 0.25 (29)</td>
</tr>
<tr>
<td>vWF (U/mL)</td>
<td>1.53 ± 0.67 (40)</td>
<td>1.40 ± 0.57 (43)</td>
<td>1.28 ± 0.59 (40)</td>
<td>1.18 ± 0.44 (40)</td>
<td>1.07 ± 0.46 (40)</td>
<td>0.92 ± 0.33 (29)</td>
</tr>
<tr>
<td>IX (U/mL)</td>
<td>0.53 ± 0.24 (61)</td>
<td>0.63 ± 0.19 (76)</td>
<td>0.51 ± 0.15 (67)</td>
<td>0.67 ± 0.23 (62)</td>
<td>0.86 ± 0.25 (47)</td>
<td>1.09 ± 0.27 (29)</td>
</tr>
<tr>
<td>X (U/mL)</td>
<td>0.40 ± 0.14 (60)</td>
<td>0.49 ± 0.16 (76)</td>
<td>0.59 ± 0.14 (67)</td>
<td>0.71 ± 0.18 (62)</td>
<td>0.78 ± 0.20 (47)</td>
<td>1.06 ± 0.23 (29)</td>
</tr>
<tr>
<td>XI (U/mL)</td>
<td>0.38 ± 0.14 (60)</td>
<td>0.55 ± 0.16 (74)</td>
<td>0.53 ± 0.13 (67)</td>
<td>0.69 ± 0.14 (62)</td>
<td>0.86 ± 0.24 (47)</td>
<td>0.97 ± 0.15 (29)</td>
</tr>
<tr>
<td>XII (U/mL)</td>
<td>0.53 ± 0.20 (60)</td>
<td>0.47 ± 0.18 (75)</td>
<td>0.49 ± 0.16 (67)</td>
<td>0.67 ± 0.21 (62)</td>
<td>0.77 ± 0.19 (47)</td>
<td>1.08 ± 0.28 (29)</td>
</tr>
<tr>
<td>PK (U/mL)</td>
<td>0.37 ± 0.16 (45)</td>
<td>0.48 ± 0.14 (51)</td>
<td>0.57 ± 0.17 (48)</td>
<td>0.73 ± 0.16 (46)</td>
<td>0.86 ± 0.15 (43)</td>
<td>1.12 ± 0.25 (29)</td>
</tr>
<tr>
<td>HMWK (U/mL)</td>
<td>0.54 ± 0.24 (47)</td>
<td>0.74 ± 0.28 (63)</td>
<td>0.77 ± 0.22 (60)</td>
<td>0.82 ± 0.32 (46)</td>
<td>0.82 ± 0.23 (46)</td>
<td>0.92 ± 0.22 (29)</td>
</tr>
<tr>
<td>Xlla (U/mL)</td>
<td>0.79 ± 0.26 (44)</td>
<td>0.94 ± 0.26 (48)</td>
<td>0.93 ± 0.27 (44)</td>
<td>1.04 ± 0.34 (44)</td>
<td>1.04 ± 0.29 (41)</td>
<td>1.05 ± 0.25 (29)</td>
</tr>
<tr>
<td>Xllb (U/mL)</td>
<td>0.76 ± 0.23 (44)</td>
<td>1.06 ± 0.37 (47)</td>
<td>1.11 ± 0.36 (46)</td>
<td>1.16 ± 0.34 (44)</td>
<td>1.10 ± 0.30 (41)</td>
<td>0.97 ± 0.20 (29)</td>
</tr>
<tr>
<td>Plasminogen (CTA, U/mL)</td>
<td>1.95 ± 0.35 (44)</td>
<td>2.17 ± 0.38 (60)</td>
<td>1.98 ± 0.36 (52)</td>
<td>2.48 ± 0.37 (44)</td>
<td>3.01 ± 0.40 (47)</td>
<td>3.36 ± 0.44 (29)</td>
</tr>
</tbody>
</table>

NOTE: All factors except fibrinogen and plasminogen are expressed as units per milliter where pooled plasma contains 1.0 U/mL. Plasminogen units are those recommended by the Committee on Thrombolytic Agents (CTA). All values are expressed as mean ± 1 SD.

Abbreviation: VIII, factor VIII procoagulant.

*Values that do not differ statistically from the adult values.

†These measurements are skewed because of a disproportionate number of high values. The lower limit that excludes the lower 2.5th percentile of the population has been given in the respective figures. The lower limit for factor VIII was 0.50 U/mL at all time points for the infant.
Laboratory. Tables 2 and 3 give the mean ± 1 SD and the number of samples tested for the coagulation factors and inhibitors, respectively. Figures 1 to 7 give the mean values ± 95% confidence intervals for the mean value and the upper and lower limits that encompass 95% of the population (± 2 SD) for each of the tests performed. The 95% confidence interval for the mean value of each test at each time point was very small (less than ±0.06%) in the coagulation tests in this population, which allowed us to accurately detect changes over time. Values that were skewed are identified in Tables 2 and 3 and the lower limit adjusted to exclude 2.5% of the population. The values that do not differ significantly from those of the adult are identified in Tables 2 and 3.

Table 2 and Fig 1 give the values for the coagulation screening tests in the first 6 months of life. The PT significantly shortened during the first month of life but was always comparable to the adult value. The APTT, which was prolonged at birth, reached adult values by 3 months of age. The TCT was in the adult range from time of birth, as was the fibrinogen level; however, there was a significant rise in the fibrinogen level on day 5 of life.

Table 2 and Fig 2 give the values for the vitamin K–dependent factors (II, VII, IX, and X) in the first 6 months of life. Each of the vitamin K–dependent factors had a distinct postnatal pattern of maturation. Levels of factor VII rapidly rose to near adult levels by day 5 of life, which contributed to the shortening of the PT at this same postnatal time point. Levels of factors II, IX, and X showed a relatively delayed rise. All four vitamin K–dependent factors were in the adult range at 6 months of life; however, the mean values for all four factors were still significantly lower in the infant compared with the adult. There was no difference between breast-fed and formula-fed infants for any of the vitamin K–dependent factors at any time point.

Table 2 and Fig 3 give the values for the four contact factors (XII, XI, PK, and HMW-K) during the first 6 months of life. The levels of these factors were all low at the time of birth. Levels of HMW-K rapidly rose to adult values by 1 month of life, whereas levels of factors XI, XII, and PK showed a gradual rise into the adult range by 6 months of age. The mean values for factors XI, XII, and PK were still significantly lower in the infant compared with the adult at 6 months of age.

Table 2 and Figs 4 and 5 give the postnatal course for factors V, VIII, vWF, plasminogen, and factor XIII with its subcomponents A and B. The mean value for factor V was in the adult range at birth and rose to 0.95 U/mL by day 5 of life. Factor VIII and vWF showed a persistently skewed distribution with a number of very elevated values. The lower limit of normal has been adjusted to reflect the true limit excluding 2.5% of the population. The mean value for factor VIII at birth was the same as the adult, whereas levels of vWF were elevated compared with the adult. Levels for both factors VIII and vWF gradually decreased over the first 6 months of life. For factor VIII, only three values out of 306 tests were below 0.40 U/mL, and these three values were all above 0.30 U/mL. Factors XIIIa and XIIIb showed essentially identical patterns with indistinguishable mean values. Adult levels for both factors XIIIa and XIIIb were achieved by day 5 of life. Plasminogen values were approximately two thirds of adult values at birth and gradually rose to near-adult values by 6 months.

Table 3 and Fig 6 give the postnatal course for the inhibitors AT-III, HCII, protein C, and protein S. All of these inhibitors had low levels at the time of birth. The mean values for AT-III were similar for the infant and adult by 3 months of age, whereas the mean value for HCII was high in the infant at 6 months of age compared with the adult. Protein C still had markedly low levels at 6 months of age.

Table 3 and Fig 7 give the values for the inhibitors, α2-M,
A knowledge of the normal postnatal development of the human coagulation system is essential to investigate thrombotic and hemorrhagic problems in the neonate. The definition of normal values of any one parameter in a single population is a difficult task. Physicians caring for infants
commonly used screening tests in infants with a suspected coagulopathy. There are reference mean values published for these tests in the first week of life; however, this study has extended our information for these tests in a number of ways. Previously the mean PT values have been reported to be prolonged at birth and to reach adult values by a week of life. This study showed that although the variability of the PT was greater in the newborn, the mean values were not significantly different from the adult. The PT did shorten in the newborn during the first month of life. Previously reported values for the APTT in the neonate were so extended our information for these tests in a number of ways. Previously the mean PT values have been reported to be prolonged at birth and to reach adult values by a week of life. This study showed that although the variability of the PT was greater in the newborn, the mean values were not significantly different from the adult. 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K deficiency can occur in the full-term neonate although the true incidence and frequency of bleeding manifestations is unclear. All of our infants received vitamin K at birth, so our reference values may apply only to other infants who have received vitamin K at the time of birth. Vitamin K deficiency has also been reported to occur later in the postnatal period in infants who have received vitamin K at birth and are breast-fed. Our sample size was too small to determine with accuracy the frequency of vitamin K deficiency at 1 month in infants who received vitamin K at birth. However, we subanalyzed our data to compare breast-fed and formula-fed infants for all of the vitamin K-dependent factors at each time point, and there was no significant difference detected, which is compatible with previously reported data at 1 month of age. Finally, our data showed that the severe form of Christmas disease or factor IX deficiency can be diagnosed at the time of birth; however, moderate and mild forms are likely not reliably diagnosed.

The levels for the four contact factors (II, XI, PK, HWM-K) were low at birth and gradually increased to values approaching the adult values by 6 months of life. The low levels of these four factors likely contribute to the prolonged APTT during the first 6 months of life. The homozygous form of factor XI can be reliably detected as early as day 5 of life because the lower limit of our range at this time was 0.20 U/mL, which is above the levels for homozygous factor XI-deficient patients.

The factor VIII molecule has been extensively studied in the immediate postnatal period. Our study showed similar results; however, the values for factor VIII were skewed, with many infants having elevated values at the time of birth. Less than 1% of the values for factor VIII were below 0.40 U/mL, and all values were above 0.30 U/mL. Thus, severe and moderate hemophilia A can be reliably diagnosed in the immediate postnatal period. vWF levels have been reported to be elevated in healthy full-term infants, and our data would be compatible with the published results. In addition, our study showed that vWF levels remain elevated until 3 months of age, thus suggesting that the elevated levels were not a brief response to the birth process itself.

Some of the inhibitors of the coagulation system have been studied in part. In our study, levels of C1E-INH, α2-M, and HCII became elevated during the first 6 months of life compared with the adult. The significance of these elevated values is unknown, but one may speculate that this may be in part compensation for the low levels of other inhibitors. Levels of AT-III, protein C, protein S, and HCII were low in the first weeks of life and all in the range in which thrombotic disorders have been described in the adult. Of some interest, protein C still had markedly depressed levels at 6 months of age. All of the inhibitors in our study except for HCII were measured by immunologic assays. Whether any of these proteins have lower biologic activity compared with immunologic levels has been questioned by other investigators but was not addressed in this particular study.

In summary, our study has determined the postnatal development of the human coagulation system in a large number of consecutively studied healthy full-term infants. Utilizing these reference values, future studies will be directed at the determination of the epidemiology and clinical impact of specific abnormalities and the role of therapeutic interventions in specific hemorrhagic and thrombotic problems in the neonate.

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Fig 7. The inhibitors C1E-INH, α2-M, α2-AP, and α1-AT in 118 healthy full-term infants throughout the first 8 months of life. The inner line represents the mean values, the inner clear area the 95% confidence interval, and the shaded area 95% of all values (±2 SD). Adult values are indicated.

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Development of the human coagulation system in the full-term infant

M Andrew, B Paes, R Milner, M Johnston, L Mitchell, DM Tollefsen and P Powers

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