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Differences Between the Sexes in Cord Blood Clotting Factors

By *P. van der Salm*[1], *J. M. H. Ubachs*[1] and *J. W. J. van Wersch*[2]

[1] *Department of Gynaecology*
[2] *Department of Haematology*
De Wever Hospital, Heerlen, The Netherlands

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Dedicated to Professor Dr. Dr. Helmut Greiling on the occasion of his 65th birthday

Summary: Sex-related differences are known to exist in the haemostatic variables of adults. In the present study, three clotting factors were measured in cord blood of 191 newborns. A sex-related difference was found for clotting factor VII, with higher plasma levels in female newborns ($p < 0.01$). Factor VIII:c also tended to be higher in female newborns, compared with male newborns ($p = 0.07$). No difference in fibrinogen concentrations was found.

The observed difference between the sexes for clotting factor VII is not easy to understand, but it is in line with studies showing higher concentrations of factor VII in females than in males throughout adult life.

Introduction

Cardiovascular disease is about twice as frequent in men than in women (1). Various studies have focused on hormonal status (2–4), lipid spectrum (5) and iron storage (6), but no conclusive explanation for this difference in incidence has been found.

Since haemostatic variables (fibrinogen, factor VII and to a lesser extent factor VIII:c) are recognized as important independent risk factors for cardiovascular disease, they have been the subject of extensive research (7–10). Sex-related difference in these haemostatic variables have been shown in young adults as well as in the elderly (11–13).

The aim of the present study was to document fibrinogen, clotting factor VII and factor VIII:c concentrations in cord blood and to determine whether sex-related differences can be demonstrated in the newborn.

Materials and Methods

Patients

Clotting factors VII, VIII:c and fibrinogen were measured in venous cord blood from 92 male and 99 female singleton newborns born between February and August 1992, with a gestational age of 37 weeks or more, and a birth weight between the 2.3rd and 97.7th percentile for gestational age (14). The haematocrit values ranged from 0.45 to 0.51 l/l. Maternal exclusion criteria were a diastolic blood pressure ≥ 90 mmHg, an endocrine disease, a coagulation disorder, or medication known to interfere with the haemostatic system. Gestational age was determined by the last menstrual date and/or ultrasound determinations. Birth weight was recorded.

Methods

Venous cord blood samples were collected in plastic, citrate-containing tubes immediately after delivery and after clamping of the umbilical cord. The tubes were filled with 9 volumes of freshly drawn blood and 1 volume of trisodium citrate (0.11 mol/l). Citrated plasma was prepared by direct centrifugation for 20 minutes at 1800 *g*, snap frozen, then stored at −70 °C. It was thawed with tap water at 37 °C for 5 minutes before use.

Fibrinogen was determined with the clotting assay of *Clauss*, a turbidimetric method employing the CTS-fibrinogen reagent on the Chromotime System (Behring, Marburg, Germany). To quantify factor VII we used the chromogenic substrate COA-set of Kabi Vitrum Diagnostica (Mölndal, Sweden). The intra-assay coefficient of variation was 6.9% at the level of 54.9%. Factor VIII:c was measured with an APTT one stage clotting assay using a deficient plasma (Behring, Marburg, Germany).

Statistics

The *Mann-Whitney* U test was used to test the significance of differences between groups at the $p < 0.05$ level.

Tab. 1 Comparison of the median and interquartile ranges in male and female neonates.

Quantities	Median (interquartile range)		Significance p
	Male neonates (n = 92)	Female neonates (n = 99)	
Gestational age (days)	279 (274– 285)	281 (274– 286)	0.64
Birth weight (g)	3525 (3200–3820)	3350 (3070–3750)	0.02
Fibrinogen (g/l)	2.2 (1.9–2.7)	2.2 (1.9–2.5)	0.68
Factor VII (%)	44 (30– 56)	50 (36– 69)	0.004
Factor VIII:c (%)	107 (61– 166)	142 (72– 192)	0.07

Results

Results for the levels of fibrinogen, clotting factor VII and factor VIII:c in the cord blood of 92 male and 99 female neonates are summarized in table 1.

Gestational age did not differ between the two sexes.

Birth weight was significantly higher in male neonates than in female neonates. The median fibrinogen concentrations were equal for male and female newborns, although the distribution was *Gaussian* in males and skewed to the right in females.

Factor VII levels were significantly higher in female than in male newborns (median values 50% and 44%, respectively, both *Gaussian* distributed).

Factor VIII:c levels tended to be higher in female than male neonates (median values 142% and 107%, respectively), but this difference was not significant (p = 0.07).

The distribution of the clotting factors for each sex separately is shown in figure 1a–c.

Discussion

Studies on gender-dependent differences of plasma fibrinogen concentrations in adults are contradictive. *Lee* et al. report higher fibrinogen concentrations in women than in men, in the age group of 40–59 years (15). *Balleisen* et al. also found higher fibrinogen concentrations in females than in males up to 29 years (13), and similar results were reported by *Folsom* et al. in subjects aged 45–64 years (12). In contrast, *Berglund* et al. could not demonstrate any influence of gender on fibrinogen concentration in 24–44 year-old patients (16), and *Tarallo*

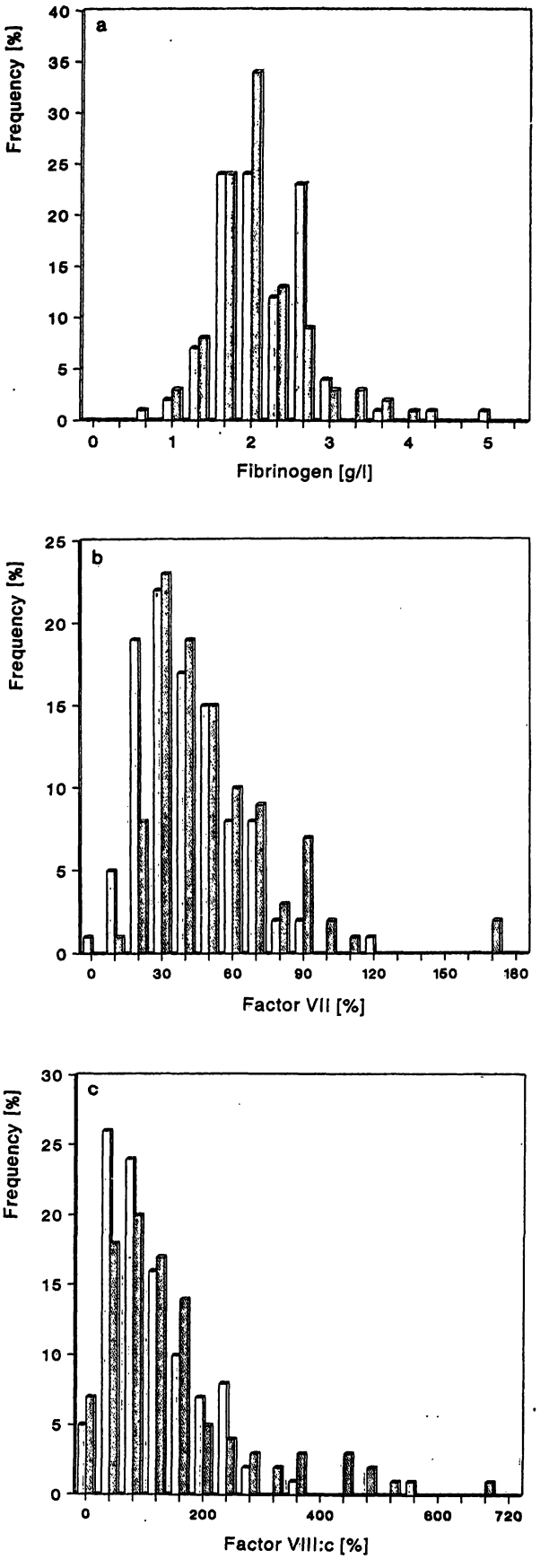

Fig. 1 Distribution of clotting factor concentrations in cord blood.
a) Fibrinogen
b) Amidolytic factor VII
c) Clotting factor VIII:c

et al. reported no statistical difference between the sexes, except in subjects aged 40–50 years (17). Reports on clotting factor VII are also inconclusive. *Balleisen* et al. described no gender influence on factor VII levels (13). *Folson* et al. found higher factor VII levels in women than in men, aged 45–64 years (12), and *Kario* et al. reported similar results for adults aged 60–98 years (11). Less research has been done on sex-related differences in factor VIII:c, but *Balleisen* et al. reported no difference (13). In the present study in newborns, no difference between the sexes could be demonstrated in plasma fibrinogen concentrations. Factor VII levels in cord blood were significantly higher in female than in male neonates. Higher plasma levels of factor VIII:c in female neonates were found, but the difference did not reach the 0.05 level of significance ($p = 0.07$), possibly because factor VIII:c levels span a wide range.

The clinical relevance of the sex-related differences in factor VII levels in newborns might be questioned, as the plasma levels are lower in males than in females. It is unlikely that this small percentage causes a difference in haemostasis between the two sexes. However, the present study provides information about the distribution of the coagulation risk factors in the sexes at birth. It has been stated that sex-related differences in haemostatic variables are related to hormonal effects.

Heller et al. found no association between testosterone and fibrinogen or factor VIII:c, but they found an inverse relationship between testosterone and factor VII in adult males (18). Since male neonates have higher testosterone values than female neonates (19), lower factor VII levels could be expected. The results of the present study are in agreement with this supposition. Moreover, oestrogen replacement therapy after onset of the menopause increases factor VII levels (12, 20). This supports the observation that female neonates – experiencing high oestrogen concentrations during the first week of life (19) – have higher factor VII levels. Less is known about hormonal influences on factor VIII:c. A rise in factor VIII:c levels in the postmenopausal period has been reported (13), but not confirmed by others (20).

Although hormonal characteristics may play a role, no definite explanation for the differences found can be given. It is striking, however, that plasma levels of factor VII, an important cardiovascular risk factor, appear to be higher in females than in males from birth to adult life, whereas cardiovascular disease is more frequent in men.

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Dr. J. W. J. van Wersch
De Wever Hospital
P. O. Box 4446
NL-6401 CX Heerlen
The Netherlands