Factor VIII levels and the risk of pre-eclampsia, HELLP syndrome, pregnancy related hypertension and severe intrauterine growth retardation

Witsenburg, C.P.J.; Rosendaal, F.R.; Middeldorp, J.M.; Meer, F.J.M. van der; Scherjon, S.A.

Thrombosis Research (2005) **115**, 387—392

THROMBOSIS RESEARCH

intl.elsevierhealth.com/journals/thre

REGULAR ARTICLE

Factor VIII levels and the risk of pre-eclampsia, HELLP syndrome, pregnancy related hypertension and severe intrauterine growth retardation

C.P.J. Witsenburg[a], F.R. Rosendaal[b,c], J.M. Middeldorp[a], F.J.M. Van der Meer[c], S.A. Scherjon[a,*]

[a]*Department of Obstetrics, Leiden University Medical Center, K6-27, PO Box 9600 2300 RC Leiden, The Netherlands*
[b]*Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands*
[c]*Haemostasis and Thrombosis Research Centre, Leiden University Medical Center, Leiden, The Netherlands*

Received 22 March 2004; received in revised form 15 September 2004; accepted 15 September 2004
Available online 12 October 2004

KEYWORDS
Factor VIII;
Uteroplacental insufficiency;
Pre-eclampsia;
HELLP syndrome;
Pregnancy related hypertension;
Intrauterine growth restriction

Abstract

Objective: Recently, acquired as well as genetic prothrombotic factors are associated with thrombotic events. These factors have also been related to conditions of uteroplacental insufficiency such as pre-eclampsia, HELLP syndrome and severe intrauterine growth restriction (IUGR). The aim of this study was to determine whether elevated factor VIII levels are associated with uteroplacental insufficiency, in particular pre-eclampsia, HELLP syndrome or pregnancy-induced hypertension and intrauterine growth retardation.
Methods: Plasma samples of 75 women with a history of pregnancy complicated by pre-eclampsia, HELLP syndrome, pregnancy induced hypertension or intrauterine growth restriction were tested for factor VIII:C (FVIII:C) levels at a minimum of 10 weeks post-partum. Laboratory results were compared to factor VIII:C levels found in a healthy control group of 272 women.
Results: Mean factor VIII:C levels were similar at 123 IU/dl in both the patient group and the controls. In a logistic regression model, after adjusting for age and blood group, no effect of factor VIII:C levels on the risk of pregnancy complications was observed, with the exception of IUGR with (OR 2.9, CI 1.0—8.7) or without hypertension (OR 2.0, CI 0.7—6.4).
Conclusion: If the elevated level of factor VIII would be the sole factor responsible for the increased risk observed, one would expect to find an effect of blood group on

* Corresponding author. Tel.: +31 71 5262872.
E-mail address: S.Scherjon@LUMC.nl (S.A. Scherjon).

0049-3848/$ - see front matter
doi:10.1016/j.thromres.2004.09.009

risk as well (blood group being an important determinant of FVIII:C). While no such effect could be shown a causal relationship between elevated levels of factor VIII and conditions of uteroplacental insufficiency such as pre-eclampsia, HELLP syndrome, pregnancy-induced hypertension and IUGR is not very likely.

Introduction

Approximately 1—5% of all pregnancies are complicated by serious conditions such as pre-eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), solutio placentae, severe intrauterine growth restriction (IUGR), foetal loss and stillbirth [1]. In general, these conditions are thought to be related to a poor trophoblastic invasion of maternal spiral arteries, leading to a syndrome known as uteroplacental insufficiency. The mechanisms of uteroplacental insufficiency are largely unknown and its aetiology is likely to be multicausal: immunological as well as genetic factors may be involved, which may include factors involved in blood clotting [2—5].

Recently, insights in the causes of thrombosis have grown, which include genetic as well as acquired risk factors such as deficiencies of antithrombin, protein C and protein S, activated protein C resistance due to the factor V Leiden mutation and prothrombin G20210A mutation. High levels of procoagulant factors, such as factor VIII, factor IX and factor XI, have also been associated with an increased risk of venous thrombosis [6—11], as has hyperhomocysteinaemia [12—14]. Only recently, these factors have been related to uteroplacental insufficiency. Thrombophilic defects, notably deficiencies of anticoagulant factors, were found in up to 50% of patients with severe pre-eclampsia and HELLP syndrome [3] and they have been associated with an increased risk of stillbirth as well as foetal growth retardation [15,16].

Elevated levels of factor VIII:C (FVIII:C) are a common risk factor for venous thrombosis [17—19]. They may also be associated with an increased risk of arterial thrombosis in coronary heart disease [20,21]. The basis of high levels of FVIII is unclear: it is partly associated with ABO blood group (lower levels in type O) and APC resistance, but additional variation in FVIII levels has been shown to cluster in families too [22]. When a cut-off point for high levels of 150 IU/dl is used the prevalence of elevated FVIII:C is high: 11% of healthy control subjects and 25% of patients with a first episode of deep-vein thrombosis were found to have FVIII:C levels >150 IU/dl [23]. Factor VIII in plasma is bound to von Willebrand factor (VWF) and its levels are to a large degree determined by the levels of VWF, which on its turn are dependent on blood group [24,25]. Elevated levels of FVIII:C in patients with venous thromboembolism have been shown to persist over time [17,31] and independent of acute-phase reactions [17,19,32].

In the 1970s and 1980s, several authors reported an elevated ratio of VWF/FVIII:C during pregnancy and an even higher ratio in pregnancies complicated by pre-eclampsia [26—29] and hypertension [30,31]. Altered coagulation status due to these conditions might increase the factor VIII:C consumption, causing plasma FVIII:C levels to go down. Elevated levels of VWF, which is known to increase in diseases associated with endothelial activation, might add to this effect.

In this study, we set out to determine whether persistent elevated factor VIII:C levels were associated with conditions of uteroplacental insufficiency in a group of 75 women with a history of pregnancy complicated by hypertensive disorders (pre-eclampsia, HELLP syndrome or pregnancy-induced hypertension) or intrauterine growth restriction.

Methods

Patients and study design

Women reporting to our clinic with a history of hypertensive complications or IUGR during a preceding pregnancy are screened for the presence of thrombophilic defects, among which factor VIII:C. Between august 1999 and July 2002 FVIII:C levels were determined in a group of 75 women with one of these complications in their index pregnancy. Plasma FVIII:C levels were measured at a minimum of 10 weeks post-partum, patients using oral contraceptives at the time of testing being excluded. With regard to the different complications of pregnancy 20 of the women had a history of IUGR only, 36 had suffered from hypertensive disorders during pregnancy and 19 women had had a combination of the 2. Laboratory results were compared to factor VIII:C levels found in 272

Table 1 Mean FVIII:C levels in patients with a history of pre-eclampsia, HELLP syndrome, pregnancy-induced hypertension and/or IUGR and healthy controls

	Blood type O			Blood type non-O			Total		
	N	Mean	95% CI	*N*	Mean	95% CI	*N*	Mean	95% CI
Patients									
PE/HELLP/HT+IUGR (*n*=19)	5	121	82—159	14	146	121—173	19	140	119—161
IUGR (*n*=20)	9	113	83—143	11	129	98—159	20	122	102—141
PE/HELLP/HT (*n*=36)	11	120	84—156	25	111	94—129	36	114	99—129
Total	25	118	100—135	50	125	112—138	75	123	112—133
Controls	111	110	104—117	161	132	128—137	272	123	120—127

healthy female controls derived from the Leiden Thrombophilia Study (LETS) [18].

Definitions

Pre-eclampsia was defined as pregnancy-induced hypertension (diastolic blood pressure ≥90 mm Hg) plus significant proteinuria (urinary protein excretion >300 mg/24 h or two 2+ or higher readings of on dipstick analysis of midstream or catheter urine samples) after 20 weeks of gestational age. Eclampsia was defined as the occurrence of generalised convulsions during pregnancy, during labour or within 7 days of delivery, not caused by epilepsy or other convulsive disorders. HELLP syndrome was defined as the presence of haemolysis (LDH>600 IU/l), elevated liver enzymes (SGOT>70 IU/l) and thrombocytopenia (<100.109/l) [33]. Intrauterine growth restriction finally was defined as a neonatal birth weight below the 10th percentile, while individuals with other causes such as gross chromosomal disorders and viral infections were excluded [34].

Laboratory tests

Venous blood samples were taken from the subjects at a minimum of 10 weeks post-partum in 106 mmol/l trisodium citrate. Factor VIII:C levels were determined by a one-stage clotting assay [18].

Statistical analysis

The analysis was performed by comparing FVIII:C levels in 75 patients and 272 female population controls. First, we compared mean levels of FVIII:C between cases and controls, with 95% confidence interval for the difference of the means. Subsequently, we calculated odds ratios as a measure for the relative risk, by cross-tabulation and logistic regression for various cut-off values. Odds ratios (and 95% confidence intervals) adjusted for blood type and age were derived from the model.

Results

We included 75 patients and 272 controls. Patients had a history of IUGR (*n*=20), pre-eclampsia, HELLP syndrome or pregnancy induced hypertension (*n*=36), or a combination of the 2 (*n*=19). Median age of the patients at the time of the blood draw was 31.6 (range 23.8—44.4 years), while for the controls it was 44.8 years (range 17—72).

In both the patient and control group, mean levels of factor VIII:C were 123 IU/dl. Blood group 0 was present in 25 (33%) of the patients and 111 (41%) of the control women. When we stratified the patients by ABO blood group, mean FVIII:C levels were 118 IU/dl for blood type O (*n*=25) and 125 IU/dl for blood type non-O (*n*=50). In the control

Table 2 Mean differences between patients and controls in FVIII:C concentration

	Blood type O			Blood type non-O			Total		
	n	Mean difference	95% CI	*n*	Mean difference	95% CI	*n*	Mean difference	95% CI
PE/HELLP/HT+IUGR (*n*=19)	5	0.15	−0.25 to 0.54	14	0.03	−0.23 to 0.29	19	0.06	−0.14 to 0.26
IUGR (*n*=20)	9	0.11	−0.18 to 0.41	11	−0.16	−0.46 to 0.15	20	−0.04	−0.23 to 0.17
PE/HELLP/HT (*n*=36)	11	0.19	−0.17 to 0.54	25	−0.31	−0.50 to −0.12	36	−0.16	−0.33 to 0.02
Total	25	0.15	−0.03 to 0.33	50	−0.18	−0.31 to −0.05	75	−0.07	−018 to 0.04

Table 3 Odds ratio (and 95% confidence intervals) in patients with a raised FVIII:C levels (above 150 IU/l) compared to controls

	Raised FVIII levels			
	Blood type O		Blood type non-O	
	Incidence	OR (95% CI)	Incidence	OR (95% CI)
PE/HELLP/HT+IUGR	20%	1.9 (0.2—18.2)	43%	2.4 (0.8—7.2)
IUGR	11%	0.9 (0.1—8.2)	36%	1.8 (0.5—6.4)
PE/HELLP/HT	27%	2.8 (0.7—12.0)	16%	0.6 (0.2—1.8)
Controls	12%		24%	

group, the mean FVIII:C levels were 110 IU/dl for blood type O (n=111) and 132 IU/dl for non-O (n=161). We also calculated mean factor VIII:C levels for the different complications of pregnancy. Factor VIII levels seemed to be the highest in patients with a history of combined IUGR/hypertensive disorders, the lowest in patients with hypertensive disorders only, and intermediate in patients with IUGR only, although confidence intervals were wide (Table 1).

Mean differences between patients and controls stratified for blood group type are given in Table 2. We only found a difference in factor VIII:C levels in patients with a non-O blood group, particularly in the group of hypertensive patients without foetal growth restriction.

The risk associated with high factor VIII:C levels was estimated stratified for blood group type for each of the pregnancy complications separately, by using factor VIII:C levels of 150 IU/l as a cut-off value. Odds ratios and confidence intervals are given in Table 3. In this comparison to controls, no specific relation is seen between raised FVIII:C levels (>150 IU/l) and the different pregnancy complications for both O and non-O blood group type.

In a multivariate logistic regression model, we assessed the contribution to risk, for each of the complications, of blood group and elevated factor VIII levels, adjusted for age. FVIII:C appeared to increase risk with factor three for hypertensive complications in combination with IUGR (adjusted OR 2.9, CI 1.0—8.7). For IUGR without hypertensive complications, a two-fold increased risk was found (adjusted OR 2.0, CI 0.7—6.3). For hypertensive complications without IUGR, no effect on risk of FVIII:C levels was observed (adjusted OR 1.2, CI 0.5—3.2) (Table 4).

Discussion

Given the recently reported association between elevated FVIII levels and thrombotic events, one might expect to find a similar association with regard to pregnancy complications. It was shown that a raised F VIII level is an independent risk factor for early recurrent miscarriage [35]. Other studies have found a raised VWF:Ag/FVIII:C ratio in hypertensive pregnant women [30,31]. This might be caused by either a raised VWF:Ag or a decreased FVIII level. The first suggestion is supported by studies in hypertensive-preeclamptic pregnant women where indeed a raised VWF:Ag level is found [36,37]. In our study, which concentrated on absolute FVIII:C levels, no clear association between FVIII:C levels postpartum and the risk of hypertensive pregnancy complications could be demonstrated. In the subgroup of patients with a history of IUGR with (OR 2.9, CI 1.0—8.7) or without hypertension (OR 2.0, CI 0.7—6.4), we found that raised FVIII:C levels were related to mildly elevated odds ratios with broad confidence intervals.

Mean factor VIII:C levels in the patient group and in the control group were not different. Stratification by ABO blood group led to similar results. For the different complications of pregnancy, FVIII levels were higher in patients with a history of a combined IUGR/hypertensive disorder, lower in patients with hypertensive disorders only and intermediate in patients with IUGR only, but the wide confidence intervals did not allow a firm conclusion.

Table 4 Odds ratio (and 95% confidence intervals) in patients with a raised FVIII:C levels (above 150 IU/l) compared to controls

	Blood group (unadjusted)	Blood group (adjusted for FVIII)	High FVIII:C (unadjusted)	High FVIII:C (adjusted for blood group)
PE/HELLP/HT+IUGR	0.5 (0.2—1.5)	0.6 (0.2—1.9)	3.2 (1.1—9.4)	2.9 (1.0—8.7)
IUGR	1.1 (0.4—2.8)	1.2 (0.4—3.3)	2.0 (0.6—6.0)	2.0 (0.7—6.4)
PE/HELLP/HT-IUGR	0.7 (0.3—1.4)	0.7 (0.3—1.5)	1.3 (0.5—3.4)	1.2 (0.5—3.2)
Total	0.7 (0.4—1.3)	0.8 (0.4—1.4)	1.8 (0.9—3.6)	1.7 (0.9—3.5)

Clinical manifestations of uteroplacental insufficiency in the mother disappear very shortly after birth. As FVIII:C levels were measured at a minimum of 10 weeks post-partum, it seems unlikely that factor VIII levels were by then still influenced as a result of these conditions. Blood group is an important determining factor in FVIII levels. Therefore, in case elevated FVIII:C was to increase the risk of these complications of pregnancy, one would expect to find an increased risk of non-O blood group on pregnancy complications as well. However, we did not find any effect of blood group, also after correction for FVIII levels, on the risk for one of the studied complications of pregnancy. This makes a causal relation between FVIII and uteroplacental insufficiency less likely.

In the multivariate logistic regression model, elevated factor VIII levels were associated with a two- to three-fold increased risk of IUGR. Again, the sample size precludes definite conclusions, but one is tempted to speculate that elevated levels of FVIII have a common background with the causes of placental insufficiency. In general, these conditions are thought to be related to a poor trophoblastic invasion of maternal spiral arteries. The mechanisms of uteroplacental insufficiency are largely unknown, but factors involved in blood clotting might well contribute to its aetiology [2—5]. Previous studies have shown an increased risk of pre-eclampsia in women with a low APC-sensitivity ratio, i.e., some form of APC-resistance, in the absence of factor V Leiden [22]. It is also known that factor VIII levels and APC-sensitivity ratios are inversely related, i.e., high factor VIII levels are associated with APC-resistance. It is likely that this represents increased thrombin generation, but, since we observed no effect from ABO-blood group, that this is acquired rather than genetically determined.

References

[1] Sibai BM. Thrombophilias and adverse outcomes of pregnancy—what should a clinician do? *N Engl J Med* 1999; **340:**50—2.

[2] de Vries JI, Dekker GA, Huijgens PC, Jacobs C, Blomberg BM, van Geijn HP. Hyperhomocysteinaemia and protein S deficiency in complicated pregnancies. *Br J Obstet Gynaecol* 1997;**104:**1248—54.

[3] Dekker GA, de Vries JI, Doelitzsch PM, Huijgens PC, von Blomberg BM, Jakobs C, et al. Underlying disorders associated with severe early-onset preeclampsia. *Am J Obstet Gynaecol* 1995;**173:**1042—8.

[4] Clarck DA. Cytokines and pregnancy. *Curr Opin Immunol* 1989;**1:**1148—52.

[5] Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-AM A, Jaffa A, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. *N Engl J Med* 1999;**340:**9—13.

[6] Dahlbäck B, Carlsson M, Svensson PJ. Familial thrombophilia due to previously unrecognized mechanism characterized by poor antioagulant response to activated protein C: prediction of a cofactor to activated protein C. *Proc Natl Acad Sci U S A* 1993;**90:**1004—8.

[7] Bertina RM, Koeleman RPC, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994;**369:**64—7.

[8] Koster T, Roosendaal FR, Ronde H, Briet E, Vandenbroucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. *Lancet* 1993;**342:**1503—6.

[9] Heijboer H, Brandjes DPM, Büller HR, Sturk A, ten Cate JW. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. *N Engl J Med* 1990;**323:**1512—6.

[10] Koster T, Rosendaal FR, Briët E, van der Meer FJ, Colly LP, Trienekens PH, et al. Protein C deficiency in a controled series of unselected outpatients: an infrequent but clear risk factor for venous thrombosis (Leiden Thrombophilia Study). *Blood* 1995;**85:**2756—61.

[11] Simioni P, Sanson BJ, Prandoni P, Tormene D, Friederich PW, Girdami B, et al. Incidence of venous thromboembolism in families with inherited thrombophilia. *Thromb Haemost* 1999;**81:**198—202.

[12] Boers GH. Mild hyperhomocysteinemia is an independent risk factor for arterial vascular disease. *Semin Thromb Hemost* 2000;**26**(3):291—5.

[13] Clarke R, Daly L, Robinson K, Naughten E, Cahalane S, Fpwler B, et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. *N Engl J Med* 1991;**324**(17): 1149—55.

[14] den Heijer M, Koster T, Blom HJ, Bos GM, Briët E, Reitsma PH, et al. Hyperhomcysteinemia as a risk factor for deep vein thrombosis. *N Engl J Med* 1996;**334:(12):**759—62.

[15] Preston FE, Rosendaal FR, Walker ID, Briet E, Berntorp E, Conard J, et al. Increased fetal loss in women with heritable thrombophilia. *Lancet* 1996;**348:**913—6.

[16] Lindoff C, Ingemarsson I, Martinsson G, Segelmark M, Thysell H, Astedt B. Preeclampsia is associated with a reduced response to activated protein C. *Am J Obstet Gynaecol* 1997;**176:**457—60.

[17] Kraaijenhagen RA, in 't Anker PS, Koopman MM, Reitsma PH, Prins MH, van den EA, et al. High plasma concentration of factor VIIIc is a major risk factor for venous thromboembolism. *Thromb Haemost* 2000;**83:**5—9.

[18] Koster T, Blann AD, Briet E, Vandenbroucke JP, Rosendaal FR. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. *Lancet* 1995;**345:**152—5.

[19] O'Donnell J, Tuddenham EG, Manning R, Kemball-Cook G, Johnson D, Laffan M. High prevalence of elevated factor VIII levels in patients referred for thrombophilia screening; role of increased synthesis and relationship to the acute phase reaction. *Thromb Haemost* 1997;**77:**825—8.

[20] Meade TW, Cooper JA, Howrth DJ, Ruddock V, Miller GJ. Factor VIII, ABO blood group and the incidence of ischaemic heart disease. *Br J Haematol* 1994;**88:**601—7.

[21] Folsom AR, Wu KK, Rosamond WD, Sharret AR, Chambless LE. Prospective study of hemostatic factors and incidence of coronary heart disease: the Artheriosclerosis Risk in Communities (ARIC) Study. *Circulation* 1997;**96:**1102—8.

[22] Clark P, Sattar N, Walker ID, Greer IA. The Glasgow Outcome, APCR and Lipid (GOAL) Pregnancy Study: signifi-

cance of pregnancy associated activated protein C resistance. *Thromb Haemost* 2001;**85:**30—5.
[23] Kamphuisen PW, Eikenboom JC, Bertina RM. Elevated factor VIII levels and the risk of thrombosis. *Arterioscler Thromb Vasc Biol* 2001;**21:**731—8.
[24] Gill JC, Endres-Brooks J, Bauer PJ, Marks WJ, Montgomery RR. The effect of ABO blood groups on the diagnosis of von Willebrand disease. *Blood* 1987;**69:**1691—5.
[25] Weis HJ, Sussman I, Hoyer LW. Stabilisation of factor VIII in plasma by the von Willebrand factor. *J Clin Invest* 1997;**60:**390—404.
[26] Redman CW, Denson KW, Beilin LJ, Bolton FG, Stirrat GM. Factor VIII consumption in pre-eclampsia. *Lancet* 1977;**2:**1249—52.
[27] Thornton CA, Bonnar J. Factor VIII-related antigen and factor VIII coagulant activity in normal and pre-eclamptic pregnancy. *Br J Obstet Gynaecol* 1977;**84:**919—23.
[28] Caires D, Arocha-Pinango CL, Rodrigues S, Linares J. Factor VIIIR: Ag/Factor VIII: C and their ratio in obstetrical cases. *Acta Obstet Gynaecol Scand* 1984;**63:**411—6.
[29] Scholtes MC, Gerretsen G, Haak HL. The factor VIII ratio in normal and pathological pregnancies. *Eur J Obstet Gynaecol Reprod Biol* 1983;**16:**89—95.
[30] During R, Schwarzlos G. Factor VIII-associated antigen/factor VIII ratio in pregnant patients with and without hypertension. *Zentralbl Gynakol* 1990;**112:**355—9.
[31] Caron C, Goudemand J, Marey A, Beaugue D, Ducroux G, Drouvin F. Are haemostatic and fibrinolytic parameters predictors of preeclampsia in pregnancy-associated hypertension? *Thromb Haemost* 1991 (Oct 1);**66(4):**410—4.
[32] O'Donnel J, Mumford A, Manning R, Laffan M. Elevation of FVIII:C in venous thromboembolism is persistent and independent of the acute phase response. *Thromb Haemost* 2000;**83:**10—3.
[33] Davey DA, MacGillivray I. The classification and definitions of the hypertensive disorders of pregnancy. *Am J Obstet Gynaecol* 1988;**158:**892—8.
[34] Bakketeig LS. Current growth standards, definitions, diagnosis and classification of fetal growth retardation. *Eur J Clin Nutr* 1998;**52(Suppl. 1)**:S1—4.
[35] Marietta M, Fachinetti F, Sgarbi L, Simoni L, Bertesi M, Torelli G, et al. Elevated plasma levels of factor VIII in women with early recurrent miscarriage. *J Thromb Haemost* 2003 (Dec);**1(12)**:2536—9.
[36] Nader SK, Al Yemeni E, Blann AD, Lip GY. Thrombomodulin, von Willebrand factor and E-selectin as plasma markers of endothelial damage/dysfunction and activation in pregnancy induced hypertension. *Thromb Res* 2004;**113(2)**:123—8.
[37] He S, Silveira A, Hamsten A, Blomback M, Bremme K. Haemostatic, endothalial and lipoprotein parameters and blood pressure levels in women with a history of preeclampsia. *Thromb Haemost* 1999 (Apr);**81(4)**:538—42.