The GOAL study: a prospective examination of the impact of factor V Leiden and ABO(H) blood groups on haemorrhagic and thrombotic pregnancy outcomes

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Summary

Factor V Leiden (FVL) and ABO(H) blood groups are the common influences on haemostasis and retrospective studies have linked FVL with pregnancy complications. However, only one sizeable prospective examination has taken place. As a result, neither the impact of FVL in unselected subjects, any interaction with ABO(H) in pregnancy, nor the utility of screening for FVL is defined. A prospective study of 4250 unselected pregnancies was carried out. A venous thromboembolism (VTE) rate of 1·23/1000 was observed, but no significant association between FVL and pre-eclampsia, intra-uterine growth restriction or pregnancy loss was seen. No influence of FVL and/or ABO(H) on ante-natal bleeding or intra-partum or postpartum haemorrhage was observed. However, FVL was associated with birth-weights >90th centile [odds ratio (OR) 1·81; 95% confidence interval (CI_{95}) 1·04–3·31] and neonatal death (OR 14·79; CI_{95} 2·71–80·74). No association with ABO(H) alone, or any interaction between ABO(H) and FVL was observed. We neither confirmed the protective effect of FVL on pregnancy-related blood loss reported in previous smaller studies, nor did we find the increased risk of some vascular complications reported in retrospective studies.

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Introduction

Factor V Leiden (FVL) occurs commonly in those of European extraction and a number of studies, predominantly case–control in design, have linked FVL with thrombosis-associated pregnancy outcomes, such as fetal loss and pre-eclampsia (Robertson *et al*, 2006). In a systematic review, however, the risk of an adverse outcome in FVL heterozygotes was a modest twofold (Robertson *et al*, 2006), a risk which was derived mainly from retrospective case–control studies [which can exaggerate an effect when compared with prospective cohorts (Klerk *et al*, 2002)]. By contrast, the high prevalence of FVL might also indicate an evolutionary advantage of the mutation. One plausible effect would be a reduction in haemorrhage, perhaps leading to protection from iron deficiency, with such a reduced bleeding risk already reported out-with pregnancy (van 't Veer *et al*, 1997; Corral *et al*, 2001; Escuriola Ettingshausen *et al*, 2001; Castoldi *et al*, 2003; Donahue *et al*, 2003; Bos *et al*, 2005). Indeed, despite the substantial difficulties in accurately assessing pregnancy haemorrhage visually (Duthie *et al*, 1991) or by routine haematology (Pritchard, 1965), a reduction in peri-partum blood loss in those with FVL has also been suggested (Lindqvist *et al*, 1998, 1999). The ABO(H) blood group system also influences haemostasis, with group O subjects carrying a lower risk of thrombosis (Koster *et al*, 1995; Clark *et al*, 2005), even perhaps when carrying FVL (Gonzalez Ordonez *et al*, 1999; Robert *et al*, 2000).

Correspondingly, an influence of FVL and ABO(H) on pregnancy-associated haemorrhage or thrombosis-linked complications requires confirmation in unselected prospective cohorts. On account of this, we examined the impact of these two parameters in an unselected prospective cohort study of ~4000 pregnancies.

Materials and methods

The Glasgow outcome APC resistance and lipid (GOAL) pregnancy study is a prospective examination of the impact of FVL on pregnancy, carried out in Glasgow, Scotland between May 1997 and February 2000. Four thousand, two hundred and fifty unselected subjects who consecutively attended for routine antenatal care at Glasgow Royal Maternity Hospital were approached for recruitment, with the majority recruited between 7 and 16 weeks gestation. Details of the recruitment, assessment, data collection and methods of FVL assessment used have been previously published (Clark *et al*, 2001). ABO(H) phenotyping was achieved by standard serology. The FVL laboratory results were blinded to the subjects, the investigators and their clinicians until 6 weeks after delivery of the index pregnancy. Ethical approval was obtained from the local ethical committee at the Glasgow Royal Infirmary NHS Trust, Scotland and written informed consent was obtained from all participating subjects.

Outcomes

The definition of the outcomes recorded are as previously reported (Clark *et al*, 2001). These include venous thromboembolism (VTE) pregnancy-induced hypertension (PIH), pre-eclampsia (PET), miscarriage (MISC – loss at <24 weeks), stillbirth (SB – loss ≥24 weeks), intra-uterine growth restriction (IUGR – defined at <5th centile) and neonatal death (NND). Singleton offspring with normalized birth weights >90th centile were also recorded. Deprivation was as assessed by Carstairs and Morris (Morris & Carstairs, 1991; Carstairs, 1995). Visual estimation of peri-partum haemorrhage is highly subjective and (given the rapid changes in blood volume) the acute assessment of laboratory red cell parameters is also unreliable (Pritchard, 1965; Duthie *et al*, 1991). Correspondingly, we defined peri-partum haemorrhage as both (i) any episode visually assessed as >500 ml (data not shown) and (ii) any episode visually assessed as >500 ml which also required clinical intervention. Such interventions for intra-partum haemorrhage (IPH) included: additional syntometrine doses, red cell transfusion or any form of surgical intervention. Similarly, interventions recorded for postpartum haemorrhage (PPH) included episodes requiring: re-admission, the administration of additional syntometrine, transfusion or any form of surgical intervention. We also recorded all per-vaginal (PV) bleeding episodes occurring <24 weeks, or ≥24 weeks which also required intervention in the form of hospital admission, additional haematinic replacement or transfusion.

Power and statistical analysis

The study was designed to examine two end-points: (i) the impact of FVL/ABO(H) on a composite of all major vascular complications (PET, IUGR, pregnancy loss and VTE) and (ii) the impact of FVL/ABO(H) on peri-partum blood loss. We assumed a combined vascular complication frequency of 13·6% [comprising VTE (0·1%) (Greer & Thomson, 2001), PET (3%) (Walker, 2000), IUGR (5%) (Neerhof, 1995), and pregnancy loss (≥5·5%) (Cashner *et al*, 1987; Samueloff *et al*, 1993)] and a peri-partum haemorrhage frequency of ∼8% in non-FVL subjects. The study was designed to have >80% power ($P = 0{\cdot}05$) to detect an approximately twofold increased risk of the composite vascular end-point in association with FVL and also at least a 55% reduction in the occurrence of clinically significant peri-partum haemorrhage in association with FVL. This estimate of effect was consistent with the 50–80% reduction in per-partum haemorrhage associated with FVL alone in previous studies (Lindqvist *et al*, 1998, 1999).

Unconditional logistic regression was performed to derive odds ratios (OR), with 95% confidence intervals (CI_{95}), for the risk of each outcome in association with FVL, blood group non-O (non-O compared with O), and FVL/non-O compared with the remainder. Where appropriate, OR were also adjusted for age, waist circumference, non-fasting lipids, parity (previous number of live births), booking diastolic blood pressure, smoking and deprivation category. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 13.0 for Windows).

Results

Of the 4250 women approached, 4157 consented to participate. In the 32 women recruited twice for separate pregnancies, data were collected from the first pregnancy only. 79 twin pregnancies were recruited and 61 women, who gave initial clinical data and samples, transferred to other areas or were lost to follow-up.

The mean age (±SD) of singleton pregnancies was 28 ± 6 years, with 45·6% primigravid. Of these, 239 women developed PIH, 66 developed PET, 174 experienced IUGR, 413 had a PV bleeding event <24 weeks and 366 had a PV bleeding episode ≥24 weeks (of which 234 required additional intervention). There were 50 MISC in singleton pregnancies, 22 SB and eight NND. 304 had an IPH or PPH that required intervention, of which 196 occurred after a non-operative delivery. 54% of PPHs occurred ≤24 h of delivery. Multiple complications were recorded in 93 women.

The characteristics of the recruits are shown (Table I). Women who developed PET were more likely to have a waist circumference ≥80 cm ($P = 0{\cdot}01$), to be primigravid ($P < 0{\cdot}01$), to have a higher booking diastolic blood pressure ($P < 0{\cdot}01$) and less likely to be smokers ($P < 0{\cdot}01$), whereas those with IUGR were less likely to be overweight ($P = 0{\cdot}03$) and more commonly were smokers ($P < 0{\cdot}01$) than pregnancies with normal growth. Women with a PV bleed ≥24 weeks were younger than those without such bleeding ($P < 0{\cdot}01$).

Samples suitable for FVL analysis were available in 3944 cases, of whom 3·61% were carriers, with two identified as homozygotes. Of the 3985 with appropriate samples, 47·6% were non-O. OR (adjusted and unadjusted) for each outcome

Table I. Baseline characteristics.

	All	IUGR <5th (n = 174)	IUGR <5th (excl. PET) (n = 161)	Miscarriage (n = 50)	SB ≥24 weeks (n = 22)	NND (n = 8)	PET (n = 66)	PIH (n = 239)	>90th centile (n = 403)	PPH or IPH (all) (n = 304)	PPH or IPH (non–op) (n = 196)	PPH or IPH (op) (n = 105)
Mean age (years) (SD)	28 (6)	28 (6)	28 (6)	29 (7)	29 (6)	29 (6)	28 (5)	29 (6)	29 (6)	29 (6)	28 (6)	29 (6)
Mean DBP mmHg (SD)	66 (9)	65 (9)	64 (8)	64 (8)	64 (7)	66 (11)	72 (10)	73 (9)	68 (9)	67 (10)	66 (9)	68 (11)
Smoker n (%)	1678 (42·6)	119 72·1)	114 (75·0)	25 (50·0)	14 (66·7)	7 (100·00)	13 (20·3)	58 (24·8)	106 (26·7)	106 (35·1)	72 (36·9)	33 (31·7)
Waist circumference ≥80 cm n (%)	1224 (45)	44 (35·8)	37 (32·7)	20 (52·6)	10 (71·4)	1 (20·0)	28 (63·6)	92 (55·4)	167 (60·5)	98 (45·8)	55 (41·0)	43 (55·1)
Primigravida n (%)	1804 (45·6)	89 (52·7)	81 (51·9)	19 (38·0)	9 (40·9)	4 (57·1)	44 (67·7)	151 (63·7)	172 (43·0)	181 (59·7)	117 (59·7)	62 (59·6)
FVL carrier n (%)	142 (3·61)	6 (3·5)	6 (3·8)	1 (2·0)	-	2 (25·0)	3 (4·7)	10 (4·3)	20 (5·0)	10 (3·3)	5 (2·6)	4 (3·8)
Non-O group n (%)	1897 (47·6)	88 (50·6)	79 (49·1)	24 (48·0)	7 (31·8)	4 (50·0)	34 (51·5)	118 (49·4)	210 (52·1)	138 (45·4)	87 (44·4)	49 (46·7)

The mean and standard deviation (SD) for age, diastolic blood pressure (DBP) at early pregnancy booking and the number (and %) of smokers, the number (and %) of those with an early pregnancy booking waist circumference ≥80 cm, as well as the number (and %) of primigravida, factor V Leiden carriers (FVL) and non-O blood group subjects for the whole cohort and for each individual complication are shown. The percentages relate to the number of subjects in whom the appropriate information was recorded in the case records or material suitable for genetic and phenotypic analysis was available. IUGR<5th, intra-uterine growth restriction <5th centile; excl PET, IUGR occurring in the absence of pre-eclampsia; miscarriage, singleton fetal loss at <24 weeks gestation; SB, still birth at ≥24 weeks gestation; NND, neonatal death; PET, pre-eclampsia; PIH, pregnancy-induced hypertension; >90th centile, singleton births with weight >90th centile; PPH, postpartum haemorrhage (requiring additional intervention); IPH, intra-partum haemorrhage (requiring additional intervention) for all deliveries and for operative (op) and non-operative (non-op) deliveries only.

are shown (Table II). For FVL, non-significant effects were observed for PIH, PET, IUGR, IUGR (excluding PET) and MISC. In the multivariate regression, there was no influence of FVL on the composite vascular outcome. Similar non-significant effects were seen when non-O were compared with group O subjects. However, for FVL alone, significant adjusted OR were observed for birth weights >90th centile (OR 1·81 CI_{95} 1·04–3·31) and for NND (OR 14·79 CI_{95} 2·71–80·74). Of the eight NND cases, two mothers were carriers of FVL, with one of the cases associated with a premature delivery at 23 weeks and the other with pulmonary hypoplasia. No interaction between FVL and non-O was observed for any outcome (Table II). In addition, no influence of either FVL and/or blood group non-O on the occurrence of antental PV bleeding, IPH/PPH >500 ml (data not shown) or IPH/PPH requiring clinical intervention was observed (Table II).

Nine subjects had had a VTE prior to the index pregnancy. Six were non-O and two (with contraceptive-associated VTE) carried FVL. During the index pregnancy five experienced a VTE, three in the puerperium and two ante-natally. None carried FVL and all, but one, were group O. Despite this, three reported a family history of VTE in a near relative.

Discussion

Factor V Leiden and ABO(H) blood groups are amongst the commonest heritable influences on coagulation. In addition to the recognized VTE risk with FVL, non-O subjects are at a twofold increased risk of venous (Koster *et al*, 1995) and perhaps arterial (Clark *et al*, 2005) thrombosis. This thrombotic risk and an accompanying reduction in haemorrhage risk in non-pregnant subjects is consistent with the influence of ABO(H) on FVIII coagulant activity/von Willebrand factor levels (Preston & Barr, 1964; Gill *et al*, 1987). Non-O has not been examined in the context of pregnancy haemorrhage, but has been associated with an increase in pregnancy-related VTE (Jick *et al*, 1969; Larsen *et al*, 2005). However, any effect on the incidence, or severity, of PET is not yet established (May, 1973; Harlap & Davies, 1974; South & Naldrett, 1974; Sezik *et al*, 2002). In the non-pregnant female, the thrombotic phenotype of FVL may be influenced by co-inheritance of non-O (Gonzalez Ordonez *et al*, 1999; Robert *et al*, 2000; Morelli *et al*, 2005), suggesting a protective effect of blood group O against VTE. Thus, an interaction between FVL and non-O in both thrombosis associated and haemorrhagic pregnancy complications is plausible.

We observed a VTE rate in the index pregnancy of 1·23/1000, of which 60% occurred in the early puerperium. Although small numbers, none carried FVL and the majority were group O. Despite this, three had a family history of VTE. Indeed, in the whole cohort, a family history of VTE did not increase the likelihood of FVL carriage (OR 1·49 CI_{95} 0·9–2·45), which might indicate that the addition of family history of VTE to a selective screening strategy may not necessarily

Table II. The impact of FVL and ABO(H) blood group on pregnancy outcome.

	FVL (OR, CI_{95})	FVL* (OR, CI_{95})	Non-O (OR, CI_{95})	Non-O* (OR, CI_{95})	FVL/non-O* (OR, CI_{95})
PPH or IPH (all)	0·89 (0·46–1·71)	0·61 (0·24–1·52)	0·90 (0·71–1·14)	0·81 (0·60–1·08)	1·05 (0·42–2·67)
PPH or IPH (non–op)	0·91 (0·32–2·63)	0·74 (0·30–1·84)	1·00 (0·82–1·22)	0·88 (0·65–1·18)	0·64 (0·15–2·66)
PPH or IPH (op)	1·12 (0·44–2·77)	0·78 (0·27–2·28)	0·82 (0·59–1·15)	0·98 (0·65–1·49)	1·45 (0·31–7·15)
IUGR <5th	0·95 (0·42–2·20)	0·91 (0·32–2·58)	1·12 (0·83–1·53)	0·99 (0·67–1·45)	1·01 (0·31–3·29)
IUGR <5th (excl. PET)	1·05 (0·46–2·47)	0·96 (0·34–2·74)	1·05 (0·77–1·45)	0·89 (0·60–1·32)	1·14 (0·35–3·71)
BWT >90th centile	1·46 (0·9–2·38)	1·81 (1·04–3·31)*	1·22 (1·0–1·50)	1·12 (0·87–1·45)	1·48 (0·74–2·97)
PIH	1·20 (0·62–2·32)	1·26 (0·64–2·30)	1·07 (0·82–1·39)	1·11 (0·84–1·45)	1·00 (0·36–2·81)
PET	1·31 (0·41–4·25)	1·83 (0·51–6·13)	1·16 (0·71–1·69)	1·22 (0·66–2·27)	0·87 (0·12–6·50)
MISC	0·54 (0·07–3·94)	0·78 (0·1–5·77)	1·01 (0·58–1·76)	0·65 (0·34–1·28)	0·54 (0·007–3·94)
SB	-	-	0·51 (0·21–1·24)	0·54 (0·22–1·35)	-
NND	8·8 (1·76–44·1)	14·79 (2·71–80·74)*	1·09 (0·27–4·37)	0·89 (0·20–4·00)	9·24 (0·95–90·06)
SB or NND	1·87 (0·44–7·96)	2·01 (0·47–8·69)	0·63 (0·30–1·33)	0·70 (0·33–1·52)	2·76 (0·35–21·90)

The unadjusted odds ratios (OR) and adjusted OR*, with 95th centile confidence limits (CI_{95}) are shown. Adjusted OR* are from a logistic regression model of demographic variables [age, parity (number of live births), non-fasting lipids and smoking history]. The results are shown for each outcome in those carrying the factor V Leiden mutation (FVL) mutation *versus* non-carriers, for those with blood group non-O *versus* those with O blood groups, and for those with FVL who were also non-O compared with the remainder. Results are shown for postpartum (PPH) or intrapartum haemorrhage (IPH) requiring additional intervention for all singleton pregnancy deliveries in those not-receiving heparins (all). Results are also shown separately for non-operative (non-op) and operative (op) singleton deliveries. Birth weights less than the 5th centile in singleton pregnancies (intra-uterine growth restriction – IUGR <5th) in all singleton pregnancies and also excluding those with pre-eclampsia [IUGR <5th (excl. PET)] as well as those singleton deliveries with a birth weight >90th centile (BWT >90th centile) are shown. Results are also shown for pregnancy-induced hypertension (PIH), miscarriage (fetal loss <24 weeks gestation – MISC), still birth (fetal loss at/after 24 weeks gestation – SB), neonatal death (NND) and for those with either a SB or NND.

improve the identification of those with FVL, or those at risk of FVL-linked pregnancy complications.

For those conditions (PET, IUGR and pregnancy loss) which have been linked with thrombophilia in predominantly retrospective studies, we found no influence of either FVL and/or non-O. However, despite this being the largest study to date, our study was not of sufficient size to exclude an effect on individual complications. We did observe an increased risk of NND in association with FVL, although both of the cases with maternal FVL carriage had other significant abnormalities. Intriguingly, mothers with babies >90th centile in weight were also more likely to carry FVL (adjusted OR 1·81 CI_{95} 1·04–3·31). Although large baby size has been linked with fetal hyper-insulinaemia and a possible increased risk of vascular disease in the offspring (Catalano & Ehrenberg, 2006), the exact nature of any link between high-birth weight and FVL is unclear and requires to be confirmed as this may be a chance observation.

We detected no effect of FVL and/or non-O on the frequency of antenatal haemorrhage. This is, perhaps, not surprising, given that most ante-partum haemorrhage is considered idiopathic. Similarly, both at and after delivery, no influence of either FVL and/or non-O on the occurrence of any haemorrhage >500 ml or any clinically significant haemorrhage was observed. Although our assessment is still relatively subjective, neither the assessment itself, nor the care subsequently offered, is likely to have been influenced by the knowledge of blood group or FVL status. Our results, therefore, do not confirm previous work (Lindqvist *et al*, 1998), which described a beneficial influence of FVL on the amount of visually assessed peri-partum blood loss.

Overall, our study suggests that, in routine practice, screening of unselected subjects for FVL would not be of value in identifying, with sufficient certainty, those at risk of haemorrhagic or thrombosis-linked disorders to allow preventative intervention, although we did not specifically address any potential benefit in screening family members of known symptomatic FVL subjects.

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