Thrombophilia in pregnancy: a systematic review

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Summary

Growing evidence suggests that thrombophilia is associated with venous thromboembolism (VTE) and adverse pregnancy outcomes. However, methodological limitations have made it difficult to obtain a clear overview of the overall risks. We conducted a systematic review to determine the risk of VTE and adverse pregnancy outcomes associated with thrombophilia in pregnancy. The effectiveness of prophylactic interventions during pregnancy was also evaluated. Major electronic databases were searched, relevant data abstracted and study quality assessed by two independent reviewers. Odds ratios (ORs) stratified by thrombophilia type were calculated for each outcome. A total of 79 studies were included in our review. The risks for individual thrombophilic defects were determined for VTE (ORs, 0·74–34·40); early pregnancy loss (ORs, 1·40–6·25); late pregnancy loss (ORs, 1·31–20·09); pre-eclampsia (ORs, 1·37–3·49); placental abruption (ORs, 1·42–7·71) and intrauterine growth restriction (ORs, 1·24–2·92). Low-dose aspirin plus heparin was the most effective in preventing pregnancy loss in thrombophilic women (OR, 1·62). Our findings confirm that women with thrombophilia are at risk of developing VTE and complications in pregnancy. However, despite the increase in relative risk, the absolute risk of VTE and adverse outcomes remains low. There is also a lack of controlled trials of antithrombotic intervention to prevent pregnancy complications. Thus, at present, universal screening for thrombophilia in pregnancy cannot be justified clinically.

Thrombotic mechanisms underlie many pregnancy complications. Pulmonary embolism (PE), arising from deep-vein thrombosis (DVT) is the leading cause of maternal death in the UK (Department of Health Welsh Office Scottish Home and Health Department and Department of Health and Social Services Northern Ireland, 1998). It is now clear that both heritable and acquired thrombophilias are associated with many thrombotic events in pregnancy. The major heritable forms of thrombophilia include deficiencies of antithrombin, protein C and protein S, abnormalities of procoagulant factors, particularly, factor V Leiden and the prothrombin G20210A gene polymorphisms. Furthermore, homozygosity for methylenetetrahydrofolate reductase (MTHFR) C677T can be associated with hyperhomocysteinaemia, which is, in turn, associated with increased risk of vascular events. The most common acquired thrombophilias are antiphospholipids, which comprise lupus inhibitors and anticardiolipin antibodies.

There is growing evidence that women with thrombophilia are at increased risk, not only of pregnancy-related venous thromboembolism (VTE), but also other vascular pregnancy complications, including fetal loss, pre-eclampsia and intrauterine growth restriction (IUGR) (Walker, 2000a). One of the early reports found that 65% of women with pre-eclampsia, IUGR, unexplained stillbirth or placental abruption had a form of heritable or acquired thrombophilia (Kupferminc *et al*, 1999). Many studies have now examined the association between thrombophilia and pregnancy complications, often with differing results. Although several reviews of thromboembolic disease in pregnancy and thromboprophylaxis have been published, many have methodological limitations or focus on a particular pregnancy complication, such as recurrent pregnancy loss or a particular thrombophilia, such as factor V Leiden (Gates, 2000; Walker, 2000b; Alfirevic *et al*, 2002; Empson *et al*, 2002; Ghee & Burrows, 2002; Morrison

et al, 2002; Greer, 2003; Rey *et al*, 2003). These methodological limitations and the fragmentation of publication of the available data on various thrombophilias and outcomes, has made it difficult for clinicians to obtain a clear overview of the overall risks of VTE and adverse pregnancy outcomes in women with thrombophilia. Thus a comprehensive review of the risk of heritable and acquired thrombophilias in pregnancy is required. The objective of this study was to assess the overall relationship between all major thrombophilias and VTE and the adverse outcomes of pregnancy loss, pre-eclampsia, IUGR and abruption. Furthermore the available data on prophylactic intervention in this situation were also evaluated.

Methods

Searching

An extensive literature search was carried out by two independent reviewers on all major electronic databases: Medline 1996 to June 2003, BIDS (EMBASE) 1980 to June 2003, the Cumulative Index to Nursing and Allied Health Literature print index 1982 to June 2003, Cochrane Database of Systematic Reviews 1998 to June 2003, Database of Reviews of Effectiveness 1995 to June 2003 and Kings Fund, UK (last accessed June 2003). Relevant keywords relating to thrombophilia, VTE and adverse pregnancy outcomes were combined with established search filters for randomised controlled trials and observational studies (NHS Centre for Review & Dissemination, 2001) to capture all potentially relevant studies. Only articles published in English were retrieved. In addition, hand searching the abstracts of recent thrombosis conferences and the references of all studies meeting the reference criteria were also carried out.

Inclusion and exclusion criteria

Studies were included in the review if they met the following criteria: (i) study population included women with one or more identified thrombophilia who were pregnant or up to 6-week postpartum; (ii) clinical outcomes included incidence of VTE events and/or adverse pregnancy outcomes were recorded; (iii) extractable data that defined categorically the presence or absence of any thrombophilic defects were available; and (iv) study design described as randomised controlled trials, prospective observational studies or retrospective observational studies. Studies with cases selected on the basis of autoimmune disease, studies without controls or with control groups that included men or current users of hormonal contraceptives were excluded.

Data abstraction and quality assessment

Data extraction was carried out independently by two investigators using pre-piloted data extraction forms, and the quality of the studies was also assessed. Major study outcomes included all VTE and adverse pregnancy incidences. Venous thromboembolism events included all objectively diagnosed DVT and PE events. Adverse pregnancy outcomes including early pregnancy loss (spontaneous loss in the first or second trimester), late pregnancy loss (spontaneous loss in the third trimester), pre-eclampsia (diastolic blood pressure ≥90 mmHg plus proteinuria; Walker, 2000b), placental abruption, IUGR (birth weight below the 10th centile for gestational age), and postpartum haemorrhage (defined as minor if blood loss was 500–1500 ml and major if blood loss was >1500 ml after childbirth) (Scottish Obstetric Guidelines and Audit Project, 1998).

To evaluate the effectiveness of prophylactic interventions in pregnant women with thrombophilia in the prevention of recurrent pregnancy loss, all the data relating to pharmacological and non-pharmacological prophylactic interventions were extracted for analysis. These include: unfractionated heparin, low molecular weight (LMW) heparins, warfarin, aspirin, dextran, recombinant hirudin, plaquinil, calf compression, foot pumps and compression stockings. In addition, data on adverse drug reactions including haemorrhage, serious wound complications, thrombocytopenia and osteoporotic fractures were also extracted if available.

This review has been designed to summarise clinical evidence across study types, therefore, a single checklist, adapted from quality checklists recommended by the Centre for Review and Dissemination was used (NHS Centre for Review & Dissemination, 2001). Seven major criteria were assessed including representative inception cohort, appropriate comparator group, blinded assessment of outcomes, adjustment for confounding, appropriate follow-up and description of cohorts. Any disagreement between the reviewers was resolved by discussion.

Analysis

Odds ratios (ORs) for each clinical outcome per woman were calculated and stratified by individual thrombophilic defects. For the purpose of our review, data relating to the first and second trimester losses were aggregated to determine the overall risk of early pregnancy loss, as some publications did not provide data on the gestation at loss. Where possible, the risks of recurrent first trimester and non-recurrent second trimester loss were calculated separately. In addition, the risk of recurrent pregnancy loss was also summarised according to the use of prophylactic interventions to determine the relative effectiveness of different interventions.

Where appropriate, meta-analysis was carried out and pooled OR were calculated based on the random effects model (DerSimonian & Laird, 1986), which accounts for interstudy variation and provides a more conservative effect than the fixed effect model (NHS Centre for Review & Dissemination, 2001). Potential sources of heterogeneity

were assessed using the standard chi-square test. In addition, the statistic I^2 was used to investigate heterogeneity by examining the extent of inconsistency across the study results (Higgins *et al*, 2003). Sensitivity analysis was carried out to assess the robustness of the results of the meta-analysis. Where heterogeneity was present between the studies, differences in study design were examined. All analyses were performed using RevMan 4.1 (Cochrane Collaboration, Oxford, UK).

Results

Of the 234 studies located through electronic databases and hand searching, 79 studies met the inclusion criteria (Fig 1) (63 case control studies, 13 cohort studies and three randomised controlled trials). Data relating to VTE and adverse pregnancy outcomes were extracted for analysis, but no studies reported incidents of postpartum haemorrhage. Overall, the methodological quality of the studies were sound; however, the major limitation common to most studies was the failure to identify additional risk factors in the populations studied (Table I).

VTE

Nine studies ($n = 2526$) assessed the risk of VTE in pregnant women with heritable thrombophilia (Grandone *et al*, 1998; Dilley *et al*, 2000; Gerhardt *et al*, 2000; Murphy *et al*, 2000; Pabinger *et al*, 2000; Martinelli *et al*, 2001a, 2002; Tormene *et al*, 2001; Ogunyemi *et al*, 2003). With the exception of homozygosity for MTHFR C677T, all heritable thrombophilias were found to be significantly associated with an increased risk of VTE (Fig 2). In particular, the OR for VTE among factor V Leiden homozygous carriers during pregnancy was as high as 34·40 (95% CI 9·86–120·05) (Gerhardt *et al*, 2000; Murphy *et al*, 2000; Martinelli *et al*, 2001a; Tormene *et al*, 2001). The pooled data on MTHFR homozygous cases indicated significant heterogeneity (Fig 2). However, women in one of the studies were given folic acid supplement, which has potential confounding effects on homocysteine levels and VTE events (Ogunyemi *et al*, 2003). This study was excluded when performing the sensitivity analysis. The remaining studies consisted of two retrospec tive case–control (Grandone *et al*, 1998; Dilley *et al*, 2000) and one prospective cohort (Murphy *et al*, 2000) studies. Meta-analysis of the case–control studies only, indicated no significant heterogeneity ($P = 0·49$) or inconsistency ($I^2 = 0\%$) and gave an OR of 1·83 (95% CI 0·95–3·51).

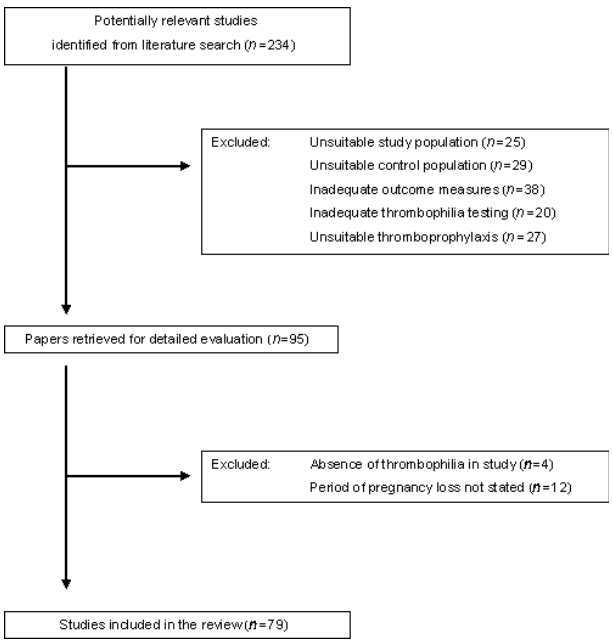


Fig 1. Selection of studies for systematic review in pregnancy.

Early pregnancy loss

Twenty-five studies ($n = 7167$) evaluated the association between thrombophilia and early pregnancy loss (Das *et al*, 1991; Infante-Rivard *et al*, 1991; Wouters *et al*, 1993; De Carolis *et al*, 1994; Ogasawara *et al*, 1996; Balasch *et al*, 1997; Grandone *et al*, 1997a; Nelen *et al*, 1997; Higashino *et al*, 1998; Chakrabarti *et al*, 1999; Hatzis *et al*, 1999; Holmes *et al*, 1999; Lissak *et al*, 1999; Tal *et al*, 1999; Fatini *et al*, 2000; Kupferminc *et al*, 2000a; Pabinger *et al*, 2000; Younis *et al*, 2000; Pickering *et al*, 2001; Pihusch *et al*, 2001; Rai *et al*, 2001; Raziel *et al*, 2001; Reznikoff-Etievan *et al*, 2001; Carp *et al*, 2002; Finan *et al*, 2002), and showed positive associations overall (Fig 3). In particular, significantly associations were observed in carriers of homozygous factor V Leiden (OR 2·71; 95% CI 1·32–5·58), heterozygous factor V Leiden (OR 1·68; 95% CI 1·09–2·58), prothrombin heterozygosity (OR 2·49; 95% CI 1·24–5·00), anticardiolipin antibodies (OR 3·40; 95% CI 1·33–8·68), lupus anticoagulants (OR 2·97; 95% CI 1·03–8·56), acquired APCR (OR 4·04; 95% CI 1·67–9·76) and hyperhomocysteinaemia (OR 6·25; 95% CI 1·37–28·42) (Fig 3). Significant heterogeneity ($P = 0·04$) and inconsistency ($I^2 = 59·1\%$) was observed with the meta-analysis of lupus anticoagulants; however, this could not be explained by study design, as all the studies were case–control studies.

Early pregnancy loss was separated into recurrent pregnancy loss in the first trimester and single pregnancy loss in the second trimester and analysed (Figs 4 and 5). Due to the limitations of the available data, the analysis on factor V Leiden incorporates both homozygous and heterozygous carriers. These women were found to be at higher risk of pregnancy loss in the second compared with the first trimester (OR 4·12; 95% CI 1·93–8·81 and OR 1·91; 95% CI 1·01–3·61 respectively) (Grandone *et al*, 1997a; Tal *et al*, 1999; Tormene *et al*, 1999; Foka *et al*, 2000; Rai *et al*,

Table I. Characteristics of included studies.

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality scores
Agorastos *et al* (2002)	Retrospective case–control	FVL; FII G20210A	Eight women with stillbirth; 16 women with pre-eclampsia; seven women with placental abruption; 15 women with IUGR; controls = 100 women with ≥1 uneventful pregnancy + no history of thrombosis	Stillbirth = fetal death >24 weeks; pre-eclampsia = BP >160/110 mmHg + proteinuria >5 g/24 h; placental abruption = grade 2/3; IUGR = birth weight <10th centile for gestational age	1, yes; 2, yes; 3, not stated; 4, no; 5, no; 6, not stated; 7, not stated
Alfirevic *et al* (2001)	Retrospective case–control	FVL, APCR; FII G20210A; MTHFR; AT, PC, PS; aCL, LA; hyperhomocysteinaemia	Cases = 129 women with stillbirth, pre-eclampsia, placental abruption or IUGR; controls = 44 women with uncomplicated pregnancies	Stillbirth = fetal death >23 weeks; severe pre-eclampsia; placental abruption requiring immediate delivery; IUGR requiring delivery <36 weeks	1, yes; 2, yes; 3, not stated; 4, no; 5, no; 6, yes; 7, not stated
Allen *et al* (1996)	Retrospective case–control	aCL	Cases = 100 women with pre-eclampsia; controls = 100 normotensive pregnant women with no proteinuria	Pre-eclampsia = BP >140/90 mmHg >20 weeks + proteinuria >100 mg/dl	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Alonso *et al* (2002)	Retrospective case–control	FVL, FII G20210A, MTHFR; AT, PC, PS; aCL, LA; hyperhomocysteinaemia	Cases = 8 women with IUFD; controls = 75 women with ≥1 successful pregnancy + no gestational complications	IUFD = fetal death ≥23 weeks	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Balasch *et al* (1997)	Retrospective case–control	FVL; PC, PS; APCR	Cases = 55 women with unexplained RSA; controls = 50 women with ≥1 child + no previous abortion	RSA = ≥2 spontaneous abortions in first trimester	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Bare *et al* (2000)	Retrospective cohort	FVL	489 women; 128 FVL carriers + 461 non-FVL carriers	Spontaneous abortion; intrauterine death	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Benedetto *et al* (2002)	Retrospective case–control	FVL; FII G20210A	Cases = 111 women with pre-eclampsia; controls = 111 normal pregnant women with no history of VTE	Pre-eclampsia = diastolic BP ≥90 mmHg + proteinuria ≥300 mg/2 h >20-week gestation	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Bocciolone *et al* (1994)	Retrospective case–control	aCL, LA	Cases = 99 women with unexplained IUFD; controls = 85 women with normal pregnancies + no history of pregnancy loss	IUFD = fetal death ≥20 weeks	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Carp *et al* (2002)	Retrospective case–control	FVL; FII G20210A; MTHFR	Cases = 108 women with RSA; controls = 82 women without miscarriages	RSA = ≥3 pregnancy losses ≤26 weeks	1, yes; 2, yes; 3, not stated; 4, no; 5, no; 6, yes; 7, yes
Chakrabarti *et al* (1999)	Retrospective case–control	aCL, LA	Cases = 50 pregnant women with unexplained RSA; controls = 30 pregnant women with no history of pregnancy loss	RSA = ≥pregnancy loss in first and second trimester	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Currie *et al* (2002)	Prospective cohort	FVL	Cases = 48 maternal–infant pairs with pre-eclampsia; controls = 46 maternal–infant pairs where pregnancy was normal	Pre-eclampsia = BP ≥140/90 mmHg >20-week gestation + proteinuria ≥300 mg/24 h	1, yes; 2, yes; 3, not stated; 4, yes and no; 5, no; 6, yes; 7, not stated
D'Elia *et al* (2002)	Retrospective case–control	FVL; FII G20210A; MTHFR	Cases = 58 women with pre-eclampsia; controls = 74 pregnant normotensive women	Pre-eclampsia = BP ≥140/90 mmHg + proteinuria ≥300 mg/24 h	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated

Table I. Continued.

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality scores
Das *et al* (1991)	Retrospective case–control	LA	Cases = 50 pregnant women with previous RSA; controls = 50 pregnant women with ≥2 live births + no spontaneous abortion	RSA = ≥3 spontaneous abortions in first or second trimester	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
De Carolis *et al* (1994)	Retrospective case–control	aCL	Cases = 181 women with RSA + 75 women with IUFD; controls = 106 women with no previous pregnancy loss	RSA = ≥2 spontaneous abortions < 20 weeks; IUFD = fetal loss >20 weeks	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
de Groot *et al* (1999)	Retrospective case–control	FVL	Cases = 163 women with pre-eclampsia; controls = 163 women with no pre-eclampsia	Pre-eclampsia = rise in BP ≥30 mmHg systolic or ≥15 mmHg diastolic ≤20 weeks + proteinuria ≥2+	1, yes; 2, yes; 3, yes; 4, yes; 5, yes; 6, yes; 7, not stated
Dilley *et al* (2000)	Retrospective case–control	FVL; FII G20210A; MTHFR	Cases = 41 women with VTE in previous pregnancy; controls = 76 women with normal pregnancies	VTE (objectively diagnosed)	1, yes; 2, yes; 3, not stated; 4, no; 5, yes; 6, yes; 7, not stated
Dizon-Townson *et al* (1996)	Retrospective case–control	FVL	Cases = 158 women with severe pre-eclampsia; controls = 403 normotensive gravid women	Severe pre-eclampsia = BP >160/110 mmHg + proteinuria ≥25 g/24 h	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Dreyfus *et al* (2001)	Retrospective case–control	aCL, LA	Cases = 180 pregnant women with pre-eclampsia; controls = 360 pregnant women with no hypertension or proteinuria	Pre-eclampsia = BP ≥140/90 mmHg >20-week gestation + proteinuria ≥300 mg/24 h	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Farquharson *et al* (2002)	Randomised controlled trial	aCL, LA	Participants = 98 women with ≥3 consecutive pregnancy losses diagnosed with aCL or LA; intervention = low-dose aspirin or low-dose aspirin plus low molecular weight heparin	Live birth rate; gestation at delivery; birth weight; preterm delivery; pregnancy-induced hypertension	1, yes; 2, N/A; 3, yes; 4, yes; 5, no; 6, yes; 7, yes
Fatini *et al* (2000)	Retrospective case–control	FVL; AT, PC; hyperhomocysteinaemia	Cases = 59 women with RSA; controls = 70 women with normal pregnancies	RSA = ≥3 fetal losses in the first trimester (7- to 12-week gestation)	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Finan *et al* (2002)	Retrospective case–control	FVL; FII G20210A	Cases = 110 women with RSA; controls = 267 parous women with uncomplicated pregnancies	RSA = ≥2 confirmed pregnancy losses of unknown cause in the first trimester	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Foka *et al* (2000)	Retrospective case–control	FVL; FII G20210A; MTHFR	Cases = 80 women with RSA; controls = 100 women with ≥1 successful pregnancy + no pregnancy loss	RSA = ≥2 fetal losses in the first or second trimester	1, yes; 2, yes; 3, not stated; 4, no; 5, no; 6, yes; 7, not stated
Franklin and Kutteh (2002)	Prospective cohort	aCL, LA	Participants = 79 women with ≥2 consecutive pregnancy losses who were positive for aCL or LA; intervention = aspirin alone or aspirin plus heparin	Live birth rate; gestational age at birth; birth weight; minor bleeding; thrombocytopenia; major bleeding; fractures	1, yes; 2, N/A; 3, no; 4, yes; 5, no; 6, yes; 7, no
Gerhardt *et al* (2000)	Retrospective case–control	FVL; FII G20210A; MTHFR; AT, PC, PS; LA	Cases = 119 women with VTE in pregnancy or postpartum period; controls = 233 women	VTE (objectively diagnosed)	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated

Table I. Continued.

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality scores
Goddijn-Wessel *et al* (1996)	Retrospective case–control	Hyperhomocysteinaemia	Cases = 84 women with placental abruption; controls = 46 women with normal pregnancy outcome	Placental abruption = presence of tender, hypertonic uterus and disseminated intravascular coagulation and/or retroplacental haematoma with/without signs of infarction	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Grandone *et al* (1997b)	Retrospective case–control	FVL; MTHFR	Cases = 96 women with pre-eclampsia; controls = 129 parous women with uneventful pregnancies	Pre-eclampsia = BP ≥140/90 mmHg + proteinuria ≥300 mg/24 h	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Grandone *et al* (1997a)	Retrospective case–control	FVL	Cases = 27 women with RSA; controls = 118 parous women with no fetal loss	RSA = ≥2 unexplained fetal loss in the first trimester	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Grandone *et al* (1998)	Retrospective case–control	FVL; FII G20210A; MTHFR; AT, PC, PS; aCL, LA	Cases = 42 women with VTE in previous pregnancy or postpartum period; controls = 213 parous women with no venous or arterial thrombosis	VTE (objectively diagnosed)	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, yes
Grandone *et al* (1999)	Retrospective case–control	FVL; FII G20210A; MTHFR	Cases = 140 women with gestational hypertension with or without proteinuria; controls = 216 normotensive gravid women	Pre-eclampsia = BP ≥140/90 mmHg + proteinuria ≥300 mg/24 h	1, yes; 2, yes; 3, not stated; 4, yes; 5, yes; 6, yes; 7, not stated
Gris *et al* (1999)	Retrospective case–control	FII G20210A; MTHFR; AT, PC, PS; aCL, LA; APCR	Cases = 232 women with ≥1 unexplained late fetal loss; controls = 464 women with successful pregnancies	Late fetal loss = intrauterine fetal death >22 weeks	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Gris *et al* (2004)	Prospective cohort	FVL; FII G20210A; PS	Participants = 160 women with one unexplained pregnancy loss from 10 weeks with FVL, FII G20210A or PS deficiency; intervention = low-dose aspirin or low molecular weight heparin	Live birth rate; gestation at delivery; neonatal birth weight; thrombocytopenia; abnormal skin reactions; haemorrhages; bone pain	1, yes; 2, N/A; 3, yes; 4, yes; 5, yes; 6, yes; 7, yes
Hatzis *et al* (1999)	Retrospective case–control	FII G20210A; AT, PC, PS; LA; APCR	Cases = 56 women with unexplained RSA; controls = 148 women with no pregnancy loss	RSA = ≥2 pregnancy loss <16th week of amenorrhea	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Higashino *et al* (1998)	Retrospective case–control	aCL	Cases = 476 women with RSA; controls = 100 women with no pregnancy complications	RSA = ≥2 pregnancy losses in first trimester	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Holmes *et al* (1999)	Retrospective case–control	MTHFR	Cases = 173 women with recurrent fetal loss; controls = 67 healthy parous women with no pregnancy loss or VTE	Recurrent fetal loss = ≥3 consecutive miscarriages ≤23 weeks	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Infante-Rivard *et al* (1991)	Retrospective case–control	aCL, LA	Cases = 289 women with fetal loss and 867 control women with no fetal loss; cases = 42 women with pregnancy loss >21 weeks and 126 controls women with no fetal loss	Spontaneous abortion = fetal loss ≤20 week; pregnancy loss = fetal loss >21 weeks	1, yes; 2, yes; 3, not stated; 4, yes; 5, yes; 6, yes; 7, not stated
Infante-Rivard *et al* (2002)	Retrospective case–control	FVL; FII G20210A; MTHFR	Cases = 493 newborns with IUGR; controls = 472 newborns with no IUGR	IUGR = birth weight <10th centile for gestational age	1, yes; 2, yes; 3, not stated; 4, yes; 5, yes; 6, yes; 7, not stated
Kim *et al* (2001)	Retrospective case–control	FVL; MTHFR	Cases = 281 women with pre-eclampsia; controls = 360 women with ≥2 term pregnancies unaffected by pre-eclampsia	Pre-eclampsia = BP ≥140/90 mmHg + proteinuria ≥300 mg/24 h	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated

Table I. Continued.

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality scores
Kupferminc *et al* (1999)	Retrospective case–control	FVL; FII G20210A; MTHFR; AT, PC, PS; aCL, LA	12 women with stillbirth; 34 women with severe pre-eclampsia; 20 women with placental abruption; controls = 110 women with normal pregnancies	Stillbirth = fetal death >23-week gestation; pre-eclampsia = BP >160/110 mmHg + proteinuria >5 g/24 h; placental abruption = grade 2 or 3	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Kupferminc *et al* (2000b)	Retrospective case–control	FVL; FII G20210A; MTHFR; AT, PC, PS; aCL	Cases = 63 women with severe pre-eclampsia; controls = 126 women with normal pregnancies	Severe pre-eclampsia = BP>160/110 mmHg + proteinuria >5 g/24 h	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Kupferminc *et al* (2000a)	Retrospective case–control	FII G20210A	27 women with pregnancy loss; 16 women with stillbirth; 80 women with pre-eclampsia; 27 women with placental abruption; 72 cases with IUGR; controls = 156 women with normal pregnancies	Pregnancy loss = fetal loss <22 weeks; stillbirth = fetal death >23-week gestation; severe pre-eclampsia = BP >160/110 mmHg + proteinuria >5 g/24 h; placental abruption = requiring immediate delivery; birth weight <10th centile for gestational age	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Kupferminc *et al* (2002)	Retrospective case–control	FVL; FII G20210A; AT, PC, PS; APA	Cases = 26 women with mid-trimester IUGR; controls = 52 women with at least one normal pregnancy	IUGR; birth weight; gestation at delivery	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, not stated; 7, N/A
Kutteh (1996)	Prospective cohort	aCL, LA	Participants = 50 women with ≥3 consecutive, spontaneous pregnancy losses who were positive for aCL and LA; intervention = low-dose aspirin or low-dose aspirin plus heparin	Live birth rate; gestational age at birth; birth weight; minor bleeding episodes; thrombocytopenia; pre-eclampsia; IUGR; major bleeding	1, yes; 2, N/A; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Kutteh and Ermel (1996)	Prospective cohort	aCL, LA	Participants = 50 women with ≥3 consecutive, spontaneous pregnancy losses who were positive for aCL and LA; intervention = low-dose aspirin and either low-dose heparin (10 000 U) or high-dose heparin (20 000 U) twice daily	Live birth rate; gestational age at birth; birth weight; minor bleeding episodes; thrombocytopenia; pre-eclampsia; IUGR; major bleeding	1, yes; 2, N/A; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Lissak *et al* (1999)	Retrospective case–control	MTHFR	Cases = 41 women with RSA; controls = 18 women with ≥2 live term deliveries + no pregnancy loss	RSA = ≥2 fetal loss ≤16 weeks	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Many *et al* (2002)	Retrospective case–control	FVL; FII G20210A; MTHFR; AT, PC, PS; aCL	Cases = 40 women with IUFD; controls = 80 women with uneventful pregnancies	IUFD = pregnancy loss ≥27 weeks	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Martinelli *et al* (2000)	Retrospective case–control	FVL; FII G20210A; MTHFR	Cases = 67 women with unexplained late fetal loss; controls = 232 women with ≥1 normal pregnancies and no fetal losses	Late fetal loss = fetal death ≥20 weeks	1, yes; 2, yes; 3, yes; 4, yes; 5, no; 6, yes; 7, not stated
Martinelli *et al* (2001b)	Retrospective case–control	FVL; FII G20210A; MTHFR; AT, PC, PS; aCL, LA	Cases = 61 women with previous history of IUGR; controls = 93 parous women with uneventful pregnancies	IUGR = birth weight <10th percentile for gestational age	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated

Table I. Continued.

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality scores
Martinelli *et al* (2001a)	Retrospective cohort	FVL; FII G20210A; AT, PC, PS	15 women homozygous for FVL; 39 women double heterozygous for FVL + FII G20210A; 182 women with normal coagulation.	DVT by Doppler ultrasound or venography	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Martinelli *et al* (2002)	Retrospective case–control	FVL; FII G20210A; AT, PC, PS	Cases = 119 women with first episode of DVT and/or PE in pregnancy or postpartum period; controls = 232 women with ≥1 pregnancy and no thrombosis	VTE (objectively diagnosed)	1, yes; 2, yes; 3, yes; 4, no; 5, no; 6, yes; 7, not stated
Meinardi *et al* (1999)	Retrospective cohort	FVL	Participants = 228 carriers of FVL and 122 non-carrier relatives	Miscarriage = fetal loss ≤20 weeks; stillbirth = fetal loss >20 weeks	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Mello *et al* (1999)	Retrospective case–control	FVL; AT, PC, PS; aCL, LA; APCR	Cases = 46 women with pre-eclampsia; controls = 80 women with normal pregnancies	Pre-eclampsia = BP ≥140/90 mmHg + proteinuria ≥300 mg/24 h	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Morrison *et al* (2002)	Retrospective cohort	FVL; FII G20210A; MTHFR	Participants = 404 women with pre-eclampsia, 303 with gestational hypertension and 164 with no raised bp	Pre-eclampsia = BP ≥90 mmHg + proteinuria ≥0·3 g/24 h	1, yes; 2, yes; 3, not stated; 4, no; 5, no; 6, yes; 7, yes
Murphy *et al* (2000)	Prospective cohort	FVL; AT, PC, PS; aCL, LA.	Participants = 593 primigravid women	VTE (objectively diagnosed); recurrent fetal loss = ≥2 previous unexplained losses at any point during pregnancy; pre-eclampsia = BP >140/90 mmHg + proteinuria ≥1 by Dipstick; IUGR = birth weight <10th percentile for gestational age	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Nagy *et al* (1998)	Retrospective case–control	FVL	Cases = 69 women with severe pre-eclampsia; controls = 129 women with no pre-eclampsia	Severe pre-eclampsia = BP >160/110 mmHg + proteinuria >1000 mg/24 h	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Nelen *et al* (1997)	Retrospective case–control	MTHFR	Cases = 185 women with unexplained REPL; controls = 113 women with no pregnancy loss	REPL = ≥2 fetal loss <17 weeks	1, yes; 2, yes; 3, no; 4, yes; 5, no; 6, yes; 7, not stated
O'Shaughnessy *et al* (1999)	Retrospective case–control	FVL; MTHFR	Cases = 283 women with pre-eclampsia; controls = 100 women with pregnancies uncomplicated by pre-eclampsia	Pre-eclampsia = BP ≥140/90 mmHg + proteinuria ≥300 mg/24 h	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Ogasawara *et al* (1996)	Retrospective case–control	LA	Cases = 195 women with unexplained recurrent miscarriage; controls = 100 women	Recurrent miscarriage = ≥2 pregnancy loss in first or second trimester	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Ogunyemi *et al* (2003)	Retrospective case–control	FVL; FII G20210A; MTHFR; AT, PC, PS; aCL, LA; hyperhomocysteinaemia	Cases = 30 pregnant women with DVT or PE; controls = 30 pregnant women without VTE	VTE (objectively diagnosed)	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Owen *et al* (1997)	Retrospective case–control	Hyperhomocysteinaemia	Cases = 21 women with placental abruption; controls = 19 women	No definition of placental abruption given	1, yes; 2, no; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Pabinger *et al* (2000)	Retrospective case–control	FVL	Cases = 64 women homozygous for FVL with ≥1 pregnancies; controls = 52 women with no FVL with ≥1 pregnancies	VTE (objectively diagnosed); miscarriage = fetal loss ≤23 weeks; stillbirth = intrauterine death >23 weeks	1, yes; 2, no; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated

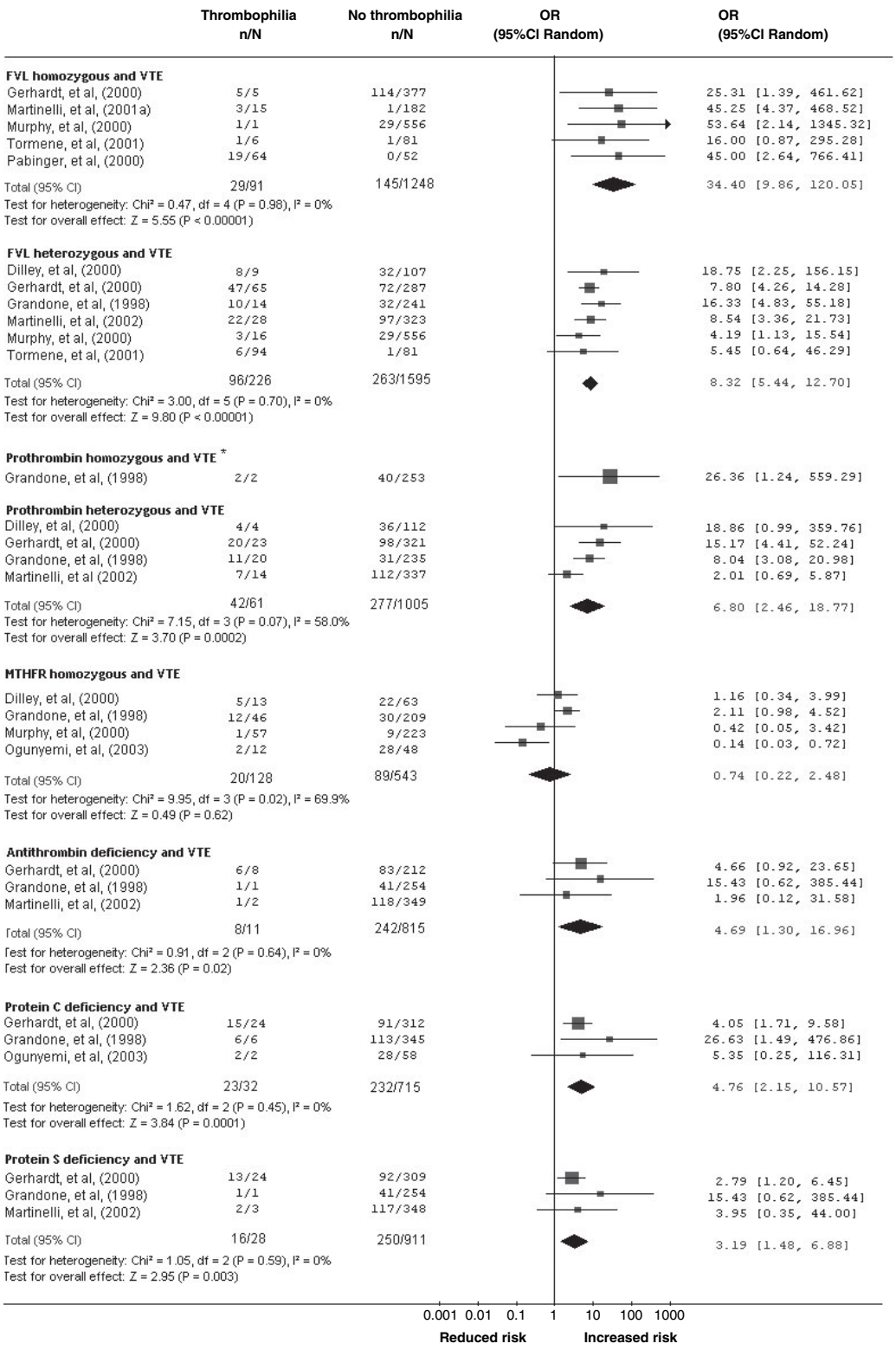
Table I. Continued.

Source	Study design	Thrombophilia	Participants	Outcome measure	Quality scores
Pattison *et al* (2000)	Randomised placebo-controlled trial	aCL, LA	Participants = 50 women with a history ≥3 recurrent miscarriages and positive for aCL and LA; intervention = identically packaged tablets of a placebo or aspirin (75 mg daily)	Live birth rate; gestational age at birth; birth weight; bleeding in pregnancy; hypertension or pre-eclampsia.	1, yes; 2, N/A; 3, yes; 4, yes; 5, no; 6, yes; 7, yes
Pauzner *et al* (2001)	Prospective cohort	aCL, LA	Participants = 42 women with previous fetal loss and/or previous VTE, in the presence of aCL and LA; intervention = low molecular weight heparin and low-dose aspirin or warfarin	Live birth rate; gestation at delivery; birth weight; teratogenicity; maternal bleeding; thrombotic events	1, yes; 2, N/A; 3, no; 4, yes; 5, no; 6, yes; 7, not stated
Pickering *et al* (2001)	Retrospective case–control	FII G20210A	Cases = 91 women with recurrent early pregnancy loss; controls = 66 women with no history of miscarriage or thrombosis	Early pregnancy loss = ≥3 fetal loss ≤12 weeks	1, yes; 2, yes; 3, not stated; 4, yes; 5, yes; 6, yes; 7, not stated
Pihusch *et al* (2001)	Retrospective case–control	FVL; FII G20210A; MTHFR; AT, PC, PS; aCL	Cases = 102 women with RSA; controls = 128 women without miscarriage	RSA = ≥2 fetal loss (25-week gestation	1, yes; 2, yes; 3, not stated; 4, no; 5, no; 6, yes; 7, not stated
Rai *et al* (1997)	Randomised controlled trial	aCL, LA	Participants = 90 women with history (3 consecutive miscarriages with positive results for aCL and LA; intervention = low-dose aspirin or low-dose aspirin plus heparin (5000 U twice daily)	Live birth rate; gestation at delivery; birth weight; VTE; thrombocytopenia; fractures; bruising at injection site	1, yes; 2, N/A; 3, yes; 4, yes; 5, no; 6, yes; 7, yes
Rai *et al* (2001)	Retrospective case–control	FVL; APCR	Cases = 904 women with a history of recurrent early miscarriage; controls = 150 women with no previous adverse pregnancy complication	Recurrent early miscarriage = (3 fetal loss <12 weeks	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Raijmakers *et al* (2001)	Retrospective case–control	MTHFR	Cases = 167 women with pre-eclampsia; controls = 403 population-based control women with no pre-eclampsia	Pre-eclampsia = diastolic BP >90 mmHg + proteinuria >20-week gestation	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Raziel *et al* (2001)	Retrospective case–control	FVL; FII G20210A; MTHFR; AT, PC, PS; APCR; hyperhomocysteinaemia	Cases = 36 women with RPL; controls = 40 women with (1 successful pregnancy	RPL = (2 pregnancy losses in 1st or 2nd trimester	1, yes; 2, yes; 3, not stated; 4, no; 5, no; 6, yes; 7, not stated
Reznikoff-Etievan *et al* (2001)	Retrospective case–control	FVL; FII G20210A; AT, PC, PS,; aCL, LA	Cases = 260 women with early unexplained recurrent miscarriage; controls = 240 healthy women	Early recurrent miscarriage = (2 fetal loss <10 weeks	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Rigo *et al* (2000)	Retrospective case–control	FVL; MTHFR	Cases = 120 pre-eclamptic women; controls = 101 healthy pregnant women	Severe pre-eclampsia = BP >160/110 mmHg + proteinuria >3 g/24 h	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Rothbart *et al* (1999)	Retrospective case–control	FVL	Cases = 14 women with IUFD; controls = 14 women with no fetal death	IUFD = fetal demise (24 weeks without apparent explanation	1, yes; 2, yes; 3, not stated; 4, no; 5, no; 6, yes; 7, not stated
Schjetlein *et al* (1998)	Retrospective case–control	aCL, LA	Cases = 200 women with pre-eclampsia; controls = 97 normotensive women	Pre-eclampsia = BP (140/90 mmHg	1, yes; 2, yes; 3, yes; 4, yes; 5, no; 6, yes; 7, not stated

Table I. Continued.

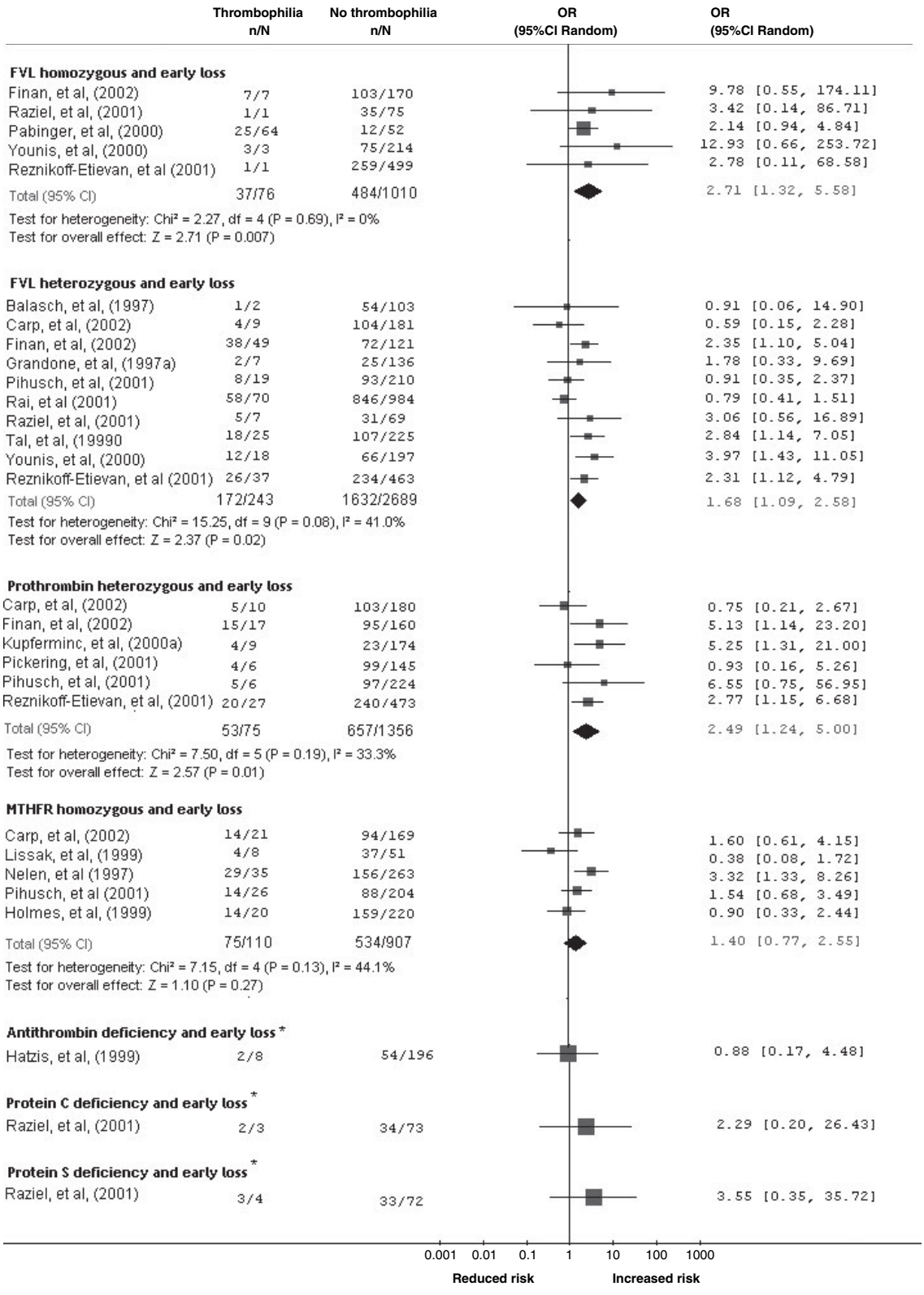
Source	Study design	Thrombophilia	Participants	Outcome measure	Quality scores
Tal *et al* (1999)	Retrospective case–control	Acquired APCR (FVL −ve); ACPR caused by FVL	Cases = 125 women with pregnancy loss; controls = 125 women with (1 live births but no past fetal loss	Pregnancy loss = first or second trimester	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Tormene *et al* (1999)	Prospective cohort	FVL	Cases = 65 women with FVL; controls = 22 women with no FVL	Intrauterine fetal death >24 weeks	1, yes; 2, not stated; 3, N/A; 4, yes; 5, no; 6, yes; 7, yes
Tormene *et al* (2001)	Retrospective case–control	FVL	Cases = 105 women with FVL; controls = 81 female non-carriers	VTE (objectively diagnosed)	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Van Pampus *et al* (1999)	Retrospective case–control	FVL; aCL; APCR; hyperhomocysteinaemia;	Cases = 345 women with severe pre-eclampsia; controls = 67 women with uncomplicated pregnancies	Pre-eclampsia = diastolic BP (110 mmHg + proteinuria <34-week gestation	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Wiener-Megnagi *et al* (1998)	Retrospective case–control	FVL; AT, PC, PS; aCL, LA; APCR	Cases = 27 women with placental abruption; controls = 29 women with normal medical and obstetric histories + no previous miscarriages	Placental abruption based on profuse vaginal bleeding in third trimester of pregnancy + clinical observation of placenta after its expulsion or extraction	1, yes; 2, yes; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Wouters *et al* (1993)	Retrospective case–control	Hyperhomocysteinaemia	Cases = 102 women with unexplained RSA; controls = 41 women	RSA = (2 pregnancy losses (16 weeks of menstrual age	1, yes; 2, yes; 3, not stated; 4, not stated; 5, no; 6, yes; 7, not stated
Yasuda *et al* (1995)	Prospective cohort	aCL	Participants = 860 pregnant women	Fetal death >24 weeks; pre-eclampsia (definition by the International Society for the Study of Hypertension in Pregnancy); IUGR = birth weight <10th percentile for gestational age	1, yes; 2, N/A; 3, not stated; 4, yes; 5, no; 6, yes; 7, not stated
Younis *et al* (2000)	Retrospective case–control	FVL; APCR	Cases = 78 women with unexplained recurrent pregnancy losses; controls = 139 women with 1 successful pregnancy and no history of pregnancy loss	Two pregnancy losses in first or second trimester	1, yes; 2, yes; 3, not stated; 4, no; 5, no; 6, yes; 7, not stated

Quality criteria: 1, representative inception cohort; 2, comparator group reliably ascertained; 3, blinded assessment of outcomes; 4, confounding factors comparable; 5, adjust for confounding; 6, appropriate follow-up; 7, description of dropouts; FVL, factor V Leiden; MTHFR, methylenetetrahydrofolate reductase; AT, antithrombin deficiency; PC, protein C deficiency; PS, protein S deficiency; aCL, elevated anticardiolipins; LA, lupus anticoagulants; APCR, acquired activated protein C resistance, IUFD, intrauterine fetal death, IUGR, intrauterine growth restriction; REPL, recurrent early pregnancy loss, RSA, recurrent spontaneous abortion; VTE, venous thromboembolism, BP, blood pressure.



* Data was only available for one study, therefore meta-analysis was not carried out for this thrombophilia.

Fig 2. Risk of venous thromboembolism (VTE) in woman with thrombophilia. FVL, factor V Leiden; PTM, prothrombin; ATM, antithrombin; PC def, protein C deficiency; PS def, protein S deficiency. The square on each line represents the point estimate for the odds ratio for each single study; its size of the square varies according to study size and variance. Black diamonds represent the overall average odds ratio and the confidence interval from pooling all the studies together in the meta-analysis.



* Data was only available from one study, therefore meta-analysis was not performed for this mutation.

Fig 3. Risk of early loss in woman with thrombophilia. The square on each line represents the point estimate for the odds ratio for each single study; its size of the square varies according to study size and variance. Black diamonds represent the overall average odds ratio and the confidence interval from pooling all the studies together in the meta-analysis.

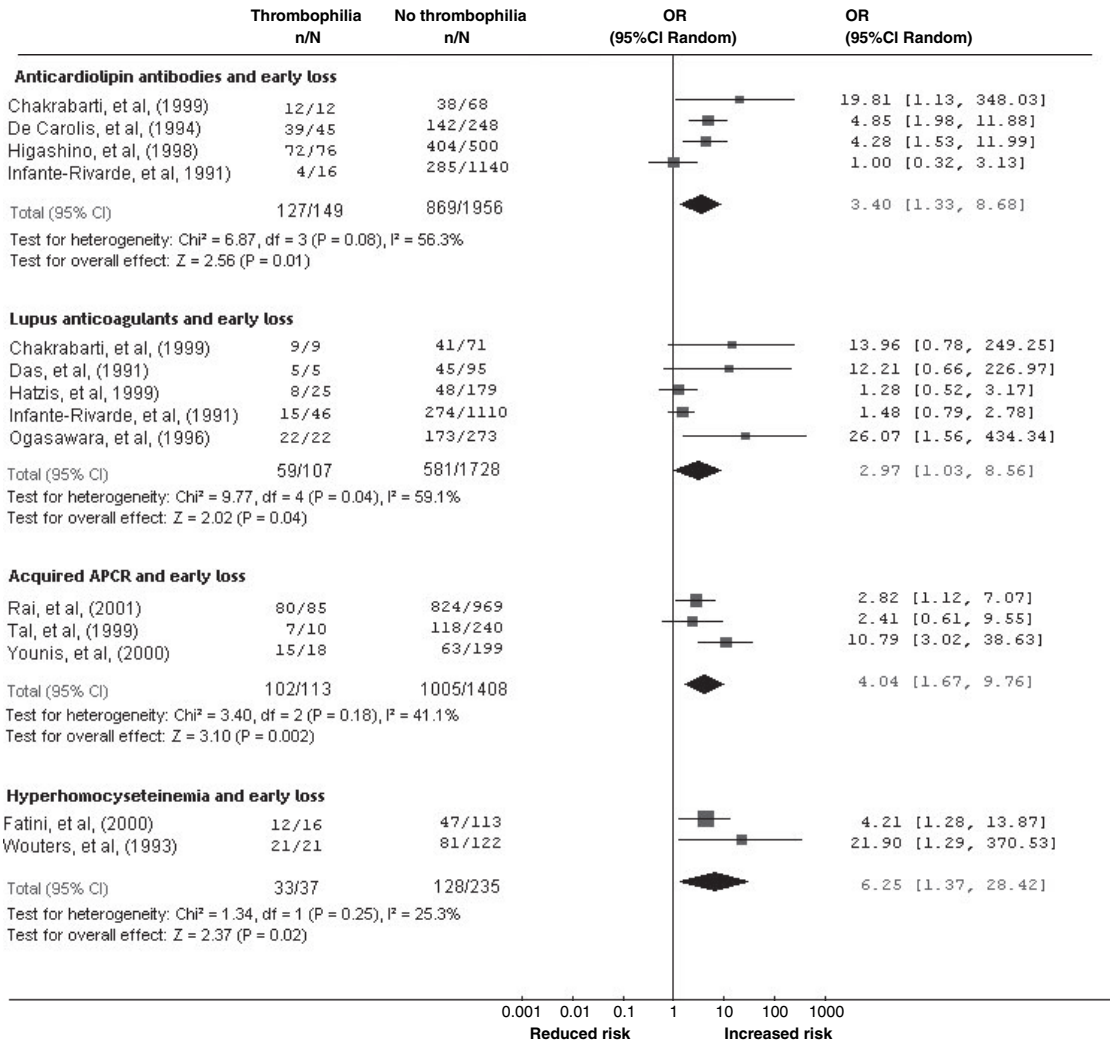


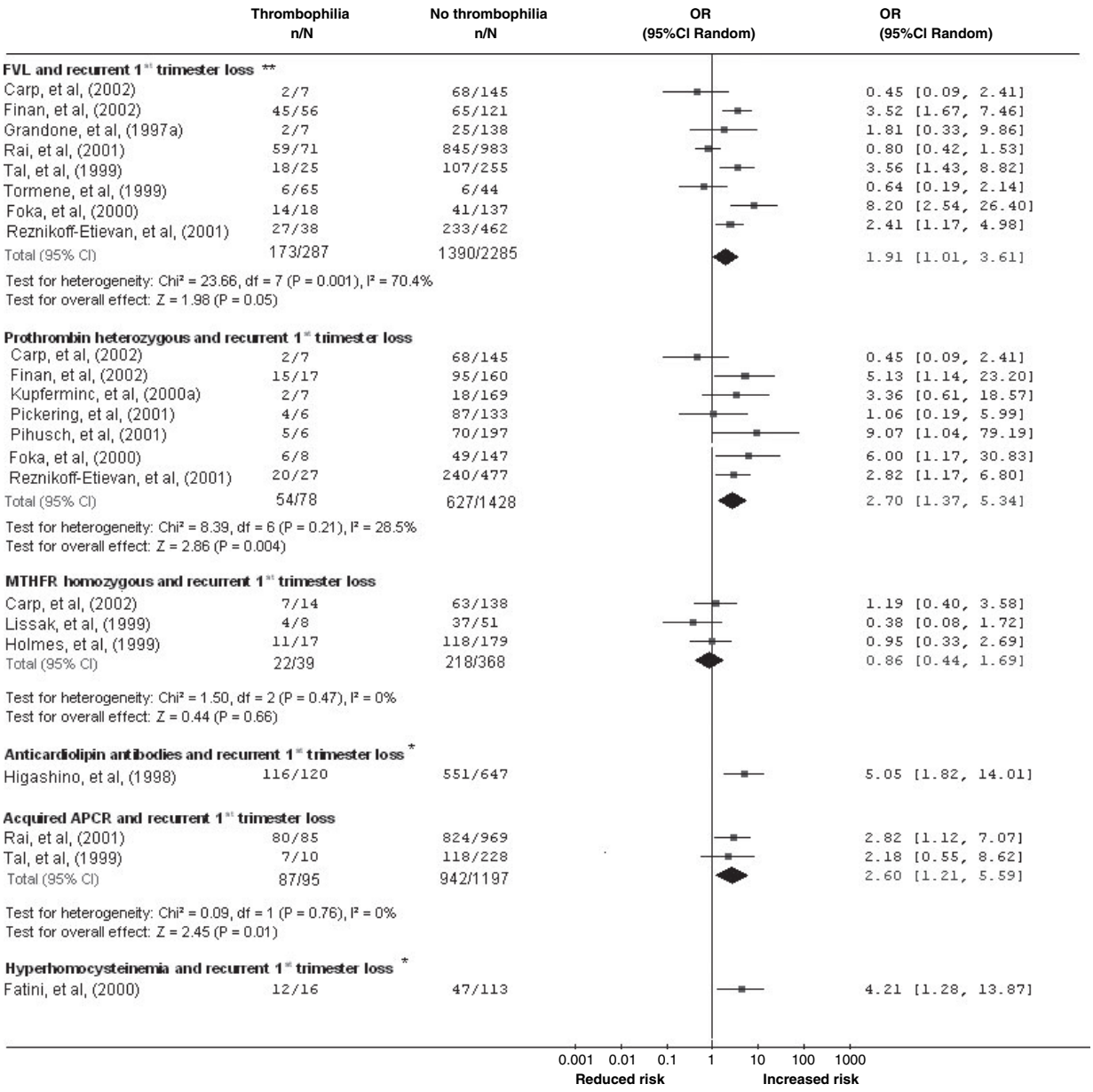
Fig 3. Continued.

2001; Reznikoff-Etievan *et al*, 2001; Carp *et al*, 2002; Finan *et al*, 2002). However, there was evidence of heterogeneity in the analysis of recurrent first trimester loss ($P = 0{\cdot}001$); this could not be explained by the difference in study design. A similar trend was observed with prothrombin heterozygosity. The risk of non-recurrent second trimester loss (OR 8·60; 95% CI 2·18–33·95) compared with recurrent first trimester loss (OR 2·70; 95% CI 1·37–5·35) was over threefold (Foka *et al*, 2000; Kupferminc *et al*, 2000a; Pickering *et al*, 2001; Pihusch *et al*, 2001; Reznikoff-Etievan *et al*, 2001; Carp *et al*, 2002; Finan *et al*, 2002) (Figs 4 and 5).

In contrast, acquired activated protein C resistance was associated with a higher risk of recurrent pregnancy loss in the first trimester (OR 2·60; 95% CI 1·21–5·59) than non-recurrent loss in the second trimester (OR 1·59; 95% CI 0·19–13·44) (Tal *et al*, 1999; Rai *et al*, 2001). However, the calculated risk relating to non-recurrent second trimester loss was non-significant and was based on data from only one study.

Late pregnancy loss

Data relating to late pregnancy loss were extracted from 15 studies ($n = 4038$) (Infante-Rivard *et al*, 1991; Bocciolone *et al*, 1994; De Carolis *et al*, 1994; Yasuda *et al*, 1995; Gris *et al*, 1999; Meinardi *et al*, 1999; Rothbart *et al*, 1999; Bare *et al*, 2000; Kupferminc *et al*, 2000a; Martinelli *et al*, 2000; Pabinger *et al*, 2000; Alfirevic *et al*, 2001; Agorastos *et al*, 2002; Alonso *et al*, 2002; Many *et al*, 2002); significant associations were observed in carriers of heterozygous factor V Leiden (OR 2·06; 95% CI 1·10–3·86), heterozygous prothrombin (OR 2·66; 95% CI 1·28–5·53), protein S deficiency (OR 20·09; 95% CI 3·70–109·15) and anticardiolipin antibodies (OR 3·30; 95% CI 1·62–6·70) (Fig 6). No evidence of heterogeneity was observed.



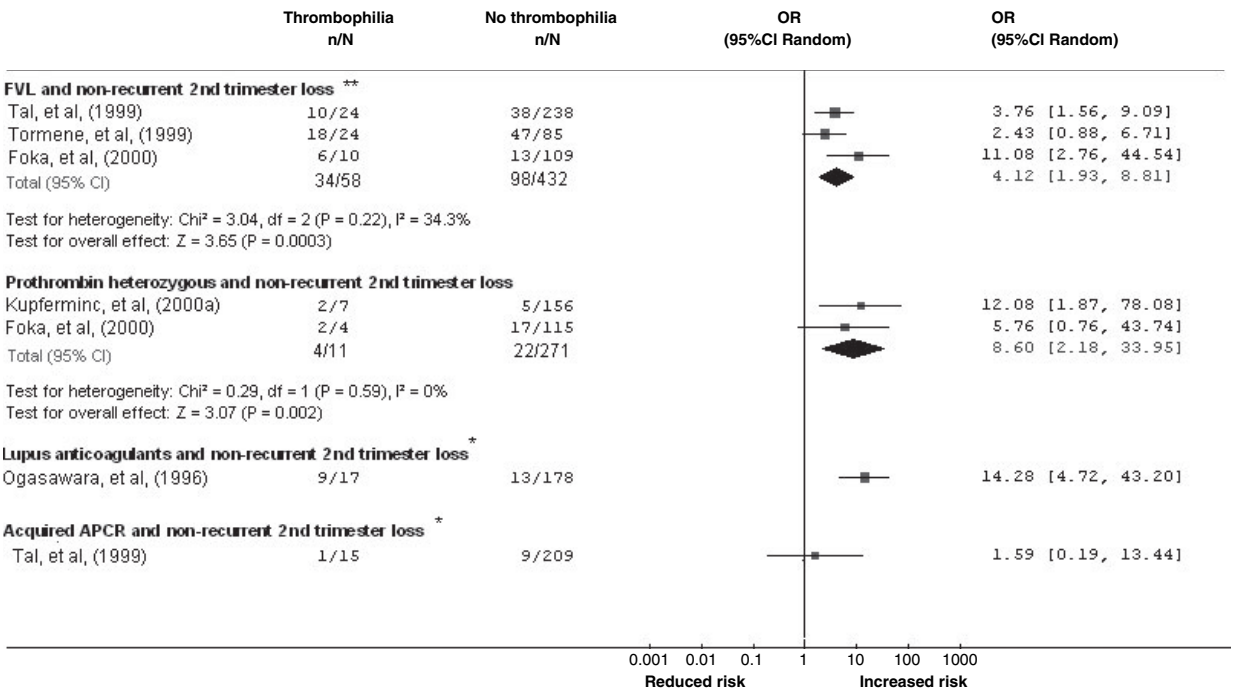
* Data was only available for one study, therefore meta-analysis was not carried out for this thrombophilia.

** For the Factor V Leiden mutation, homozygous and heterozygous carriers were grouped together as it was not possible to extract data for each state.

Fig 4. Risk of recurrent first trimester pregnancy loss with thrombophilia. The square on each line represents the point estimate for the odds ratio for each single study; its size of the square varies according to study size and variance. Black diamonds represent the overall average odds ratio and the confidence interval from pooling all the studies together in the meta-analysis.

Pre-eclampsia

Twenty-five studies ($n = 11\,183$) assessed the risk of pre-eclampsia in pregnancy women with thrombophilia (Yasuda *et al*, 1995; Allen *et al*, 1996; Dizon-Townson *et al*, 1996; Grandone *et al*, 1997b, 1999; Nagy *et al*, 1998; Schjetlein *et al*, 1998; de Groot *et al*, 1999; Kupferminc *et al*, 1999, 2000a,b; Mello *et al*, 1999; O'Shaughnessy *et al*, 1999; Van Pampus *et al*, 1999; Murphy *et al*, 2000; Rigo *et al*, 2000; Alfirevic *et al*, 2001; Dreyfus *et al*, 2001; Kim *et al*, 2001; Raijmakers *et al*, 2001; Agorastos *et al*, 2002; Benedetto *et al*, 2002; Currie *et al*, 2002; D'Elia *et al*, 2002; Morrison *et al*, 2002). The risk of pre-eclampsia was significantly associated with heterozygous factor V Leiden (OR 2·19; 95% CI 1·46–3·27), heterozygous prothrombin (OR 2·54; 95% CI 1·52–4·23), MTHFR homozygosity (OR 1·37; 95% CI 1·07–1·76), anticardiolipin antibodies (OR 2·73; 95% CI 1·65–4·51) and hyperhomocysteinaemia (OR 3·49; 95% CI 1·21–10·11) (Fig 7). Evidence of



* Data was only available for one study, therefore meta-analysis was not carried out for this thrombophilia.

** For the Factor V Leiden mutation, homozygous and heterozygous carriers were grouped together as it was not possible to extract data for each state.

Fig 5. Risk of non-recurrent second trimester pregnancy loss with thrombophilia. The square on each line represents the point estimate for the odds ratio for each single study; its size of the square varies according to study size and variance. Black diamonds represent the overall average odds ratio and the confidence interval from pooling all the studies together in the meta-analysis.

heterogeneity was present in the analysis on heterozygous factor V Leiden ($P = 0{\cdot}04$). The studies included in the analysis consisted of diagnoses of both mild and severe pre-eclampsia. Sensitivity analysis was performed by analysing the studies reporting mild and severe pre-eclampsia independently. When restricting the analysis to mild pre-eclampsia only (Grandone *et al*, 1997b, 1999; Nagy *et al*, 1998; de Groot *et al*, 1999; Mello *et al*, 1999; O'Shaughnessy *et al*, 1999; Rigo *et al*, 2000; Kim *et al*, 2001; Benedetto *et al*, 2002; D'Elia *et al*, 2002;), an OR of 2·30 (95% CI 1·27–4·16) was obtained, but heterogeneity remained ($P = 0{\cdot}01$). However, when restricting the analysis to severe pre-eclampsia only (Dizon-Townson *et al*, 1996; Nagy *et al*, 1998; de Groot *et al*, 1999; Van Pampus *et al*, 1999; Alfirevic *et al*, 2001), an OR of 2·04 (95% CI 1·23–3·36) was obtained and evidence of heterogeneity was removed ($P = 0{\cdot}31$).

Placental abruption

Seven studies ($n = 922$) evaluated the association between thrombophilia and placental abruption (Goddijn-Wessel *et al*, 1996; Owen *et al*, 1997; Wiener-Megnagi *et al*, 1998; Kupferminc *et al*, 1999, 2000a; Alfirevic *et al*, 2001; Agorastos *et al*, 2002). Overall, thrombophilia was associated with an increased risk of placental abruption, but significant associations were only observed with heterozygous factor V Leiden (OR 4·70; 95% CI 1·13–19·59) and heterozygous prothrombin (OR 7·71; 95% CI 3·01–19·76) (Fig 8).

IUGR

Five studies ($n = 195$) were included in the analysis of IUGR (Yasuda *et al*, 1995; Martinelli *et al*, 2001b; Agorastos *et al*, 2002; Infante-Rivard *et al*, 2002; Kupferminc *et al*, 2002). There was a general trend of increased IUGR risk in pregnant women with thrombophilia; however, based on data from one study (Yasuda *et al*, 1995), significant association was observed only with anticardiolipin antibodies (OR 6·91; 95% CI 2·70–17·68) (Fig 9).

Prophylactic interventions

Eight studies ($n = 619$) evaluated the effectiveness of prophylactic interventions in pregnant women with thrombophilia (Kutteh, 1996; Kutteh & Ermel, 1996; Rai *et al*, 1997; Pattison *et al*, 2000; Pauzner *et al*, 2001; Farquharson *et al*, 2002; Franklin & Kutteh, 2002; Gris *et al*, 2004). No data on the prevention of VTE events were found. Four of the studies assessed the effectiveness of heparin plus aspirin *versus* aspirin alone for recurrent pregnancy loss associated with antiphospholipids (Kutteh, 1996; Rai *et al*, 1997; Farquharson *et al*, 2002; Franklin & Kutteh, 2002). A pooled OR of 1·62 (95% CI

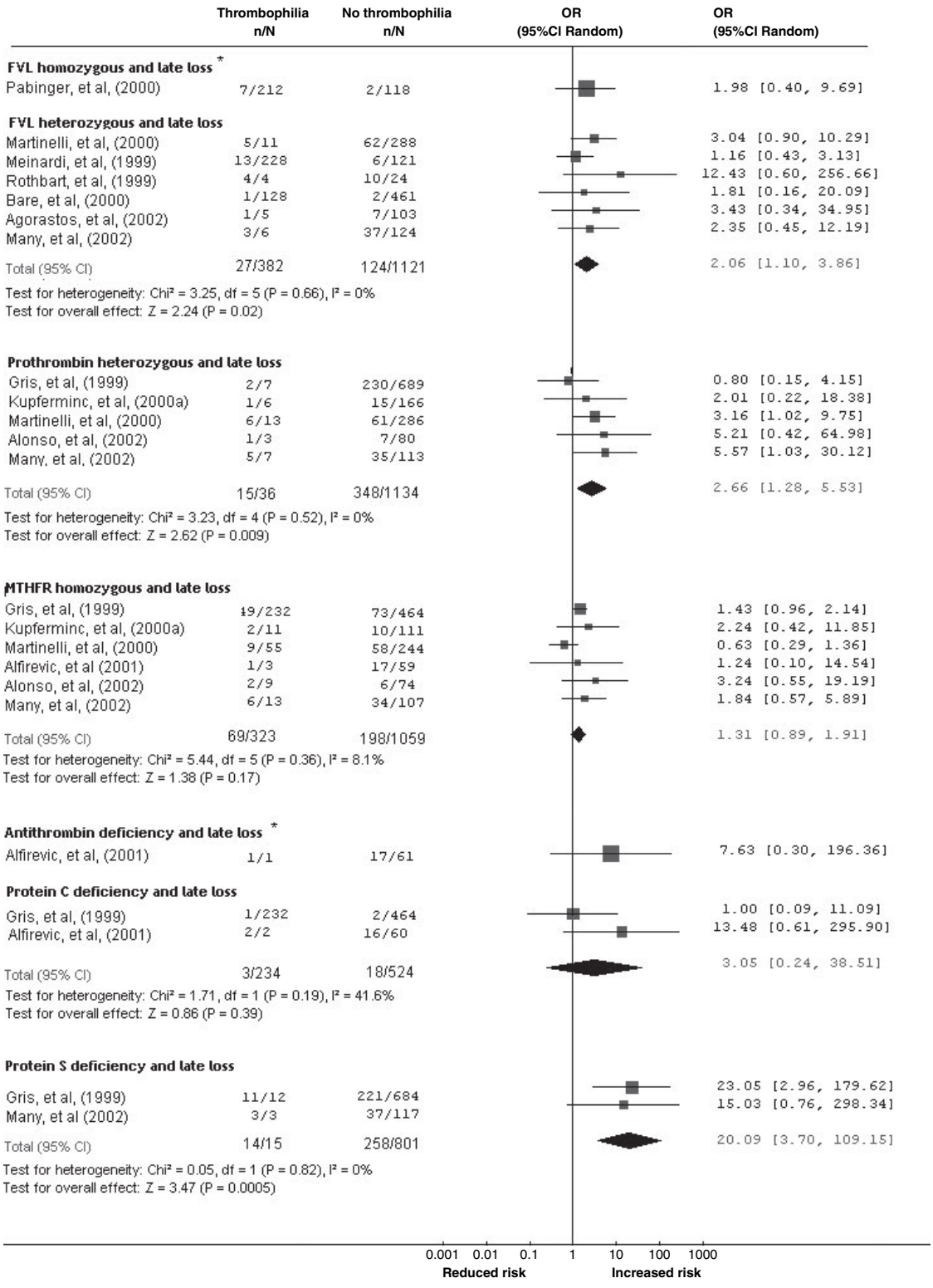
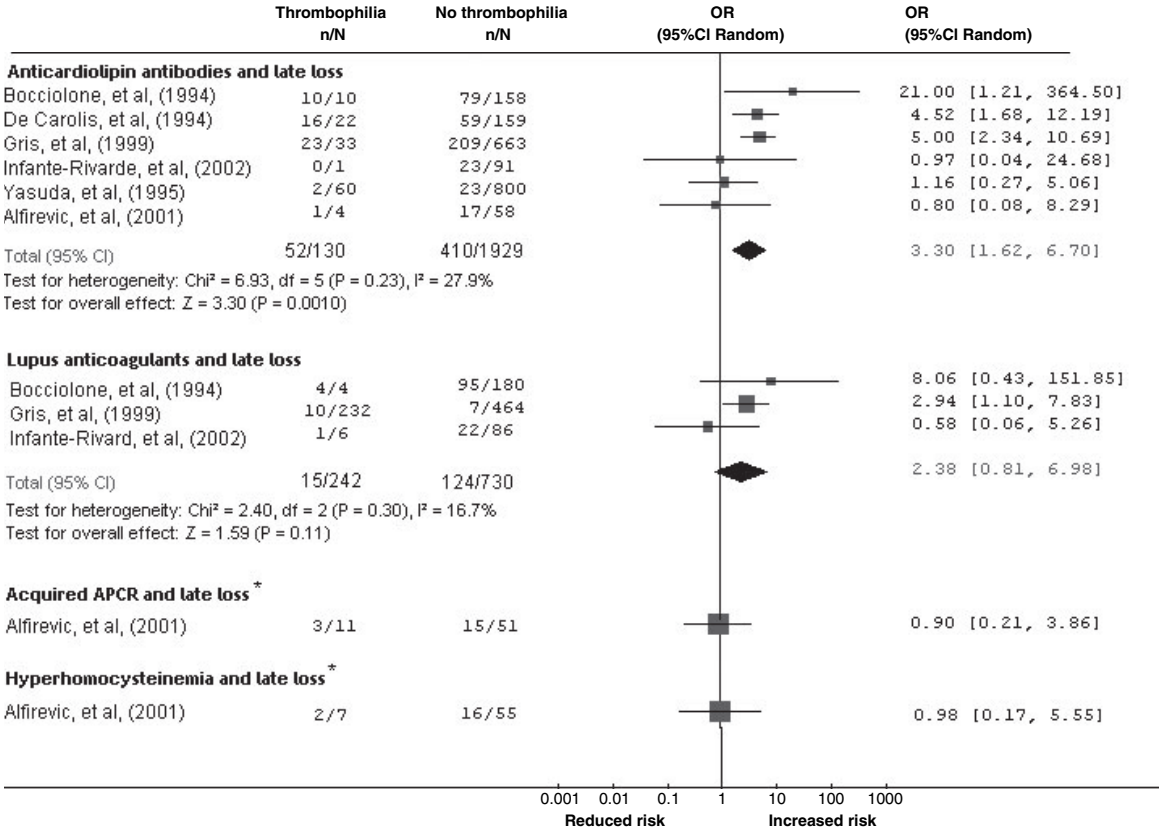


Fig 6. Risk of late pregnancy loss per woman with thrombophilia. FVL, factor V Leiden; PTM, prothrombin; PC, protein C; PS, protein S; ACL, anticardiolipin antibodies; LA, lupus anticoagulant. The square on each line represents the point estimate for the odds ratio for each single study; its size of the square varies according to study size and variance. Black diamonds represent the overall average odds ratio and the confidence interval from pooling all the studies together in the meta-analysis.



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0·51–5·10) was estimated in favour of low-dose aspirin plus heparin in preventing recurrent pregnancy loss. However, minor bleeding (including haematuria, nosebleeds, gum bleeds and bleeding at the injection site) occurred in two of the studies and a pooled OR of 1·68 (95% CI 0·38–7·39) was estimated in favour of low-dose aspirin alone (Kutteh, 1996; Rai *et al*, 1997).

In one study, low-dose aspirin and LMW heparin were compared in women with a single unexplained fetal loss from the 10th week of pregnancy (Gris *et al*, 2004). Patients treated with LMW heparin were more likely to have a healthy live birth (OR, 15·5; 95% CI 7·0–34·0). Small for gestational age infants were more frequent in patients treated with low-dose aspirin. No other side effects of the treatment were evident in either patients or newborns. Other studies compared the effectiveness of low-dose aspirin *versus* a placebo (Pattison *et al*, 2000), low-dose and high-dose heparin (Kutteh & Ermel, 1996), and warfarin and heparin (Pauzner *et al*, 2001). Therefore, as the prophylactic therapies in these studies are not comparable, the results could not be combined in a meta-analysis.

Discussion

This is the first systematic review to present the overall relationship between all major thrombophilias and VTE and the adverse outcomes of pregnancy loss, pre-eclampsia, IUGR and abruption. These data show that both heritable and acquired thrombophilias are associated with VTE and adverse pregnancy outcomes, so confirming and extending results from previous systematic reviews, which have examined particular aspects of these associations (Gates, 2000; Greer, 2003; Rey *et al*, 2003).

Venous thromboembolism was significantly associated with all heritable thrombophilias except in women homozygous for MTHFR C677T, where in contrast to the non-pregnant situation, there was no elevation in risk. The mechanism underlying this lack of association in pregnancy is unclear. It is possible that folic acid supplements taken in pregnancy could reduce homocysteine levels in these women and so reduce the risk of VTE, but there is minimal data on the use of vitamin supplements in the studies reported and this possibility could not be examined with the available data. The risk of VTE with homozygous factor V Leiden was the highest risk observed for any thrombophilia, with a relative risk of 34·4 (95% CI 9·86–120·05), reducing to 8·32 (95% CI 5·44–12·70) with heterozygous factor V Leiden. While these are significant increases in relative risk, the absolute risk remains modest. For example, the underlying incidence of VTE in pregnancy is considered to be around 1:1000. Thus, these relative risks translate to absolute risks of 3·4% and 0·8% respectively. Of note, women

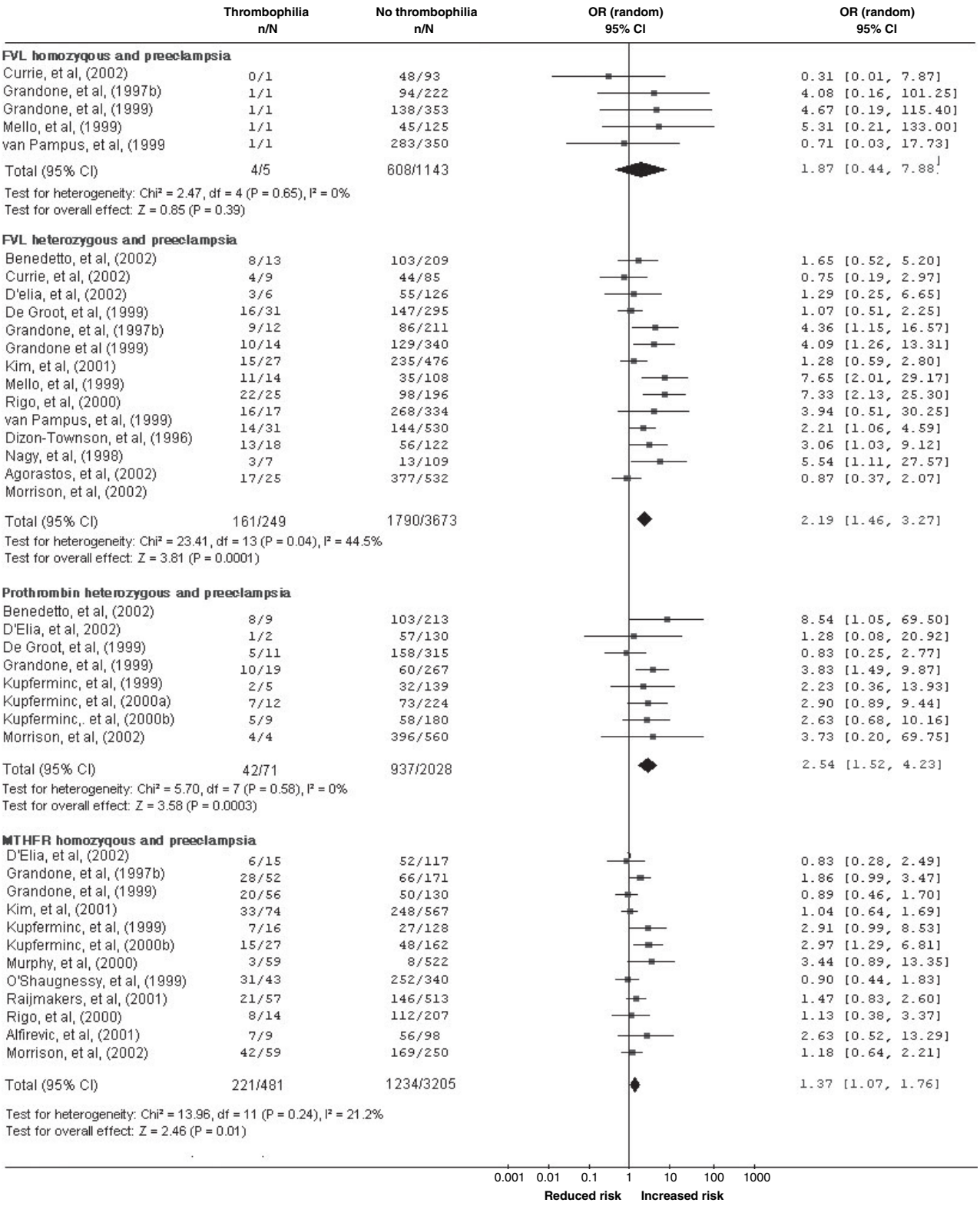


Fig 7. Risk of pre-eclampsia in women with thrombophilia. The square on each line represents the point estimate for the odds ratio for each single study; its size of the square varies according to study size and variance. Black diamonds represent the overall average odds ratio and the confidence interval from pooling all the studies together in the meta-analysis.

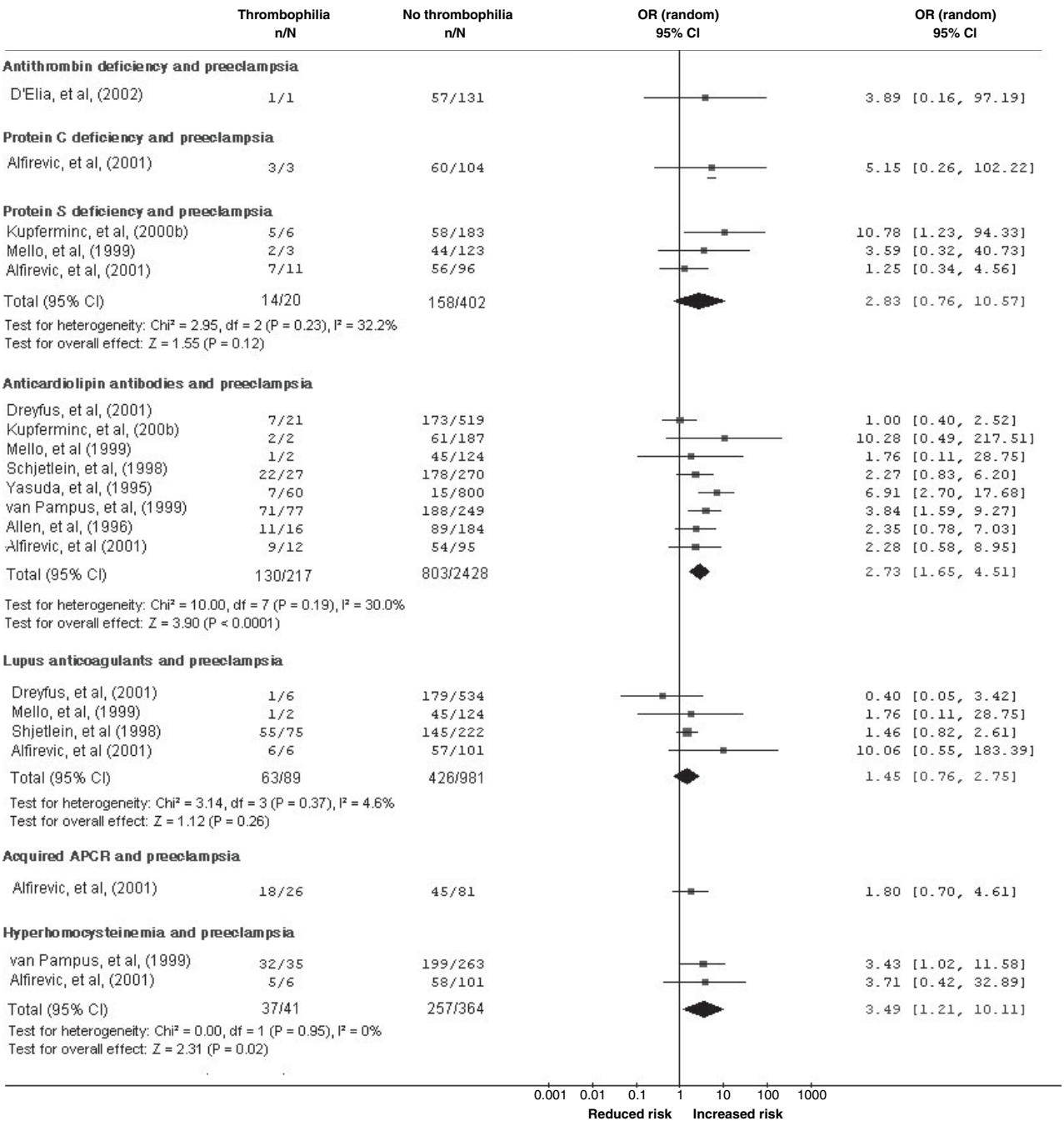
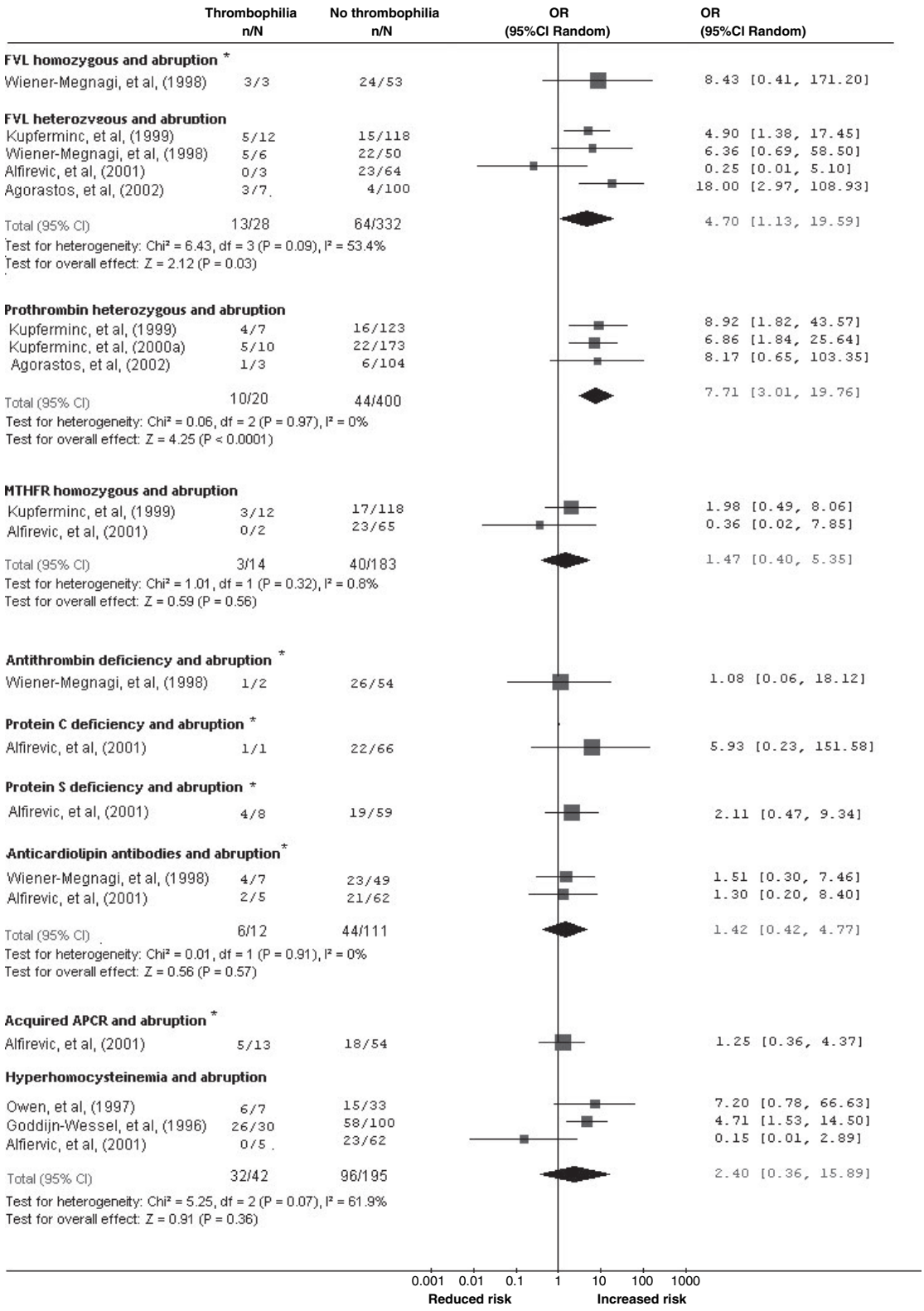


Fig 7. Continued.

heterozygous for factor V Leiden and homozygous for prothrombin G20201A were judged to be at a higher risk of VTE than any other pregnancy complication studied. No studies were found that measured the risk of pregnancy-related VTE in women with elevated anticardiolipin antibodies, lupus anticoagulants or acquired activated protein C resistance, therefore, the risk of VTE in pregnancy with acquired thrombophilia remains unclear. Furthermore, the risk of DVT and PE could not be established separately as all studies measured VTE as a single outcome.

Of the inherited thrombophilias, only women homozygous for factor V Leiden or heterozygous for prothrombin G20210A had a significant association with early loss. Women homozygous for factor V Leiden or with hyperhomocysteinaemia were at a significantly higher risk of suffering an early pregnancy loss compared to women with other thrombophilias. Moreover, the risk of early pregnancy loss with hyperhomocysteinaemia was greater than the risk of any other pregnancy complication with this condition. The acquired thrombophilias, including elevated anticardiolipin antibodies,



* Data was only available for one study, therefore meta-analysis was not carried out for this thrombophilia.

Fig 8. Risk of placental abruption in women with thrombophilia. The square on each line represents the point estimate for the odds ratio for each single study; its size of the square varies according to study size and variance. Black diamonds represent the overall average odds ratio and the confidence interval from pooling all the studies together in the meta-analysis.

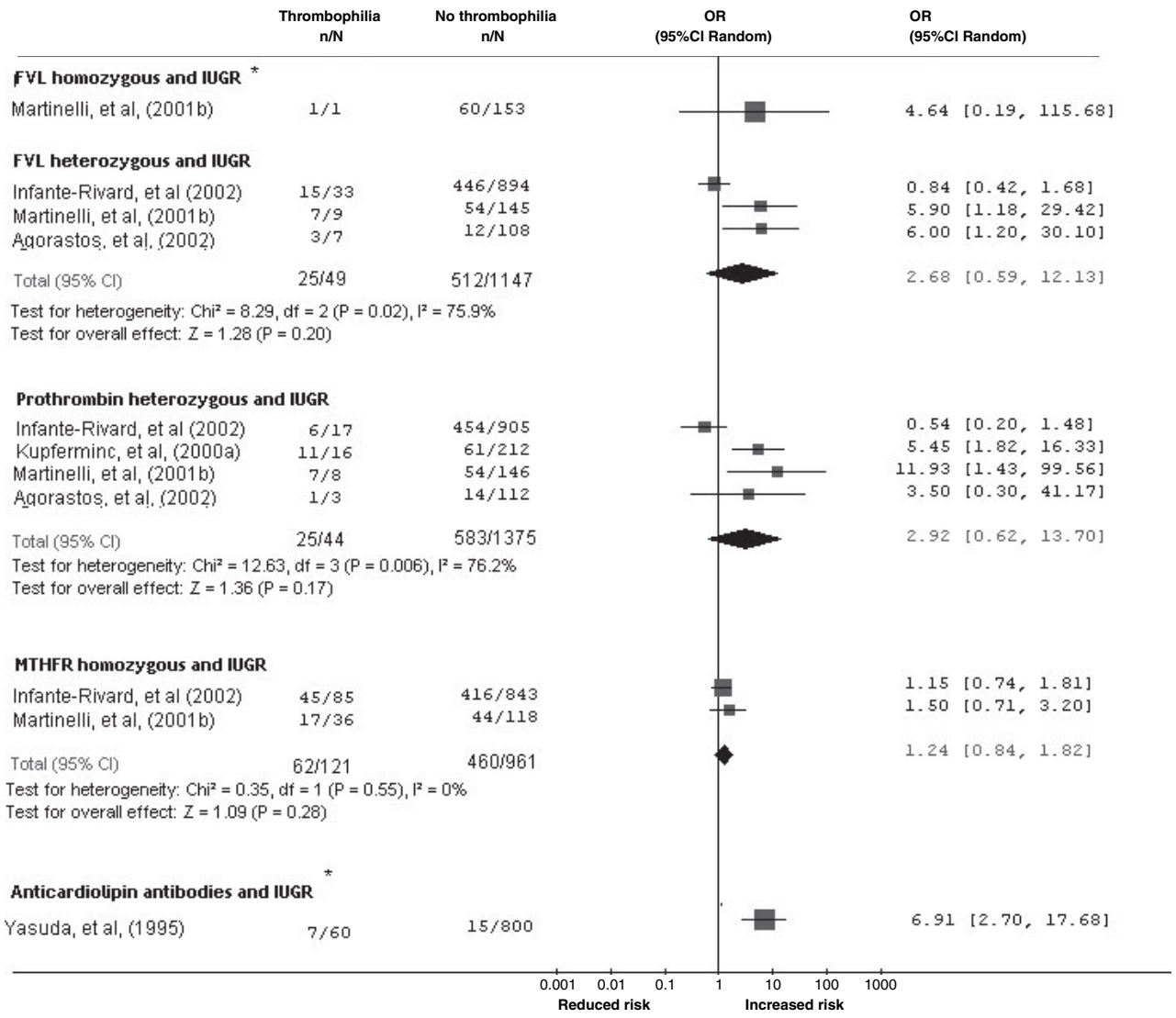


Fig 9. Risk of intrauterine growth restriction in women with thrombophilia. The square on each line represents the point estimate for the odds ratio for each single study; its size of the square varies according to study size and variance. Black diamonds represent the overall average odds ratio and the confidence interval from pooling all the studies together in the meta-analysis.

lupus anticoagulants and acquired activated protein C resistance, were also significantly associated with pregnancy loss before 24-week gestation. The magnitude of risk was modest; however, early pregnancy loss is a very heterogeneous condition and only a proportion of these losses will be related to thrombophilia. A stronger association was found with recurrent miscarriage, which is likely to be more specific for an underlying thrombophilia. When early pregnancy loss was classified according to recurrent loss in the first trimester and non-recurrent loss in the second trimester, a higher risk of second trimester loss for both factor V Leiden and prothrombin G20210A heterozygotes was calculated. This is consistent with a recent analysis on thrombophilia and recurrent pregnancy loss (Rey *et al*, 2003). Although there were insufficient data to ascertain the risk of second trimester pregnancy loss with lupus anticoagulants, the risk of recurrent first trimester pregnancy loss was higher than for any other pregnancy complication with this acquired thrombophilia.

Of all thrombophilias, late pregnancy loss was most strongly associated with protein S deficiency. Women heterozygous for either factor V Leiden or prothrombin G20210A or with lupus anticoagulants were also at significantly increased risk of loss beyond 24-week gestation. The remaining thrombophilias studied were not significantly associated with late loss. These findings are consistent with another systematic review (Alfirevic *et al*, 2002), which established that women with protein S deficiency were at the highest risk of unexplained stillbirth after 20 weeks.

In comparing early pregnancy loss before 24 weeks and late loss beyond this stage of gestation, we found that in women heterozygous for factor V Leiden or prothrombin G20210A, the risk of late pregnancy loss was higher than that for early loss. These findings are consistent with another systematic review on heritable thrombophilia and fetal loss (Rey *et al*, 2003), who also found a significant association between factor V Leiden and fetal loss, the association being more robust if fetal loss arose after 19-week gestation. Our results for acquired thrombophilias indicated that elevated anticardiolipin antibodies and lupus anticardiolipins were associated with higher risk of early pregnancy loss. Studies that did not specify the timing of pregnancy loss were excluded from the review. Data from these studies were pooled together to examine whether including these studies would have influenced the final results. The results from the 12 studies showed that factor V Leiden and prothrombin G20210A were associated with pregnancy loss. Therefore, as these results were obtained before exclusion of these studies, it is unlikely that excluding these studies would influence the final results.

With regard to pre-eclampsia, significant associations with hyperhomocysteinaemia, elevated anticardiolipin antibodies, heterozygosity for factor V Leiden and prothrombin G20210A were found. Pre-eclampsia was the only outcome for which a significant association with homozygosity for MTHFR C677T was found. The increase in risk of pre-eclampsia with thrombophilia is modest. Thrombophilia may contribute to the severity of pre-eclampsia because of an exaggerated effect of the disorder on the haemostatic system in women with thrombophilia (Morrison *et al*, 2002). The highest risk of placental abruption was in women heterozygous for prothrombin G20210A, followed by heterozygous factor V Leiden and hyperhomocysteinaemia. These results are similar to those established by other systematic reviews (Gates, 2000; Alfirevic *et al*, 2002). In IUGR, the highest risk was in women homozygous for factor V Leiden, followed by heterozygotes for prothrombin G20210A. Alfirevic *et al* (2002) concluded that pregnant women with elevated anticardiolipin antibodies and protein S deficiency were at highest risk of IUGR. However, their findings were based on only three studies involving very small numbers of women. Additionally, they did not use a prespecified definition of IUGR.

Studies measuring the effectiveness of prophylactic interventions were lacking, in keeping with the findings of the Cochrane review on this area, which included data published up to 2003 (Walker *et al*, 2005). It remains to be established whether intervention with LMW heparin is of benefit in women with thrombophilia and an underlying pregnancy complication. Further randomised controlled trials are needed to explore this possibility. Other studies included compared different treatments; therefore, it was not possible to group these studies together. Several studies measured the effectiveness of plaquinil in treating pregnancy-related VTE. This drug is no longer used in clinical practice and as these findings are irrelevant, they were not included in this review.

Systematic reviews have several limitations, including selection bias and varying methodological quality of studies. All studies included in this review were independently judged as moderate to high quality using a standardised checklist. Laboratory methods for individual studies used standardised techniques and specific cut-off values to identify thrombophilia. Furthermore, testing for deficiencies of antithrombin, protein C and protein S was performed at least 6 weeks after pregnancy in all studies. Publication bias can arise in systematic reviews. We restricted this review to studies that were published in English. It is well understood that in the field of obstetrics and gynaecology, good quality studies are published in English (Egger *et al*, 2003). Therefore, it is believed that excluding non-English studies would make no significant difference to the results.

Due to the fact that not all studies tested for all major thrombophilias, we cannot eliminate the possibility that some control women without the thrombophilia studied were carriers of thrombophilias that were not tested for. This possibility could lead to underestimation of the association between thrombophilia and the adverse outcomes studied. Additionally, it is clear for VTE that individuals from symptomatic thrombophilic kindred differ in risk from unselected individuals or those from asymptomatic kindred with the same thrombophilic genotype. This is likely to be due to an additional (often unidentified) defect or interaction. While this is clear for thrombosis, we have little information of this in pregnancy complications, but it remains likely that the same or similar factors could operate.

Despite strict inclusion criteria, there were instances of interstudy heterogeneity. A possible explanation for such heterogeneity is genetic variations between ethnic populations studied. The studies included in the review were conducted among participants of different ethnic backgrounds. Thrombophilia defects are known to vary according to race, in particular, thrombophilia is more prevalent in Caucasians (Franco *et al*, 1998; Rosendaal *et al*, 1998). This is supported by a study included in this review, where a higher OR was obtained when analysis was restricted to white women only (Dilley *et al*, 2000). Another factor that could contribute to the heterogeneous results was different sensitivity and specificity of the laboratory methods used in testing for thrombophilia.

An often overlooked area is the risk of VTE associated with ovarian stimulation for assisted conception therapy, where women are exposed not only to the pregnancy-associated risks of VTE but also the effects of hyperestrogenism. Hyperstimulation is associated with procoagulant changes in the haemostatic and fibrinolytic systems and increased risk of venous and arterial thrombosis, although the overall rate of thrombosis in assisted conception is low (Gompel *et al*, 2002). Women with thrombophilia may be at particular risk, and jugular vein thrombosis has been reported following *in vitro* fertilisation in a compound heterozygote for protein S deficiency and prothrombin G20210A despite therapeutic anticoagulation with a LMW heparin (Reid & Perry, 2001). Thus, in view of the established risk of VTE with thrombophilia in pregnancy,

women with possible thrombophilia undergoing assisted conception therapy require special consideration with regard to their risk of thrombosis and need for prophylaxis.

Conclusions

Recent debate has focused on whether universal screening for thrombophilia should be performed prior to pregnancy. Our review has confirmed that women with thrombophilia are at increased risk of developing complications during pregnancy. However, despite the increase in relative risk, the absolute risk of VTE and adverse outcomes in pregnancy remains low. Furthermore, aside from recurrent pregnancy loss in antiphospholipid syndrome and prevention of VTE, there is insufficient evidence on the benefit of antithrombotic interventions to guide therapy. While there is recent evidence suggesting this possibility in adverse pregnancy outcomes (Brenner *et al*, 2005), benefit cannot be concluded in the absence of controlled clinical trials. Such trials are urgently required. Thus, at present, universal screening for thrombophilia in pregnancy cannot be justified clinically.

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