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The Impact of Inherited Thrombophilia on Placental Haemostasis and Adverse Pregnancy Outcomes

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1. Introduction

While the last century has seen substantial developments in our understanding of many human diseases, there are still vast gaps in our knowledge about many physiological and pathological processes. This is particularly so in obstetrics, where advances in care have resulted in significant declines in both maternal and perinatal mortality in developed countries. Yet, despite this, conditions such as pre-eclampsia, fetal growth restriction, stillbirth, miscarriage and placental abruption remain to a large extent idiopathic. Prediction and prevention of these complications remains limited, with timely delivery representing the only effective treatment strategy in cases of pre-eclampsia, fetal growth restriction and placental abruption. This will often result in the delivery of a premature infant who requires the investment of significant community and family resources – financial, physical, intellectual and emotional – to develop their full potential. The longer term sequelae of fetal growth restriction such as adult onset diabetes, hypertension and obesity, (Barker et al. 1993) and the effects of prematurity such as chronic lung disease (Askie et al. 2005) and neurodevelopmental impairment (Guellec et al. 2011) represent significant additional burdens. Any improvements that can be made in our understanding and treatment of these serious human pregnancy disorders, therefore has the potential to impact significantly not only on maternal well being, but also on the well-being of future generations.

A consistent finding among patients experiencing many of these complications is that of areas of thrombosis on histological examination of the placenta (Salafia et al. 1995a; Salafia et al. 1995b). This has prompted the suggestion that disturbances in coagulation may contribute to the aetiology of these conditions. The recognition of the association between inherited thrombophilias and venous thromboembolism has sparked significant interest in the possibility that inherited thrombophilias may also play a role in these pregnancy complications. In this review, the current state of understanding regarding inherited thrombophilia and adverse pregnancy outcome will be critically examined.

2. Inherited thrombophilias and adverse pregnancy outcomes: The limitations of case control studies

The association between inherited thrombophilias and adverse pregnancy outcomes has been intensely debated for the past 15 years. Early case-control studies suggested significant

associations between maternal inherited thrombophilias and pregnancy complications such as pre-eclampsia (Dekker et al. 1995; van Pampus et al. 1999; Kupfermanc et al. 2000), fetal growth restriction (Martinelli et al. 2001; Agorastos et al. 2002), placental abruption (Wiener-Megnagi et al. 1998; Kupfermanc et al. 1999), stillbirth (Preston et al. 1996; Many et al. 2002) and recurrent miscarriage (Grandone et al. 1997; Younis et al. 2000). Despite the potential for confounding (de Vries et al. 2009) and bias (Sibai 2005) inherent in these early case control studies, their great strength is the fact that they examined the association between thrombophilias and severe, early onset complications. These complications are rare but extremely serious by virtue of the increased likelihood of long term maternal and perinatal sequelae. Follow up case control studies often included patients with milder forms of the condition, later onset of disease and delivery at more advanced gestations, and as a result, often failed to confirm the significant associations between thrombophilias and adverse pregnancy outcomes demonstrated in early case control studies. This is best exemplified by contrasting two studies investigating the association between fetal growth restriction and inherited thrombophilia (Infante-Rivard et al. 2002; Kupfermanc et al. 2002). Kupfermanc and colleagues restricted their analysis to the subgroup of women delivering severe early onset growth restricted babies with a birthweight below the 3rd centile and antenatal ultrasound evidence of oligohydramnios (Kupfermanc et al. 2002) while Infante-Rivard used the more liberal definition of birthweight less than the 10th centile (Infante-Rivard et al. 2002). Kupfermanc and colleagues calculated the highly significant odds ratio of 4.5 (2.3 – 9.0) for the association between any inherited thrombophilia and fetal growth restriction (FGR), whereas Infante-Rivard concluded that an association between fetal growth restriction and inherited thrombophilias did not exist. Such a difference is likely to be due to differences in the clinical definitions chosen. On the one hand Kupfermanc's FGR population represents a small unique subgroup representing less than 0.2% of their entire obstetric population (Kupfermanc et al. 2002). Meanwhile Infante-Rivard's FGR population represents a much broader group which is likely to include many women with healthy babies that are merely constitutionally small. This is further supported by the low rates of significant placental pathology in this group (Infante-Rivard et al. 2002). Most importantly, however, the majority of Infante-Rivard's cohort are likely to have excellent perinatal outcomes with low rates of prematurity and associated morbidity, a finding that contrasts starkly with the high perinatal mortality (approximately 60%), universal prematurity and associated morbidity described in Kupfermanc's study (Kupfermanc et al. 2002). While it is true that a statistically significant association is seen with the Kupfermanc study, it must be emphasised that this is a highly specific, high risk population and these findings cannot necessarily be extrapolated to general obstetric populations.

The limitation to the study validity that is imposed by varying clinical definitions is evident not just with fetal growth restriction as described above, but also pre-eclampsia, fetal loss and placental abruption. Studies investigating the relationship between miscarriage and thrombophilias have variably defined recurrent miscarriage as two or more first trimester losses (Younis et al. 2000), three or more first trimester losses (Rai et al. 2001) or any number of second trimester losses (Raziel et al. 2001). Furthermore, miscarriage and stillbirth have not infrequently been combined making dissection of individual associations very difficult (Preston et al. 1996).

The potential for publication bias in case control studies with positive association studies being rapidly published while studies that do not confirm these associations have been delayed has also been suggested in several meta-analyses that examined the potential impact of publication bias (Howley et al. 2005; Facco et al. 2009). In addition, many of the

early “positive” studies were published in high impact journals (Dekker et al. 1995; Preston et al. 1996; de Vries et al. 1997; Kupferminc et al. 1999; Rey et al. 2003) and were thus rapidly disseminated amongst the obstetric and haematology communities. Rapid translation of these preliminary research findings into clinical practice has also been a key issue. This has happened simply because thrombophilia tests were readily available to clinicians who were keen to take advantage of them. Furthermore, the publication of eminent guidelines (Bates et al. 2004) and influential articles (Kupferminc et al. 1999) advising of the merits of testing women who experience adverse pregnancy events (before the appearance of evidence to support treatment or prophylaxis for subsequent pregnancies) has resulted in the very high uptake of thrombophilia testing by obstetricians. This has confounded ongoing rigorous research examining the efficacy of testing and treatment in this field.

Another significant limitation of case-control studies is the variation in the ethnic distribution of inherited thrombophilias. A number of studies have now highlighted the significant ethnic variation in the prevalence of various thrombophilias (Rees et al. 1995; Herrmann et al. 1997; Said et al. 2006; Said et al. 2008) but it is important to note that even within predominantly Caucasian populations, significant ethnic variation in the prevalence of inherited thrombophilias exists by virtue of different migration patterns (Said et al. 2006). Failure to take into account the specific prevalence of inherited thrombophilias in the ethnic group being studied, and account for the potential interaction of other co-inherited thrombophilias, can result in studies that are underpowered and thus unable to answer questions regarding the association between inherited thrombophilias and adverse obstetric outcomes.

3. Meta-analysis of case control studies

A number of meta-analyses examining the association between inherited thrombophilias and adverse pregnancy outcomes on the basis of case control studies have been undertaken (McLintock et al. 2001; Alfirevic et al. 2002; Rey et al. 2003; Howley et al. 2005; Lin and August 2005; Robertson et al. 2006; Facco et al. 2009). Meta-analyses of case control studies are limited by the significant heterogeneity of the included studies but nevertheless attempt to provide a clinically relevant evidence base to support decision making regarding testing for inherited thrombophilias in these obstetric conditions. As stated previously however, meta-analyses have limited validity due to the effects of publication bias and clinical heterogeneity.

As with case control studies, meta-analyses examining the association between inherited thrombophilias and pre-eclampsia have invariably concluded that overall, the strength of association may be weak at best with the greatest association observed with severe early onset disease. Lin and August included a total of 31 published studies and 7522 patients in their meta-analysis and calculated a modest odds ratio of 1.81 (1.14 - 2.87) for the association between the factor V Leiden mutation and pre-eclampsia overall and an odds ratio of 2.24 (1.28 - 3.94) for severe pre-eclampsia (Lin and August 2005). In contrast a statistically significant association was not observed with either the prothrombin gene mutation or the MTHFR 677 polymorphism. Once again, however, funnel plot analysis for publication bias suggested the possibility of publication bias due to the absence of smaller, negative studies available for inclusion in the meta-analysis.

A comprehensive review of published studies investigating genetic risk factors for placental abruption revealed a positive association between the prothrombin gene mutation (OR 6.67,

3.21 - 13.88, 7 included studies) and the factor V Leiden mutation (OR 2.35, 1.62 - 3.41, 10 studies) (Zdoukopoulos and Zintzaras 2008). Interestingly the strength of these associations increased significantly when studies comprising non-Caucasian women were excluded since both these mutations are more frequently present in Caucasian compared to non-Caucasian populations.

Rey and colleagues took up the challenge of dissecting the associations between inherited thrombophilias and fetal loss in their meta-analysis published in *The Lancet* in 2003 (Rey et al. 2003). After categorising fetal loss as early recurrent loss and late non-recurrent loss (after 19 weeks), they concluded first trimester recurrent fetal loss was associated with factor V Leiden (OR 2.01, 1.13 - 3.58) and prothrombin gene mutation (OR 2.05, 1.18 - 3.54) while late non-recurrent loss was associated with factor V Leiden (OR 3.26, 1.82 - 5.83), prothrombin gene mutation (OR 2.30, 1.09 - 4.87) and protein S deficiency (OR 7.39, 1.28 - 42.83) (Rey et al. 2003).

The relationship between fetal growth restriction and inherited thrombophilias has been the subject of several meta-analyses of case control studies (Dudding and Attia 2004; Howley et al. 2005; Robertson et al. 2006; Facco et al. 2009) The most recent of these meta-analyses reported a very modest overall summary odds ratio for the association between factor V Leiden and fetal growth restriction of 1.23 (1.04 - 1.44), however, when cohort studies were removed from the analysis the OR was 1.91 (1.17 - 3.12) (Facco et al. 2009). Further exploration of the data confirmed the effects of publication bias by demonstrating a significant odds ratio when early (pre-2004) studies were analysed (OR 2.04, 1.05 - 3.96, 6 studies) whereas a non-significant odds ratio was calculated when publications from 2004 - 2008 were included (OR 1.19, 0.02 - 2.39, 8 studies) (Facco et al. 2009).

4. Prospective cohort studies

While case control studies and their meta-analyses provide important data about the association between inherited thrombophilias and adverse pregnancy outcomes, they have an important limitation in that they cannot examine the “natural history” of thrombophilias and hence cannot ascribe causality. Prospective cohort studies are necessary to address this question of the potential for causality. In contrast to case control studies, prospective cohort studies need to recruit participants prior to the onset of any disease state and hence often require large numbers, making them costly and time consuming. However, undertaking prospective cohort studies in the setting of pregnancy has several advantages. Firstly, in contrast to prospective cohort studies investigating risk factors for cardiovascular disease and cancer, the time period is quite short and can be restricted to the duration of the pregnancy (ie 9 months) rather than the many years it may take for cardiovascular disease or cancers to develop in asymptomatic people. Secondly, pregnant women (at least in developed countries) are far more likely to attend for medical care at an early (asymptomatic) phase allowing non-biased ascertainment. Finally, many of the endpoints are easily measurable, routinely collected and not subject to observer or recall bias (e.g. birthweight, gestation at delivery, mode of delivery etc).

A number of prospective cohort studies have now been undertaken in a variety of different ethnic populations. These prospective cohort studies have confirmed that inherited thrombophilias are indeed common with prevalence estimates for the factor V Leiden mutation ranging from 2.7% (Murphy et al. 2000; Dizon-Townson et al. 2005) to 10.9%

(Lindqvist et al. 1999). Likewise the prothrombin gene mutation is seen in 2.4% (Said et al. 2010a) to 6.2% (Salomon et al. 2004) of women.

Three prospective cohort studies have examined only the association between factor V Leiden and adverse pregnancy events, and all failed to detect a statistically significant difference in the rate of pregnancy complications such as pre-eclampsia, fetal growth restriction, placental abruption or stillbirth amongst carriers of this mutation (Lindqvist et al. 1999; Dizon-Townson et al. 2005; Clark et al. 2008) (although one did show an association between neonatal death and factor V Leiden (Clark et al. 2008)). Dudding et al examined both factor V Leiden and prothrombin gene mutation and concluded that neither mutation was associated with the development of either pre-eclampsia or fetal growth restriction (Dudding et al. 2008). Another study examined factor V Leiden and MTHFR 677 and found no significant increase in the risk of adverse pregnancy outcomes although the small sample size (n=584) and low prevalence of factor V Leiden (2.7%) meant that this cohort was underpowered to detect a significant difference (Murphy et al. 2000). Three studies investigated factor V Leiden, prothrombin gene mutation and also the MTHFR 677 polymorphism (Salomon et al. 2004; Karakantza et al. 2008; Said et al. 2010a). No significant correlation was seen between any of these thrombophilias and adverse pregnancy outcomes in the study from Israel (Salomon et al. 2004). The second study, in a relatively small Greek cohort of 392 women, reported significant associations between factor V Leiden and MTHFR 677 and placental abruption (Karakantza et al. 2008). Said et al also reported significant associations between factor V Leiden and stillbirth (OR 8.85, 1.60 - 48.92), prothrombin gene mutation and placental abruption (OR 12.15, 2.45 - 60.39) and a composite outcome comprising severe pre-eclampsia, small for gestational age (below the 5th centile), placental abruption and stillbirth (OR 3.58, 1.20 - 10.61) in a cohort of 1707 asymptomatic nulliparous women (Said et al. 2010a). In contrast, Silver et al reported no association between the prothrombin gene mutation and adverse pregnancy events in a larger cohort of 4167 women (Silver RM et al. 2010). However, most importantly, all prospective cohort studies have confirmed that carriers of these inherited thrombophilias can experience completely uncomplicated pregnancies (Rodger et al. 2010; Said et al. 2010a).

An interesting finding from the Australian prospective cohort study (Said et al. 2010a) was the observation that homozygous carriers of the MTHFR 1298 polymorphism appeared to be at reduced risk of adverse pregnancy outcomes, and in particular fetal growth restriction. While the MTHFR 1298 polymorphism is not generally regarded as a thrombophilia in its own right and does not appear to be associated with hyperhomocysteinaemia, heterozygous coinheritance of the MTHFR 677 and MTHFR 1298 polymorphisms does appear to be associated with hyperhomocysteinaemia. Said et al have attributed their curious finding to the fact that the two MTHFR polymorphisms were in linkage disequilibrium suggesting that the protective effect observed with MTHFR 1298 homozygosity may in fact be due to the fact that these patients were protected from the risk of hyperhomocysteinaemia associated with homozygosity of MTHFR 677 (Said et al. 2010a). This possibility further supports the notion that absence of association in many prospective cohort studies may be because of failure to test for the wider range of "known" thrombophilias as well as the cumulative effect of common, less thrombogenic thrombophilias or unknown thrombophilias. Few studies have examined the MTHFR 1298 polymorphism to date to confirm or refute these findings.

5. Meta-analysis of cohort studies

A meta-analysis of these prospective cohort studies was published in 2010 (Rodger et al. 2010). This meta-analysis included 10 studies with 21,833 women and found no statistically significant increase in the risk of pre-eclampsia amongst women carrying the factor V Leiden mutation (OR 1.23, 0.89 - 1.70) (Rodger et al. 2010) (Figure 1). Likewise, the prothrombin gene mutation did not appear to confer an increase in the risk of pre-eclampsia with a pooled odds ratio of 1.25 (0.79 - 1.99) when 6 studies including 14,254 women were included (Rodger et al. 2010) (Figure 2). Similar non-significant findings were observed for the association between both of these thrombophilic mutations and placental abruption and delivery of a small for gestational age baby. In fact the only statistically significant association observed in this detailed meta-analysis was the significant association between pregnancy loss and the factor V Leiden mutation (Figure 1). It is important to note, however, the significant heterogeneity in the definition of pregnancy loss in the included studies, which comprised spontaneous miscarriage or stillbirth variably (Rodger et al. 2010).

This meta-analysis was adequately powered to detect an absolute increase of 2% in the rate of pre-eclampsia in carriers of the factor V Leiden mutation (from 3.2% to 5.2%) and an absolute increase of 3% in carriers of the prothrombin gene mutation. However, despite the large numbers of patients included in this meta-analysis, the study had inadequate power to detect a two-fold increase in the risk of placental abruption amongst carriers of the prothrombin gene mutation.

However, even with such a large meta-analysis failing to confirm significant associations between individual inherited thrombophilias and adverse pregnancy outcomes, several interpretations remain. First, of course, it is quite plausible that thrombophilia is simply not causative of these pregnancy complications. However, an interaction between inherited thrombophilia in susceptible people remains possible. Such an interaction may well result in augmentation of the pathological processes leading to conditions such as pre-eclampsia, or fetal growth restriction in susceptible people, resulting in earlier onset and more severe disease in these people. Such an explanation would be supported by the apparent contradiction between case-control studies and prospective cohort studies. An alternative possibility is that additional, as yet unidentified thrombophilias may result in a cumulative effect that determines the disease phenotype once a critical threshold is reached. This hypothesis is supported by observations from case-control studies that demonstrate the presence of multiple inherited thrombophilias being more commonly found in women with more severe complications than in apparently asymptomatic women. This issue would be relevant in the many case-control and cohort studies that only examine a single thrombophilic polymorphism rather than a panel of common polymorphisms.

A key feature of the association between inherited thrombophilias and pregnancy complications that has been particularly borne out by the prospective cohort studies is the lack of specificity between individual thrombophilias and particular complications. For example both the factor V Leiden mutation and the prothrombin gene mutation have been variably associated with normal pregnancy outcomes, fetal growth restriction, pre-eclampsia, placental abruption, stillbirth and recurrent miscarriage. Conversely, the phenotype of these disorders appears identical regardless of which thrombophilic mutation (if any) is carried. In addition, in a patient who carries one of these mutations, it is unclear what additional modifying factors will determine the precise outcome.

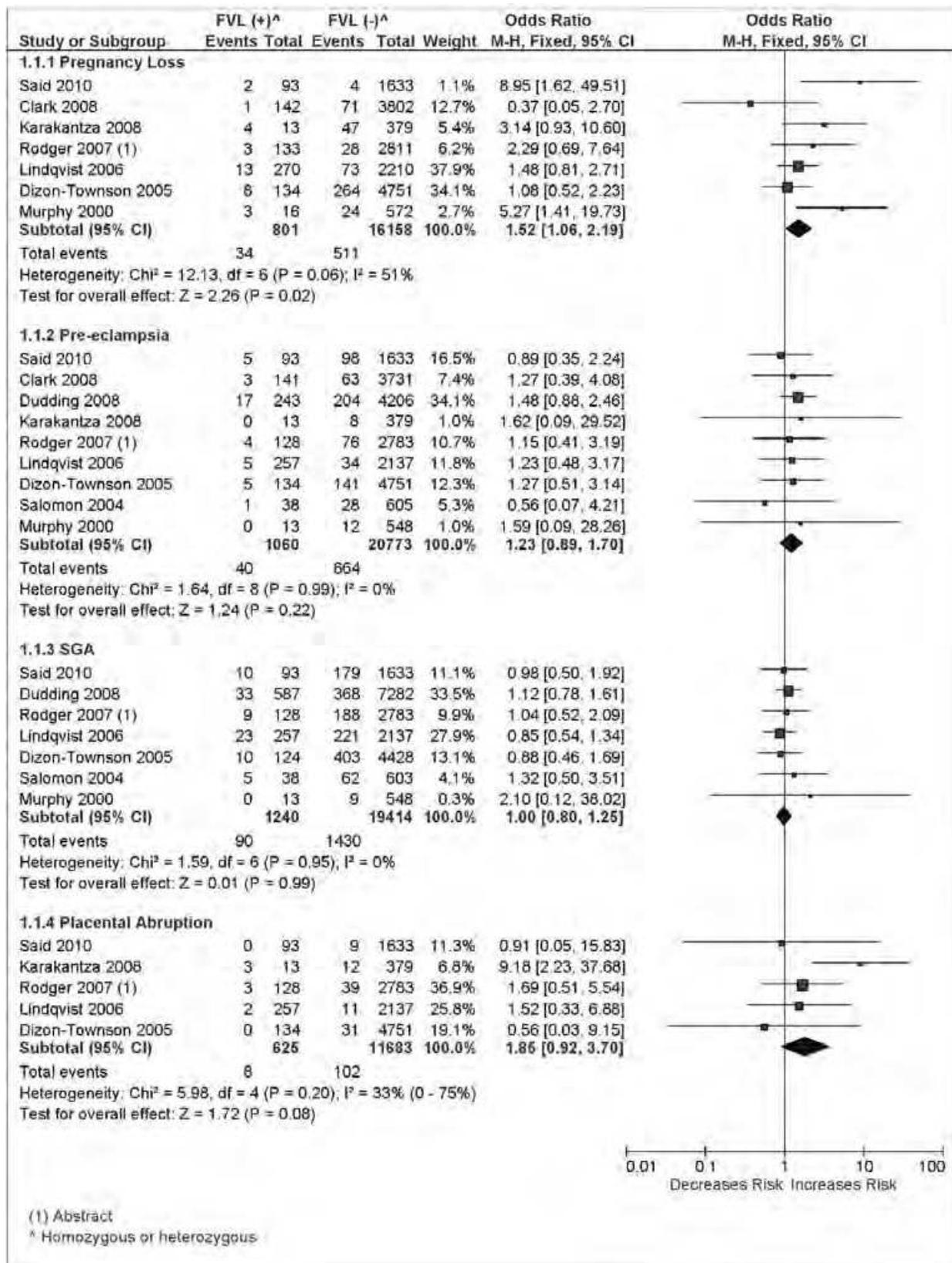


Fig. 1. Meta-analysis of pregnancy complications in women who are heterozygous or homozygous for factor V Leiden. (Rodger et al. 2010)

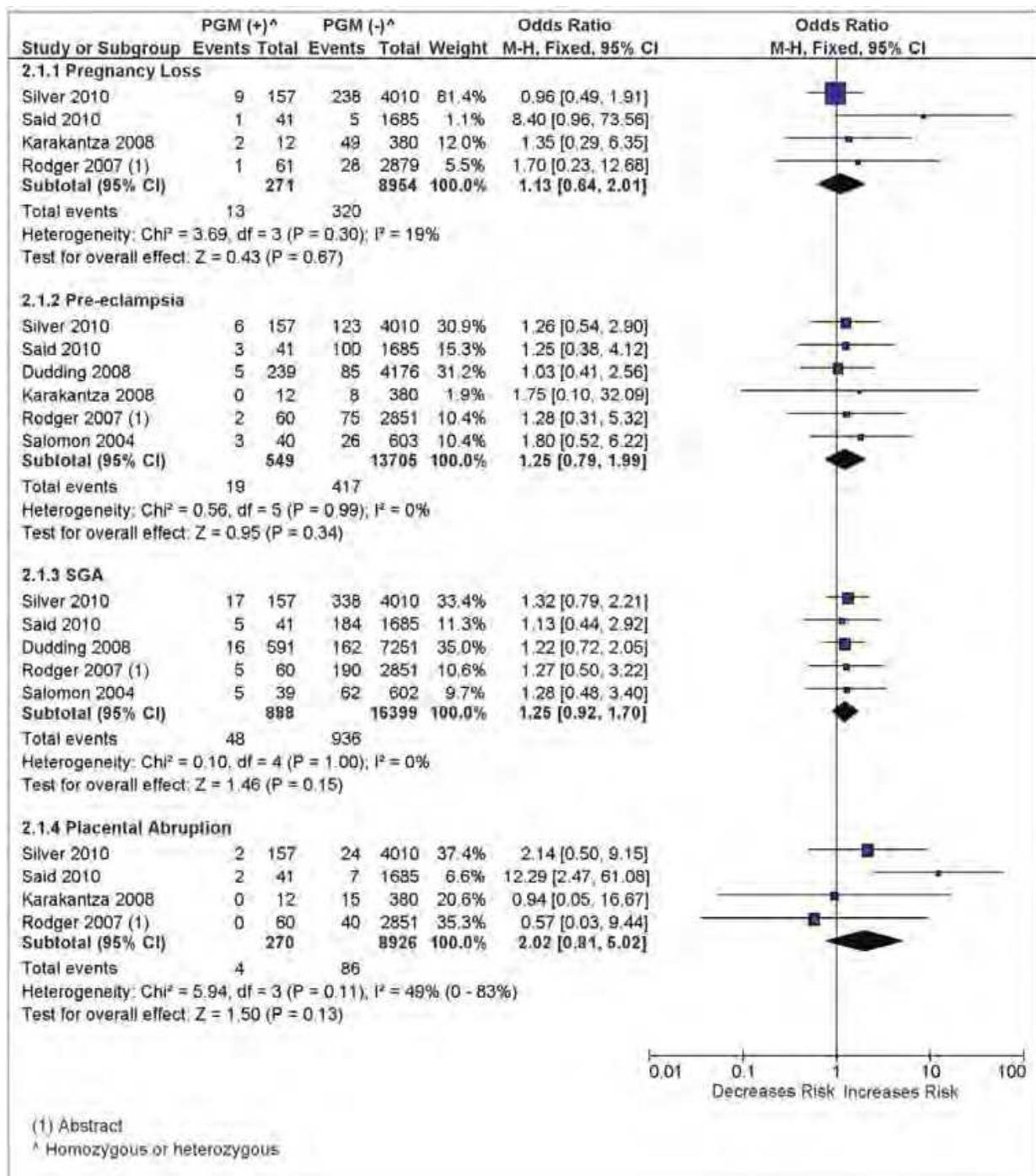


Fig. 2. Meta-analysis of pregnancy complications in women who are heterozygous or homozygous for prothrombin gene mutation. (Rodger et al. 2010)

Given the range of potential thrombophilias that could be investigated in an individual, the lack of specificity with disease states and the possibility of “unknown” or unidentified thrombophilias contributing to the phenotype, the appropriateness of investigating women for inherited thrombophilias to predict the risk for future pregnancy complications must be questioned. Thrombophilia testing is expensive. Furthermore there are conflicting data concerning the subsequent risks of recurrent adverse pregnancy outcomes such as pre-eclampsia (van Rijn et al. 2006; Facchinetti et al. 2009) in women who carry an inherited

thrombophilia compared to those who don't, so the benefits of detecting these markers remain uncertain. This in turn makes the rationale of treating subsequent pregnancies with prophylactic heparins questionable. An alternative approach is to treat the disease phenotype rather than simply the test result!

6. Placental thrombotic lesions and inherited thrombophilias

Placental vasculopathy is a histopathological diagnosis which is increasingly being recognised in association with a variety of clinical pathologies including pre-eclampsia, fetal growth restriction, placental abruption and stillbirth. In addition, a number of reports regarding the association between these pathologic features and cerebral palsy have been published (Arias et al. 1998; Kraus and Acheen 1999). Redline and Pappin were amongst the first to report these specific placental lesions and their association with adverse neonatal outcomes. In addition they defined the pathologic criteria for diagnosis of this condition (Redline and Pappin 1995). While Kraus and Acheen (Kraus and Acheen 1999) have demonstrated that these lesions precede fetal death in cases of stillbirth, the precise pathophysiological mechanism resulting in the vascular thrombosis and fibrosis is unknown. Nevertheless it has been considered plausible that procoagulant states such as thrombophilias may contribute.

Many and colleagues (Many et al. 2001) investigated the contribution of maternal thrombophilias to the pathologic placental features in women with severe pregnancy complications and concluded that placental abnormalities such as infarcts and fibrinoid necrosis were more common in the placentae of women with pregnancy complications and thrombophilia compared to those with the same complications without thrombophilia. Of note, however, the women with thrombophilia and complications delivered at an earlier gestation and had lower birthweight babies compared to their non-thrombophilic counterparts. Thus whether these differences truly represent a difference in thrombophilia state or simply a difference in phenotypic state must be questioned. Likewise, Gogia and Machin (Gogia and Machin 2008) investigated the association between the specific placental lesions of maternal floor infarction (n=40), massive perivillous fibrin deposition (n=87) and fetal thrombotic vasculopathy (n=7) and identified a range of maternal thrombophilic markers in 40%, 23% and 71% respectively of the women with these placental histopathological diagnoses. The prevalence of thrombophilias in these women was significantly higher than the background prevalence of these same thrombophilias in the published literature.

In contrast, Mousa and Alfirovic (Mousa and Alfirovic 2000) were unable to detect a difference in placental histopathology amongst 43 thrombophilic women with adverse pregnancy outcome, who were compared to 36 non-thrombophilic women with the same adverse pregnancy outcomes. The validity of this study has however been questioned given that histopathological examination was performed as part of routine clinical investigation and management rather than being performed in a rigorous standardised manner, thereby leaving the final results and therefore conclusions potentially subject to bias (Khong et al. 2001). Likewise, Kahn et al examined the association between inherited thrombophilias and placental lesions reflecting underperfusion in a nested case-control study, and concluded that although the placental lesions were more common in cases of pre-eclampsia compared to controls, there was no correlation with maternal thrombophilia (Kahn et al. 2009).

In one of the largest studies to date, Rogers and colleagues prospectively collected and examined 105 placentae from women carrying the factor V Leiden mutation and 225

controls matched for maternal age, ethnicity and hospital (Rogers et al. 2010). They reported an increase in the frequency of syncytial knots (adjusted OR 3.6, 1.5 - 8.7 after controlling for hypertension, pre-eclampsia, small for gestational age fetus and preterm delivery before 35 weeks) and hypervascular villi (adjusted OR 3.4, 1.2 - 9.4 after controlling for mode of delivery) in placentae from women who were heterozygous for the factor V Leiden mutation. In contrast to the previous studies, this study did not demonstrate an increase in the frequency of placental infarcts, small for gestational age placentae or fetal thrombotic vasculopathy. An important limitation of this study, however, was that although testing for the prothrombin gene mutation and MTHFR 677 polymorphism were performed, the numbers were too small to assess whether these polymorphisms also contributed to the placental pathological findings. Furthermore, subjects did not undergo testing for other known thrombophilias, raising the possibility that the pathologic lesions observed in control subjects may also be attributable to other thrombophilias

7. Fetal thrombophilias

It is of course plausible that it is the fetal thrombophilic status that is the strongest predictor of adverse pregnancy outcomes, fetal thrombotic vasculopathy and associated placental lesions. Given that inherited thrombophilias are generally inherited in an autosomal dominant fashion, the fetus would only have a 50% chance of inheriting maternal thrombophilias and this may explain why not all pregnancies appear to be affected. Placental tissue carries (in most cases) the same genotype as the fetus. A thrombophilic tendency in the placenta could therefore be conferred via the inheritance of paternally derived thrombophilias. The possibility that it is the fetal genotype, rather than the maternal, contributing to the development of fetal growth restriction was first suggested by a case report describing dizygotic twins with severe growth discordance. The patient had a past history of fetal growth restriction, placental abruption and pulmonary embolism and was found to be a compound heterozygote for the two MTHFR polymorphisms (677 and 1298) (Khong and Hague 2001). The twins demonstrated differential inheritance of the parental MTHFR genes, with the placenta of the smaller twin also demonstrating features of thrombotic vasculopathy. While dizygotic twins provide a unique opportunity for assessing the possible impact of fetal inheritance of thrombophilias, it is important to remember that a number of twins will have significant growth discordance which will partly relate to unequal utero-placental share, aside from any difference in thrombophilia state.

Ariel and colleagues investigated the association between fetal thrombophilia status and placental lesions but were unable to identify a statistically significant difference in the prevalence of placental thrombotic lesions between neonatal or maternal carriers of thrombophilia (Ariel et al. 2004). Rogers also investigated the potential contribution of fetal thrombophilias to the histopathologic appearance and found an increase in the frequency of avascular villi in placentae from 50 infants who carried the factor V Leiden mutation (Rogers et al. 2010). Forty of these infants inherited the mutation from the mother while 10 inherited it from the father. Of note, fetal inheritance of factor V Leiden was not associated with fetal thrombotic vasculopathy, placental infarction or small for gestational age placentae (Rogers et al. 2010).

An Australian study (Gibson et al. 2006) reported a significant association between fetal inheritance of the prothrombin gene mutation (heterozygous or homozygous) and fetal growth restriction (birthweight less than the 10th centile) in babies born prior to 28 weeks

(odds ratio 5.71, 95% CI 1.49 - 21.93). Subgroup analysis for those babies with a birthweight less than the fifth centile also confirmed this finding.

Livingston also undertook a case control study investigating the relationship between maternal and fetal inherited thrombophilias and pre-eclampsia (Livingston et al. 2001). Although the large population of African American patients included in the study (and thus low prevalence of inherited thrombophilias) may have biased this study, Livingston concluded that neither maternal nor fetal inherited thrombophilias were associated with pre-eclampsia.

Given these various reports, the association between inherited thrombophilias and placental thrombotic lesions appears to be weak at best and there are numerous confounding issues that must be considered such as the presence of additional maternal medical disorders, pregnancy complications and the complexities of the maternal-fetal genetic and immune interactions. Therefore recommendations for routine testing of entire families on the basis of placental findings (as suggested by Gogia (Gogia and Machin 2008)) are thus premature and raise concerns about the ethical implications of testing asymptomatic carriers.

8. The role of anticoagulants in preventing pregnancy complications in thrombophilic women

Despite the contradictory findings of studies investigating the association between inherited thrombophilias and adverse pregnancy outcomes, anticoagulant treatment for pregnant women who carry inherited thrombophilias has been embraced by many on the basis of small, non-randomised studies (Riyazi et al. 1998; Kupferminc et al. 2001; Ogueh et al. 2001; Grandone et al. 2002) and several larger randomised controlled trials with methodological limitations (Gris et al. 2004; Brenner et al. 2005). The rationale for anticoagulant treatment relies on the effect of anticoagulants in treating venous thromboembolism. A number of large scale randomised controlled trials investigating the role of low molecular weight heparins in preventing miscarriage in women who experience recurrent miscarriages have recently reported negative results (Clark et al. 2010; Kaandorp et al. 2010; Visser et al. 2011). Meanwhile, the FRUIT study, (FRagmin®) in pregnant women with a history of Uteroplacental Insufficiency and Thrombophilia: a randomised trial (FRUIT) ISRCTN87325378), has recently been completed and demonstrated a small but statistically significant reduction in the risk of recurrent early onset pre-eclampsia or small for gestational age infant in thrombophilic women with a previous history of early onset pre-eclampsia or fetal growth restriction (de Vries et al. 2011). This multicentre trial randomised 139 thrombophilic women with prior adverse pregnancy outcomes (pre-eclampsia or small for gestational age infant with delivery prior to 34 weeks) to receive low molecular weight heparin (Fragmin®) (dosage adjusted for maternal weight) and aspirin 80mg or aspirin 80mg alone. Overall there was a statistically significant reduction in the primary outcome of pre-eclampsia or small for gestational age infant requiring delivery prior to 34 weeks, $p=0.012$ without any significant increase in the risk of adverse effects (de Vries et al. 2011).

While these data are encouraging, it must be emphasised that thrombophilic women with a history of prior adverse pregnancy outcomes such as those included in this study, represent only a very small proportion of the overall subgroup of women at risk of these serious pregnancy events and that many of these women do in fact achieve successful pregnancy outcomes with the far less expensive, less invasive and simple treatment regime of low dose aspirin which has been shown in an individual patient data meta-analysis to reduce the risk

of recurrent pre-eclampsia and fetal growth restriction by up to 10% (Askie et al. 2007). The findings of the FRUIT study need to be confirmed in other, larger populations before this treatment should be recommended and certainly before this practice is extrapolated to other subgroups of thrombophilic patients (eg those with a prior stillbirth). The TIPPS study (Thrombophilia in Pregnancy Prophylaxis Study, ISRCTN87441504) is an ongoing multicentred randomised trial that will provide further data in this regard and may help to resolve some of these dilemmas.

However, as stated previously, the vast majority of women with these pregnancy complications do not have an identifiable thrombophilic marker, yet the mechanisms contributing to thrombotic lesions within the placenta remain uncertain. Moreover, the potential for anticoagulant prophylaxis to be of benefit in these women, as well as in women with identified thrombophilias, is limited by our lack of knowledge and understanding about the mechanisms involved in regulation of haemostasis in the placenta and potential actions of heparins in this organ.

9. Regulation of haemostasis in the placenta

Thrombotic lesions are observed commonly in placentae from women who experience pregnancy complications (Salafia et al. 1995a; Salafia et al. 1995b). Mechanisms regulating haemostasis within the placenta remain poorly understood (Sugimura et al. 2001; Lockwood et al. 2011; Said 2011). However, there is clear evidence of enhanced activation of the coagulation and fibrinolytic systems within both the uteroplacental and systemic circulations of women with pre-eclampsia compared to those with uncomplicated pregnancies (Higgins et al. 1998). As described previously, analysis of the published case-control studies reporting associations between inherited thrombophilias and adverse pregnancy events suggest that these associations are strongest with the more severe and earlier onset complications rather than with milder, later-onset conditions suggesting in fact that thrombophilias may exacerbate an underlying tendency toward the condition rather than causing it per se.

In vivo, coagulation and inflammatory pathways are intimately related (reviewed by Esmon (Esmon 2005)). The coagulation cascade is triggered with the exposure of tissue factor at the site of injury. Tissue factor is abundantly expressed in the decidua and first trimester trophoblast cells. Thus, invasion of the decidua during the first trimester by extravillous trophoblast cells is accompanied by profound local thrombin generation (which ultimately activates platelets and allows conversion of fibrinogen to fibrin) which protects against local haemorrhage. At the same time inflammatory processes are triggered which result in the production of inflammatory cytokines such as tumour necrosis factor- α (TNF- α), endotoxin and CD40 ligand, all of which induce tissue factor expression on the surface of white blood cells (especially monocytes), thereby augmenting the coagulation cascade (Esmon 2005). Furthermore, inflammatory mediators such as interleukin 6 (IL 6) increase both platelet numbers and platelet activation (Esmon 2005). These factors all contribute to the systemic procoagulant state observed in pregnancy. However, this system must be tightly regulated locally to prevent uncontrolled thrombosis. Thrombomodulin is also widely expressed on trophoblast cells (Isermann et al. 2003; Weiler 2004). The binding of thrombin to thrombomodulin results in activation of protein C. There is a modest but progressive increase in systemic protein C levels during the first half of pregnancy which may help to regulate haemostasis (Said et al. 2010b). Furthermore, it is now recognized that activated

protein C plays an important role in the regulation of the inflammatory system through suppression of Tumour Necrosis Factor- α (TNF α) and inflammatory cytokine expression (Esmon 2001; Tótl L J et al. 2008), which is mediated by protein C inhibition of Nuclear Factor- κ B (NF- κ B) translocation (Murakami et al. 1997).

Proteoglycans are macromolecules located within vessel walls and these are also abundantly expressed in human placentae. Being membrane bound, they act locally with exceptionally low levels detectable in maternal plasma (Giri and Tollefsen 2006). Proteoglycans were previously regarded as simply structural molecules responsible only for maintaining the "shape" and structural integrity of organs. It is now known that these molecules have important biological functions including anticoagulant properties, interactions with growth factors (particularly angiogenic growth factors such as VEGF and PlGF) (Santra et al. 2008) and anti-inflammatory properties, making them a potentially important group of candidate molecules in regulating placental haemostasis and potentially playing a role in the pathogenesis of pregnancy disorders (Schaefer and Iozzo 2008; Whitelock et al. 2008; Said 2011). Proteoglycans comprise a core protein to which sulphated glycosaminoglycans (GAG) chains are covalently linked. There are four types of GAG chains located in the blood vessel wall: Chondroitin Sulphate (CS), Dermatan Sulphate (DS), Heparan Sulphate (HS) and Hyaluronan (HA). (Iozzo 2005) Placentae contain two major types of proteoglycans; those containing heparan sulphate (syndecans, perlecan) (Jokimaa et al. 1998) and those containing dermatan sulphate (decorin and biglycan) (Murthi et al. 2010; Swan et al. 2010). HS chains bind Antithrombin (AT) - a potent inhibitor of thrombin - through a pentasaccharide sequence, and DS chains bind Heparin Cofactor II (HCII) through a highly charged sequence (Chen and Liu 2005). GAG bound AT and HCII undergo a conformational change, which in turn facilitates the inhibition of thrombin (Brinkmeyer et al. 2004). The cellular localization of proteoglycans to endothelium and cells in contact with circulating blood, suggest an important role for these molecules in localized anticoagulation. Previous studies have demonstrated significant reductions in mRNA expression of decorin (Swan et al. 2010) and biglycan (Murthi et al. 2010) in placentae from pregnancies affected by fetal growth restriction (FGR) compared to gestation matched control placentae using semi-quantitative RT-PCR (relative to the house keeping gene GAPDH). Warda et al also demonstrated a significant reduction in the expression of GAG synthesizing enzymes in preeclamptic placentae compared to controls (Warda et al. 2008). This reduction translated to a significant alteration in GAG structure raising the possibility that the altered GAG structure may have functional corollaries which may contribute to the development of pre-eclampsia.

Proteoglycans also play important roles in angiogenic pathways by acting as receptors for growth factors. Disordered angiogenesis has been implicated as a key pathogenic mechanism contributing to pregnancy disorders such as pre-eclampsia and fetal growth restriction (comprehensively reviewed by Young et al (Young et al. 2010)) Vascular endothelial growth factor (VEGF) plays an important role in stabilizing the endothelium in mature blood vessels (Maharaj et al. 2008). Placental growth factor (PlGF) has structural homology to VEGF and is thought to amplify VEGF signalling (Autiero et al. 2003). VEGF and PlGF are highly expressed by invasive cytotrophoblasts involved in spiral artery remodeling. However, in preeclamptic pregnancies, VEGF and PlGF levels are substantially lower than non-preeclamptic controls (Young et al. 2010). The soluble form of the VEGF receptor fms-like tyrosine kinase (sFlt1), an antagonist of VEGF, is significantly elevated in pre-eclamptic pregnancies (Young et al. 2010). Similarly transforming growth factor β (TGF-

ß) and endoglin (Eng) levels are higher in pre-eclamptic pregnancies compared to controls although whether this is a primary pathologic mechanism or a compensatory mechanism resulting from ongoing placental ischemia remains uncertain. sFlt1 and sEng, the soluble forms of FLt1 and Eng respectively are released into maternal plasma during pre-eclampsia and exert their antiangiogenic effects on maternal endothelium leading to a state of generalized endothelial dysfunction (Young et al. 2010).

The interaction between haemostatic pathways and angiogenic pathways is further illustrated by the finding that thrombin significantly augments first trimester (but not term) decidual expression of sFlt-1 (Lockwood et al. 2007). Thus, dysregulation of the complex haemostatic pathway by any one of a range of possible mechanisms during the first trimester, has the potential to lead to a cascade of events which may collectively lead to the pathophysiological processes observed in pregnancies complicated by adverse events such as pre-eclampsia.

The combination of endothelial dysfunction, altered blood flow dynamics secondary to abnormal vasculature and the hypercoagulable state of pregnancy provides a plausible background for the development of intravascular microthrombi, which in turn can result in a positive feedback loop leading to greater tissue ischaemia, ongoing oxidative stress and endothelial dysfunction thus perpetuating intravascular thrombosis and ultimately leading to the characteristic placental lesions we observe in pregnancy disorders such as pre-eclampsia, placental abruption, fetal growth restriction and stillbirth. It is plausible that dysregulation of these processes are far more important in leading to the pathogenesis of adverse pregnancy events than inherited thrombophilias.

10. The role of anticoagulants in “non-thrombophilic” patients

Recent randomised controlled trials (RCTs) investigating the role of low molecular weight heparins (LMWH) in preventing adverse pregnancy outcomes in non-thrombophilic women have suggested beneficial effects (Rey et al. 2009; Gris JC et al. 2010) raising the possibility that it is a primary placental haemostatic defect contributing to the pathogenesis of these conditions rather than a maternal thrombophilia. Data from these RCT's are supported by non-randomised observational studies in which non-thrombophilic women with previous obstetric complications and associated evidence of placental vasculopathy had improved obstetric outcomes when treated with LMWH in subsequent pregnancies (Kupferminc et al. 2011). These studies are indeed promising and suggest the more rational use of anticoagulants using an appropriate “phenotype” driven approach (ie on the basis of disease severity and corroborating placental histopathological findings) rather than just a genotype (presence of thrombophilia) driven approach. However a note of caution must be applied. Firstly, the precise mechanism by which low molecular weight heparins achieve beneficial obstetric outcomes remains obscure. Heparin is a synthetic glycosaminoglycan with augmented anticoagulant activity. Whether heparins produce their therapeutic effects in these pregnancy situations via their anticoagulant action or whether through non-anticoagulant (inflammatory or angiogenic mechanisms as discussed previously) has not yet been determined. Understanding these mechanisms may provide the basis for developing more efficacious and safe agents. Secondly, none of the randomised trials published to date have been adequately powered to assess uncommon but serious potential consequences of treatment. Although low molecular weight heparins are generally regarded as “safe” (Greer and Nelson-Piercy 2005), they have important implications for labour epidural use

(Horlocker et al. 2010) and risks of wound bleeding and haematoma (van Wijk et al. 2002) following operative delivery. These comparatively minor risks are particularly important given the third issue which is the fact that prophylaxis is given to prevent recurrence of placental mediated complications, but untreated women appear to only have a risk of at most 25-30% (van Rijn et al. 2006; Rey et al. 2009) for these recurrent complications, therefore potentially 70% or more of these women are exposed to this treatment without necessarily needing it. Strategies to better predict who will benefit from such therapy are urgently needed but what does appear clear is that prediction on the basis of presence or absence of a known inherited thrombophilia is not a useful or worthwhile strategy. Kingdom et al attempted to better stratify women by incorporating a range of tests of placental function prior to including women in a pilot randomised trial of unfractionated heparin in women at risk of placental mediated obstetric complications (Kingdom et al. 2011). However, even despite this rigorous screening process, only 12% of women developed pre-eclampsia and 25% of the infants had intrauterine growth restriction in the standard care arm (Kingdom et al. 2011). The high prevalence of placental pathology, however was confirmed with only 5/31 normal placentae (4 in the unfractionated heparin group and one in the standard care group) identified. Although this study was underpowered to determine whether unfractionated heparin is beneficial in this setting, it does highlight the need for improved identification and stratification of patients who may benefit from this somewhat invasive therapy. Furthermore, the choice of unfractionated heparin in this study contrasts with that of previous studies which predominantly use low molecular weight heparins.

11. Conclusions

Inherited thrombophilias are common amongst women of reproductive age. However, we can be reassured by the prospective cohort studies and the meta-analysis of such studies that the majority of asymptomatic women who carry these inherited thrombophilias will not experience adverse pregnancy outcomes. What is less certain is the potential adjuvant role that thrombophilias may play in women at increased risk for other reasons of these complications or in women who are developing these complications. Also of concern is the large number of women who experience adverse pregnancy complications who do not carry a recognisable inherited or acquired thrombophilia. Understanding the precise mechanisms regulating coagulation within the placenta will be an important priority in order to establish the most efficacious therapeutic options for this majority of women experiencing these complications. Only then should the effects of and differences between the variety of available anticoagulants be investigated to ensure that these therapeutic agents are used in the most effective and rational manner to either treat or prevent serious adverse pregnancy events.

12. References

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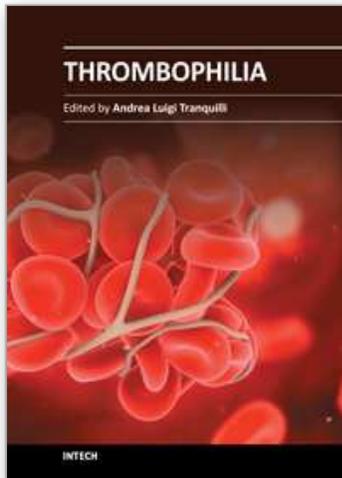
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Thrombophilia

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Thrombophilia(s) is a condition of increased tendency to form blood clots. This condition may be inherited or acquired, and this is why the term is often used in plural. People who have thrombophilia are at greater risk of having thromboembolic complications, such as deep venous thrombosis, pulmonary embolism or cardiovascular complications, like stroke or myocardial infarction, nevertheless those complications are rare and it is possible that those individuals will never encounter clotting problems in their whole life. The enhanced blood coagulability is exacerbated under conditions of prolonged immobility, surgical interventions and most of all during pregnancy and puerperium, and the use of estrogen contraception. This is the reason why many obstetricians-gynecologists became involved in this field aside the hematologists: women are more frequently at risk. The availability of new lab tests for hereditary thrombophilia(s) has opened a new era with reflections on epidemiology, primary healthcare, prevention and prophylaxis, so that thrombophilia is one of the hottest topics in contemporary medicine.

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