Controversias sobre estudios de trombofilia y profilaxis anticoagulante para la prevención de complicaciones recurrentes en el embarazo

Controversies in thrombophilia testing and anticoagulant prophylaxis for the prevention of recurrent pregnancy complications

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Introduction

Thrombophilias are associated with an increased risk of pregnancy-related venous thromboembolism (VTE)[1] and some studies have also suggested that they may also be linked to placental-mediated pregnancy complications[2]. The latter association remains controversial, however. Despite limited data, health care providers and patients have been increasingly intervening with thrombophilia testing and antithrombotic therapy in order to prevent recurrent adverse pregnancy outcomes. This article will review the evidence examining the association between thrombophilia and placental-mediated pregnancy complications, as well that for antithrombotic therapies aimed at preventing these events.

Placental-mediated pregnancy complications

Successful pregnancy outcome is dependent on trophoblast invasion into the uterine vasculature and the development and maintenance of adequate uteroplacental circulation. Adverse pregnancy outcomes such as pregnancy loss, pre-eclampsia, small for gestational age, and placental abruption are not infrequent in the general population and are thought to result from inadequate placentation and placental insufficiency[2,3]. Placental-mediated pregnancy complications are an important cause of maternal, fetal, and neonatal morbidity and mortality[4].

Pregnancy loss complicates 12%-15% of all clinically recognized pregnancies[2,5,6]; however, recurrent loss is much less common. Approximately 5% of

women will suffer two successive losses, while three consecutive miscarriages will affect approximately 1% of women of reproductive age[2,5]. Pre-eclampsia, which is characterized by new onset of hypertension during pregnancy in combination with proteinuria, occurs in 2% to 8% of all pregnancies and is a leading cause of both fetal and maternal morbidity and mortality[6]. Although placental abruption, in which there is the complete or partial separation of the placenta before birth, is relatively uncommon (occurring in 0.5% of gestations), it is a major cause of antepartum hemorrhage and carries a high risk of fetal mortality[7,8]. Small for gestational age may result in long-term effects including developmental delay, poor school performance, and a significantly lower likelihood of academic and professional success[9]. Women with prior placental-mediated pregnancy complications are at increased risk of developing the same, another, or multiple placental-mediated complications in subsequent pregnancies[10].

The association between thrombophilia and pregnancy complications

A number of studies have examined the association between thrombophilia and complications of pregnancy; however, methodologic limitations and heterogeneity in study design and populations, along with the rarity of some thrombophilias (e.g. deficiencies of antithrombin, protein C and protein S) have made it difficult to obtain an accurate assessment of association and risk[11]. Although the most compelling data for a link between thrombophilia and adverse pregnancy outcomes derive from studies in women with antiphospholipid antibodies (APLAs), some research has also suggested an association between adverse pregnancy outcomes (and their severity) and hereditary thrombophilias[1,11].

Hypercoagulability and thrombosis is unlikely to be the sole mechanism by which thrombophilia could potentially increase the risk of pregnancy complications. Animal and *in vitro* studies suggest that controlled activation of the hemostatic system plays an important role in placental and fetal development[12-16]. Although thrombosis of the placental vessels and placental infarction may be observed in patients with placental mediated pregnancy complications, this is not invariably true and these findings may be absent in affected women[17,18]. In addition, placental infarction and thrombosis can be detected in placentae from women with placental-mediated complications who do not have thrombophilia[19,20]. Thus, it is more likely that effects of thrombophilia are not limited to thrombosis and that changes in coagulation and complement activation-mediated trophoblast growth and differentiation, as well as early placentation, may also be involved in the occurrence of these adverse pregnancy outcomes through as yet unknown mechanisms[17,21-24].

Antiphospholipid antibodies and adverse pregnancy outcomes

The definition of obstetric APLA syndrome includes repeated unexplained pregnancy loss before the 10th week of gestation, unexplained loss at or after the 10th week, or premature birth before the 34th week of gestation because of pre-eclampsia in the presence of persistent positivity for APLAs (including lupus anticoagulants, moderate or high titer IgG or IgM isotype anticardiolipin antibodies or antibodies to $ß_2$ glycoprotein I)[25]. Although there is evidence to support an association between APLAs and increased risk of recurrent and late pregnancy loss[1,26-31], the link between these antibodies and other placental mediated pregnancy complications remains controversial (**Table 1**)[31]. Most of the data supportive of an association are derived from small case-control studies with important methodologic limitations, including selection and recall bias; however, methodologically stronger cohort studies are often underpowered to detect associations.

In a systematic review and meta-analysis of 28 studies examining the association between APLAs and placental-mediated complications in women without autoimmune disease[31], lupus anticoagulants were associated with pre-eclampsia (odds ratio (OR) 2.34; 95% confidence interval (CI), 1.18-4.64), intrauterine growth restriction (OR 4.65; 95% CI, 1.29-16.71) and late fetal loss (OR 4.29; 95% CI, 1.34-13.68) amongst case control studies but only with late fetal loss amongst the methodologically stronger cohort studies (OR 10.59; 95% CI, 1.87-59.88) **(Table 1)**. Similarly, while anticardiolipin antibodies were associated with pre-eclampsia (OR 1.52; 95% CI, 1.05-2.20) and late loss (OR 4.29; 95% CI, 1.34-13.68) amongst case-control studies, the only statistically significant association seen in the cohort studies was with fetal loss less than 10 weeks (OR 8.85; 95% CI, 1.84-42.50)[31]. Data for

antibodies ß$_2$ glycoprotein I were limited. Another systematic review that examined recurrent fetal loss in women with APLAs without associated autoimmune disorders reported significant associations with lupus anticoagulant positivity (OR 13.35; 95% CI, 4.49-39.70), as well as elevated IgG (OR 3.57; 95% CI, 2.26-5.65) and IgM (OR 5.61, 95% CI, 1.26-26.03) anticardiolipin antibodies[30]. The relationship between anti-ß$_2$ glycoprotein I antibodies and recurrent loss was not statistically significant; however, again, data were limited and the absence of an association could be due to lack of power. These results, therefore, suggest that APLAs appear to be associated with fetal loss but that the association with other placental-mediated pregnancy complications is inconsistent.

Table 1. Risk of placental mediated pregnancy complications in women with antiphospholipid antibodies but no autoimmune disease

Complication	Lupus anticoagulant OR (95% CI)	Anticardiolipin antibody[1] OR (95% CI)	Anti-ß$_2$glycoprotein I antibody[1] OR (95%CI)
	Cohort studies (n=8)		
Pre-eclampsia[31]	5.2 (0.6-44.6)	1.8 (0.4-8.2)	19.2 (6.3-57.8)
Intrauterine growth restriction[31]	13.9 (0.7-294.1)	2.8 (0.8-10.6)	20.0 (4.6-87.4)
Loss>10 weeks[31]	10.6 (1.9-59.9)	8.9 (1.4-42.5)	23.5 (1.2-455.0)
	Case control studies (n=20)		
Pre-eclampsia[31]	2.3 (1.2-4.6)	1.5 (1.1-2.2)	9.6 (0.3-1.0)[3]
Intrauterine growth restriction[31]	4.7 (1.3-16.7)	2.0 (0.2-20.0)	Not available
Loss >10 weeks[31]	4.7 (1.1-20.8)	4.3 (1.3-13.7)	2.8 (0.3-28.8)
	Case control studies		
Recurrent loss >24 weeks[30]	7 studies 13.4 (4.5-39.7)	ACA IgG (10 studies) 3.6 (2.3-5.9) ACA IgM (4 studies 5.6 (1.3-25.0)	4 studies 2.1 (0.7-6.5)

1IgG or IgM; insufficient data to restrict analysis to moderate/high titer antibodies
Data are from references 30 and 31.

Inherited thrombophilias and adverse pregnancy outcomes

There has been substantial interest in examining whether heritable thrombophilias are also associated with adverse pregnancy outcomes. In a large meta-analysis of predominantly case control studies that examined the association between thrombophilia and various pregnancy complications in 7,167 women, the factor V Leiden and prothrombin gene mutations were associated with early (first or second trimester) and early recurrent loss, as well as pre-eclampsia and placental abruption, although wide confidence intervals around the point estimates of some associations indicate uncertainty of the findings[1]. Statistically significant associations were also seen between late loss after 24 weeks and the factor V Leiden mutation, the prothrombin gene mutation and protein S deficiency[1], although the latter positive association was based on a total of 15 patients with this thrombophilia.

These results are in contrast to those of a meta-analysis limited to methodologically stronger cohort studies[32]. In this meta-analysis of 11 prospective cohort studies with data from over 25,000 women, the pooled risk ratio (RR) for pregnancy loss in women with factor V Leiden (absolute risk 3.6%) compared to women without this mutation (absolute risk 2.9%) was minimally elevated at 1.79 (95% CI, 1.06–3.03), suggesting a weak association. However, in this meta-analysis there was no statistically

significant association between the presence of factor V Leiden mutation and pre-eclampsia (RR 1.21; 95% CI, 0.92–1.61), small for gestation age (RR 1.03; 95% CI, 0.85–1.24) or placental abruption (RR 1.85; 95% CI, 0.62-5.43). The results also failed to demonstrate a statistically significant association between the prothrombin mutation and either pre-eclampsia (RR 1.15; 95% CI, 0.70–1.89), small for gestational age (RR 1.11; 95% CI, 0.80–1.54), placental abruption (RR 2.19, 05% CI, 0.09-51.82) or pregnancy loss (RR 1.67; 95% CI, 0.42–6.70). Therefore, this meta-analysis suggests that women with the factor V Leiden or prothrombin gene mutations are not at significantly increased risk of these complications. Although there is no clear association between these thrombophilias and unselected pre-eclampsia, placental abruption and small for gestational age, an association with severe phenotypes of these complications remains possible. There remains a lack of good data on risk of pregnancy complications in women with less common thrombophilias, including deficiencies of antithrombin, protein C, or protein S.

Use of antithrombotic therapy to prevent pregnancy complications

Highly effective strategies to prevent recurrent placental-mediated pregnancy complications are lacking. Anticoagulants and aspirin are commonly utilized therapeutic agents used to prevent pregnancy complications in thrombophilic women. In addition to reducing the risk of placental thrombosis through an antithrombotic effect, heparins also have immunomodulatory effects (e.g. anti-inflammatory, anti-complement) that could have a positive impact on women at risk of placental-mediated pregnancy complications[33-37].

The use of antithrombotic therapy during pregnancy requires consideration of potential risks to the fetus, as well as to the mother. Potential fetal complications of maternal antithrombotic therapy include teratogenicity, bleeding and pregnancy loss. Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) do not cross the placenta[38-40] and, therefore, are safe for the fetus[41-44]. LMWH has a better maternal safety profile than UFH and is the preferred anticoagulant for use in pregnancy[45,46-48]. Significant bleeding in pregnant women receiving LMWH is uncommon[44,46,48]. Although heparin-induced thrombocytopenia (HIT) can occur with LMWH therapy[49], reported cases during pregnancy are rare[46]. LMWHs also have a lower risk of osteoporosis than UFH[50] and it appears that bone loss with the use of prophylactic LMWH during pregnancy is not different from normal physiologic losses during pregnancy[51-53]. Adverse skin reactions to LMWH, including bruising, urticarial rashes, well-circumscribed erythematous lesions (due to a delayed type IV hypersensitivity reaction), skin necrosis (often due to vasculitis) and HIT, have a reported incidence during pregnancy that ranges from 1.8% to 29%[46,54,55]. Although most LMWH-induced skin lesions are benign, the diagnosis of HIT should be excluded.

Unlike UFH and LMWH, aspirin does cross the placenta. Therapy during the second and third trimester has not been shown to increase the risk of pregnancy loss, neonatal hemorrhage or growth restriction[56]. However, aspirin use during the first trimester has been reported to slightly increase the risk of gastroschisis (OR, 2.37; 95% CI, 1.44-3.88)[57], a rare anomaly that occurs in three to six of every 100,000 births in which the intestines herniate through a congenital defect in the abdominal wall on one side of the umbilical cord. That said, the reliability of this risk estimate has been questioned because of use of other drugs, the type of control subjects selected, and failure to definitively confirm the diagnosis in all patients could have biased the results. An increased risk of miscarriage with aspirin use was noted in one population-based study[58]; however, the number of aspirin users was small, aspirin doses were unknown and users may have had conditions associated with an increased risk of pregnancy loss[59]. Thus, there is no clear evidence of significant risk of harm to the fetus with aspirin therapy.

Preventing recurrent pregnancy loss

Use of antithrombotic therapy in women without antiphospholipid antibodies

Table 2 summarizes the results of randomized trials examining the impact of LMWH (with or without concomitant aspirin) on pregnancy loss in women with at least two prior miscarriages and no evidence of antiphospholipid antibodies[60-67]. Although two randomized studies of women with three or more losses reported a substantial benefit with LMWH[60,61],

both of these studies had important methodologic limitations, including a lack of blinding[60] or uncertain blinding[61], single center status[60,61], relatively high rates of loss to follow-up[60,61], lack of prospective trial registration[60,61] and an unexpectedly low live birth rate in the placebo arm[61]. These findings are in contrast to those from multiple more robust studies[62-67] that suggest that LMWH (with or without aspirin) does not reduce subsequent pregnancy loss in this population of women.

Table 2. Prevention of unexplained recurrent pregnancy loss in women without antiphospholipid antibodies: results of randomized trials with either negative screening for hereditary thrombophilia or no selection for hereditary thrombophilia status.

Study	Study characteristics	Inclusion criteria for pregnancy loss	Live birth (According to study intervention) n/N (%)
Badawy et al.[60]	• N=350; 340 available for analysis • Single center study • Required negative screening for factor V Leiden, prothrombin gene mutation, and deficiencies of protein C, protein S and antithrombin	≥3 consecutive 1st trimester losses	Enoxaparin 20 mg subcutaneously daily 161/170 (94.7%) Folic acid 151/170 (88.8%) P=0.04
Fawzy et al.[61]	• N=170; 160 available for analysis • Single center study • No required screening for hereditary thrombophilia	≥3 consecutive 1st or 2nd trimester losses (<24 weeks gestation)	Enoxaparin 20 mg subcutaneously daily 46/57 (80.7%) Prednisone + progesterone for the 1st 12 weeks; aspirin for first 34 weeks 45/53 (84.9%) Placebo 24/50 (48.0%) P vs. placebo <0.05
Dolitzky et al.[62]	• N=107; 104 available for analysis • Multicenter study • Required negative screening for factor V Leiden, prothrombin gene mutation, homozygosity of MTHFR C677T and deficiencies of protein C, protein S and antithrombin	≥3 consecutive 1st trimester losses or ≥2 2nd trimester losses	Enoxaparin 40 mg subcutaneously daily 44/54 (81.5%) 100 mg Aspirin orally daily 42/50 (84.0)% P=NS
Kaandorp et al.[63]	• N=364; 299 available for pregnancy analysis • Multicenter study • Required normal fasting homocysteine; testing for hereditary thrombophilia performed but negative results not required	≥2 losses <20 weeks gestation	Nadroparin 2850 IU subcutaneously daily + aspirin 80 mg orally daily 67/97 (69.1%) Aspirin 80 mg orally daily 61/99 (61.6%) Placebo 69/103 (67.0%) P=0.52

Clark et al.[64]	• N=294; 283 available for analysis • Multicenter study • No previously known hereditary thrombophilia; testing for hereditary thrombophilia performed but results not released until study complete	≥2 losses <24 weeks gestation	Enoxaparin 40 mg subcutaneously daily + aspirin 75 mg orally daily + intense surveillance 115/147 (78.0%) Intense surveillance 118/147 (80.3%) P=NS
Schleussner et al.[65]	• N=449; 426 available for analysis • Multicenter study • Testing for thrombophilia performed but only women homozygous for factor V Leiden or prothrombin gene mutations were excluded	≥2 consecutive early losses or 1 late loss	Dalteparin 5000 IU subcutaneously daily + multivitamins 185/215 (86.0%) Multivitamins 183/211 (86.7%) P=NS
Pasquier et al.[66]	• M=258; 256 available for analysis • Multicenter study • Required negative thrombophilia screen for factor V Leiden, prothrombin gene mutation, and deficiencies of protein C, protein S, and antithrombin	≥2 consecutive losses <15 weeks	Enoxaparin 40 mg subcutaneously daily 92/138 (66.6%) Placebo 86/118 (72.9%) P=0.34
Visser et al.[67]	• N=207 • Multicenter study • Screening for hereditary thrombophilia was performed but only women with combined thrombophilias, antithrombin deficiency, or homozygosity for factor V Leiden were not included	≥3 consecutive losses <13 weeks; ≥2 second trimester losses; or 1 third trimester loss combined with 1 first trimester loss	Enoxaparin 40 mg subcutaneously daily + aspirin 100 mg daily 41/63 (65.1%) Enoxaparin 40 mg subcutaneously daily + oral placebo 48/68 (70.6%) Aspirin 100 mg daily 46/76 (60.5%) P=NS

Use of antithrombotic therapy in women with antiphospholipid antibodies

Studies examining the impact of antithrombotic therapy in women with recurrent pregnancy loss are heterogeneous, with different inclusion criteria, laboratory criteria for diagnosis of APLA, and timing of therapy initiation. None of the studies enrolled women on the basis of antibodies to $ß_2$ glycoprotein I. In a systematic review[29] that summarized the data from 13 randomized or quasi-randomized trials of pregnant women with APLAs and a history of at least two unexplained pregnancy losses, only UFH combined with aspirin (two trials; n=150) reduced the incidence of pregnancy loss (RR 0.46; 95% CI, 0.29-0.71 when compared with aspirin alone)[68,69]. A subsequent third study reported consistent findings (n=72)[70]. Higher dose UFH was not more effective than low-dose UFH[29,71]. On its own, aspirin did not significantly reduce the risk of pregnancy loss compared with usual care[72] or placebo[73,74] (RR 1.05; 95% CI, 0.66-1.68), although given the 95% CI, a small benefit or harm cannot be excluded. LMWH combined with aspirin also failed to significantly affect the likelihood of an unsuccessful pregnancy compared with aspirin alone[29,75]. However, a subsequent meta-analysis that combined data from randomized trials testing the efficacy of heparin (either UFH or LMWH) and aspirin versus aspirin alone in patients with APLAs and recurrent pregnancy loss[76] that included an additional LMWH study pu-

blished since the first systematic review[77], reported a significantly higher frequency of live births in the aspirin and heparin group (74.3%) than in those randomized to aspirin alone (55.8%) (RR: 1.3; 95% CI, 1.0-1.7)[76]. However, when studies that used LMWH and UFH were analyzed separately, only a trend toward higher birth rate in patients receiving aspirin and LMWH was noted (RR: 1.1; 95% CI, 0.9-1.3). Although no studies comparing LMWH and UFH were included in either of the previous meta-analyses, the results of two small pilot studies suggest that the combination of LMWH and aspirin might at least be equivalent to UFH and aspirin in preventing recurrent pregnancy loss (RR for pregnancy loss in women receiving LMWH vs. UFH: 0.44; 95% CI, 0.17-1.00[78] and 0.8; 95% CI, 0.26-2.48)[79]. Therefore, for women who fulfil the laboratory criteria for APLA syndrome and meet the clinical APLA syndrome criteria based on a history of at least two pregnancy losses, antepartum administration of prophylactic- or intermediate-dose UFH or prophylactic LMWH combined with low dose aspirin, 75-100 mg/day is generally recommended, although the available data has important limitations and is quite heterogenous[45]. Most centres now use LMWH in this setting because it is more convenient and safer than UFH; however, further studies examining any differential impact of LMWH and UFH in this setting would be welcome. Finally, although the strategy of aspirin and LMWH is often extrapolated to women with antiphospholipid antibodies and a single pregnancy loss; it is important to recognize that supportive data are absent.

Use of antithrombotic therapy in women with hereditary thrombophilia

The positive effects associated with antithrombotic therapy in women with antiphospholipid antibodies and recurrent loss encouraged investigators to explore similar regimens in women with a history of pregnancy loss and hereditary thrombophilias. The earliest such randomized trial enrolled 160 women with one previous pregnancy loss after 10 weeks and either the factor V mutation, the prothrombin gene mutation or protein S deficiency and did report a higher live birth rate in women assigned to prophylactic-dose LMWH (enoxaparin) than in those allocated to low-dose aspirin (86% versus 29%, respectively; OR 15.5; 95% CI, 7-34; p<0.001)[80]. These results and the absence of other effective interventions encouraged early widespread use of LMWH for prevention of recurrent loss in thrombophilic women. However, interpretation of this study was complicated by important methodologic limitations and a higher than expected failure rate in the aspirin arm[81-84]. For example, a subsequent cohort study found the live birth rate of subsequent pregnancies after a single pregnancy loss at or later than 12 weeks gestation in carriers of factor V Leiden or the prothrombin mutation was, without intervention, 68% (95% CI, 46–85%)[85].

A recently published meta-analysis of this and seven other subsequent randomized controlled trials comparing LMWH (with or without aspirin) versus no LMWH (aspirin, placebo, no treatment) in 483 women with inherited thrombophilia and prior late (at or after 10 weeks) or recurrent early (before10 weeks) pregnancy loss found no significant difference in live birth rates with the use of LMWH when compared with no LMWH or aspirin alone (RR 0.81; 95% CI, 0.55-1.19; p=0.28), although heterogeneity was high[86]. If only multicenter studies were included, there was again no difference in live birth rates between groups (RR 1.04; 95% CI, 0.93-1.15; p=0.52) but with reduced heterogeneity. Subgroup analysis also showed no significant difference between LMWH vs. no LMWH in women with late loss (five trials with 308 women, RR 0.81; 95% CI, 0.38-1.72; p=0.48) and in those with early recurrent loss only (two trials with 66 women, RR 0.97; 95% CI, 0.80-1.19; p=0.79). These data suggest that prophylactic-dose LMWH (with or without aspirin) does not reduce the risk of pregnancy loss in women with inherited thrombophilia and prior late or recurrent early loss, compared with treatment or aspirin alone. However, the small number of women with a prior history of early recurrent loss and with less common thrombophilias means that a beneficial effect of LMWH in these subgroups cannot be excluded. The ongoing ALIFE2 randomized trial (Netherlands Trial Registration Identifier: NTR3361) that is evaluating LMWH in women inherited thrombophilia and a history of two or more miscarriages and/or intrauterine fetal death should provide more definitive information.

Preventing other placental-mediated pregnancy complications

Antithrombotic therapy in women without known thrombophilias

Meta-analyses report that aspirin use in pregnancies at increased risk of pre-eclampsia results in modest reductions in the risks of pre-eclampsia, intrauterine grown restriction, pre-eclampsia, and pre-term birth[6,45,56] and guidelines recommend initiating low-dose aspirin from 12 weeks in at risk women[45,87,88]. However, what constitutes high risk for pre-eclampsia is not strictly or consistently defined.

There are limited data on the impact of UFH or LMWH in the prevention of placental-mediated pregnancy complications other than recurrent loss in women without thrombophilia. In a six center pilot study that randomized 110 women with negative thrombophilia screening and one or more of prior severe pre-eclampsia requiring delivery prior to 34 6/7 weeks, placental abruption necessitating delivery prior to 34 6/7 weeks or resulting in fetal death after 19 6/7 weeks, unexplained birth weight less than the 5th percentile, unexplained pregnancy loss after 19 6/7 weeks or two prior unexplained losses between 12 and 19 6/7 weeks in the immediate prior pregnancy to dalteparin 5000 IU subcutaneously per day (adjusted to 4000 IU for weight less than 60 kg and 6000 IU for weight greater than 90 kg) or no prophylaxis; women randomized to dalteparin had a lower risk of the primary composite outcome of severe pre-eclampsia, birth weight less than the 5th percentile, major placental abruption or fetal death after 20 weeks gestation (5.5% versus 23.6%; p=0.016; adjusted OR 0.15; 95% CI, 0.03-0.70) [89]. However, because the trial was stopped early (which is known to exaggerate treatment effects) and the interim analysis did not reach the pre-planned level of statistical significance (p<0.005), these results must be interpreted with caution. Another randomized study examined the effect of LMWH (enoxaparin 4000 IU per day) to no drug treatment in 224 pregnant women with a prior history of severe pre-eclampsia but no pregnancy loss who tested negative for APLAs[90]. Those randomized to LMWH were less likely to develop one or more of pre-eclampsia, placental abruption, small for gestational age less than or equal to the 5th percentile, or fetal loss after 20 weeks than those assigned to no enoxaparin (8.9% versus 25.0%; HR 0.32, 95% CI, 0.16-0.66; p=0.002). A similarly designed study of 160 women with prior placental abruption but no fetal loss who tested negative for the presence of antiphospholipid antibodies[91] also reported that randomization to LMWH was associated with a reduction in the primary composite outcome of pre-eclampsia, small for gestational age less than the 5th percentile, confirmed placental abruption or fetal demise after 20 weeks from 31.3% to 12.5% (adjusted hazard ratio (HR) 0.37; 95% CI, 0.18-0.77; p=0.11). Although promising, the results of these latter two studies need to be interpreted as preliminary given both were single center non-registered pilot studies. In contrast, a well-designed, multicenter, prospective randomized trial that compared recurrence of late placental-mediated pregnancy complications in 135 women with a previous history of pre-eclampsia, HELLP (hemolysis elevated liver enzymes, and low platelets), intrauterine fetal death, fetal growth restriction or placental abruption, found no difference in those randomized to medical surveillance alone compared with those assigned open label prophylactic LMWH (nadroparin 3800 units subcutaneously per day) in addition to medical surveillance (18% versus 21%, p=0.76)[92].

A meta-analysis of six randomized controlled trials (only two of which excluded thrombophilic participants) with 848 pregnant with prior placental-mediated complications found those given prophylactic LMWH were less likely to develop the composite outcome of pre-eclampsia, birth of a small for gestational age baby (<10th percentile), placental abruption or pregnancy loss before 20 weeks than those not given LMWH (18.7% versus 42.9%, respectively; RR 0.32-0.86; p=0.01)[10]. In secondary analyses, LMWH also appeared to reduce the risk of individual outcomes including pre-eclampsia, severe or early pre-eclampsia, small for gestational age (<10th percentile and <5th percentile), and pre-mature delivery (<37 weeks and <34 weeks); as well as a composite outcome of more severe placental-mediated pregnancy complications. No statistically significant risk reduction was demonstrated for placental abruption or pregnancy loss <20 weeks in women given LMWH. Larger risk reductions were seen for more severe pregnancy complications, leading the authors to hypothesize that LMWH might most beneficial in preventing recurrent severe pla-

cental-mediated complications. This study-level meta-analysis was limited, however, by high clinical and statistical heterogeneity, likely due to inclusion of women with disparate prior pregnancy complications and dissimilar study design (e.g. single versus multicenter) and it is noteworthy that the highest quality trials suggested no treatment effect.

An individual patient data meta-analysis was subsequently undertaken given concerns about significant heterogeneity in the above study level meta-analysis[93]. When data from 1049 women in nine trials were analyzed, LMWH did not significantly reduce the risk of recurrent placental-mediated pregnancy complications compared to no LMWH (13.1% versus 20.5%, respectively; p=0.1). Again, significant heterogeneity was noted between single center and multicenter studies. Whereas in single center studies, LMWH was beneficial regardless of type or severity of prior placental-mediated pregnancy complication, in multicenter trials, prophylactic LMWH was associated with a reduction in the primary outcome in women with prior abruption (p<0.01) but none of the other subgroups. This finding, however, requires confirmation in future multi-center trials prior to adoption into routine clinical practice.

Antithrombotic therapy in women with thrombophlia

There are no published placebo-controlled randomized studies assessing the efficacy of antithrombotic therapy in preventing preeclampsia, placental abruption or small for gestational age in women with APLAs. The data regarding the use of aspirin and UFH or LMWH in the prevention of recurrent early pregnancy loss is often extrapolated to women with APLAs and a small for gestational age or pre-eclampsia. However, it is important to note that supportive data is lacking and use of the above regimens in these patients may result in overtreatment, as an intervention that prevents fetal loss may not prevent other complications.

In one multicenter randomized trial of 139 women, the combination of prophylactic LMWH (dalteparin) and low-dose aspirin started before the 12th week of gestation reduced the risk of recurrent early onset hypertensive disorder of pregnancy (i.e. pre-eclampsia, HELLP -hemolysis, elevated liver enzymes, and low platelets- or eclampsia) in women with inherited thrombophilia and a prior history of early onset hypertensive disorder of pregnancy or small for gestational age infant (less than 10th percentile) compared with low-dose aspirin alone (0% vs. 8.7%; 95% CI for risk difference 1.9%-15.5%; p=0.012)[94]. However, the overall frequency of recurrent hypertensive disorder of pregnancy irrespective of gestational age (a second primary outcome) was not different between the treatment arms.

The Thrombophilia in Pregnancy Prophylaxis Study (TIPPS) was a 26 center randomized trial that compared prophylactic dose LMWH (dalteparin 5000 IU once daily subcutaneously until 20 weeks gestation followed by 5000 IU twice daily) with no antepartum LMWH in 292 pregnant women with thrombophilia who were at increased risk of placental-mediated pregnancy complications, venous thromboembolism or both[95]. Most women carried either the factor V Leiden mutation (60%) or prothrombin gene mutation (22%). Persistent positivity for APLAs was confirmed in 8% of women. Enrollment was based on a history of one or more prior placental-mediated pregnancy complications in 51% of women. One or more components of the primary composite outcome (pregnancy loss, severe or early onset pre-eclampsia, birth of a small for gestational age infant [<10th percentile], symptomatic proximal deep vein thrombosis or pulmonary embolism, or sudden maternal death) occurred in 17.1% of those randomized to dalteparin and in 18.9% of those who did not receive dalteparin (OR 0.89; 95% CI, 0.48-1.63; p=0.70). None of the component outcomes of the primary composite outcome measure differed between the two groups and pre-specified subgroup analyses showed no significant difference between groups according to thrombophilia, previous pregnancy complications, previous venous thromboembolic events or risk factors, or aspirin use; although it should be noted that the study was not adequately powered to detect such differences. More minor bleeding events occurred in the dalteparin group (19.6% compared with 9.2% in those not receiving LMWH).

In the individual patient meta-analysis described above that examined the impact of prophylactic LMWH on the risk of recurrent placental-mediated pregnancy complications, 41.9% of the study sample was diagnosed with thrombophilia[93]. Although a beneficial effect of LMWH in thrombophilic women was noted in single center studies; this was not the case in multicenter studies.

Recommendations

Antithrombotic therapy for prevention of placental-mediated pregnancy complications

In the absence of good clinical evidence from high quality studies showing benefit, it is difficult to justify prescribing UFH or LMWH to women with a history of pregnancy loss in the absence of APLAs or to women with a history of other placental-mediated pregnancy complications, regardless of thrombophilia status. Although prophylactic dose LMWH has a favorable safety profile with respect to major bleeding, HIT, and heparin-associated osteoporosis, it is costly, requires burdensome and uncomfortable subcutaneous injections, is associated with localized skin reactions, and its use in pregnancy often results in induction of delivery and/or withholding of epidural analgesia.

Thrombophilia testing

In recent years, laboratory testing for thrombophilia has been performed on increasing numbers of patients. Screening is only useful when results will affect management decisions and when the potential benefits justify the potential drawbacks of testing, which include negative psychological effects, difficulties with insurability, bleeding risks with primary prophylaxis, additional medical expenditures, false reassurance from a negative test result, and the effect of incorporating this information into important life decisions including pregnancy, surgery, and contraceptive choice[96]. Screening should not be performed when treatment is indicated for other risk factors or there is no data to support intervention.

Given the above, the rationale for and potential benefits and drawbacks of any thrombophilia screening should be discussed with the patient before testing is undertaken. Although screening for APLAs is recommended in women with a history of recurrent loss[45], in the absence of evidence that women with APLA and a single late pregnancy loss, preeclampsia, or fetal growth restriction benefit from treatment with antithrombotics, it is unclear whether women with these latter complications should also be screened for APLAs. For similar reasons, it is suggested not to screen for inherited thrombophilia in women with a history of pregnancy complications, including pregnancy loss[45].

Declaración de conflictos de interés:
El autor declara que no posee conflictos de interés

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