Risk of pregnancy-related venous thromboembolism and obstetrical complications in women with inherited type I antithrombin deficiency: a retrospective, single-centre, cohort study

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Summary

Background Inherited quantitative (type I) deficiency of plasma antithrombin is associated with a high risk of venous thromboembolism, which further increases in pregnancy. Inherited thrombophilia also increases the risk of obstetrical complications, but data on maternal and fetal outcomes in women with antithrombin deficiency are scarce. The aim of this study was to evaluate the risk of pregnancy-associated venous thromboembolism and obstetrical complications in women with type I antithrombin deficiency.

Methods In this single-centre, retrospective cohort study, women who had been referred to our Hemophilia and Thrombosis Centre, Milan, Italy for a thrombophilia work-up from Jan 1, 1980, to Jan 1, 2018, with type I antithrombin deficiency and who had had at least one pregnancy were included. Women with type II anthithrombin deficiency were excluded from the study. Data on pregnancy-associated venous thromboembolism, pregnancy outcomes, and the use of low-molecular-weight heparin (LMWH) were collected to evaluate the risk of pregnancy-associated venous thromboembolism and obstetrical complications with or without use of LMWH.

Findings 126 women had been referred to the hospital, of whom 88 (70%) had had at least one pregnancy. Eight were excluded because of referral for venous thromboembolism during pregnancy or the puerperium, resulting in 80 (63%)women evaluated for the risk of venous thromboembolism. One woman was excluded because of referral for obstetrical complications, resulting in 87 (69%) evaluated for risk of obstetrical complications. We observed three events of venous thromboembolism in 43 pregnancies in women treated with LMWH (7·0%, 95% CI 1·8–17·8), and 17 events in 146 pregnancies in women who did not receive LMWH (11·6%, 7·2–17·6; relative risk [RR] 0·6, 95% CI 0·2–1·9; p=0·57). The risk of venous thromboembolism without LMWH was 5·4% (95% CI 0·9–16·7) in women with a negative family history of venous thromboembolism, and 11·8% (6·4–19·6) in those with a positive family history of venous thromboembolism. Of the 87 women evaluated for the risk of obstetrical complications, miscarriages occurred in 6 (13%) of 45 pregnant women treated with LMWH and 32 (20%) of 161 women who did not receive LMWH (terminations excluded). Late obstetrical complications occurred in 11 (24%) of women treated with LMWH and nine (6%) in those who did not receive LMWH (RR 4·4, 95% CI 1·9–9·9; p=0·0006).

Interpretation Our results confirm that women with type I antithrombin deficiency have a high risk of first or recurrent venous thromboembolism during pregnancy. The risk of venous thromboembolism is highest in women with a positive family history of the condition, but still relevant in those with a negative family history, suggesting that LMWH prophylaxis should also be considered in these patients.

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Introduction

Antithrombin is a natural anticoagulant protein; it is a serine protease inhibitor that inactivates thrombin (activated coagulation factor II) and the activated forms of coagulation factors VII, X, IX, XI, and XII. Its enzymatic activity is enhanced by heparin.[1] Antithrombin deficiency is a rare but severe cause of inherited thrombophilia, with a prevalence in the general population ranging from 1:500 to 1:5000. Quantitative (type I) deficiency is characterised by low functional and antigenic plasma concentration of antithrombin and is associated with a 20-fold increased risk of venous thromboembolism.[2] The qualitative (type II) deficiency, characterised by low functional and normal antigenic antithrombin concentration, is rarer than type I and its heterozygous form, and is usually associated with a smaller risk of venous thromboembolism.[3,4] During pregnancy, procoagulant changes

Research in context

Evidence before this study

Quantitative antithrombin deficiency is a rare coagulation abnormality associated with a high risk of venous thromboembolism, which further increases at certain stages of life, including during pregnancy. Low molecular weight heparin (LMWH) is the anticoagulant of choice for the prevention and treatment of pregnancy-associated venous thromboembolism and is also considered (with less robust evidence) to be effective in preventing obstetrical complications. We searched PubMed on May 3, 2019, for existing guidelines published by various scientific societies and screened their relative references. Additionally, we searched PubMed on Aug 20, 2019, for relevant scientific literature using the search terms "anthithrombin deficiency" OR "antithrombin" OR "thrombophilia" OR "inherited thrombophilia" AND "pregnancy" OR "puerperium" OR "postpartum" AND "antithrombotic treatment" OR "prophylaxis" OR "antithrombotic treatment" in all fields without restricting the search by date. The searches were restricted to publications in the English language. Because of the rarity of antithrombin deficiency, robust observational studies and randomised trials are scarce, and guidance on the management of antithrombin deficiency in pregnant women is limited. On the basis of this gap in knowledge, current guidelines of the American College of Obstetricians, the Society of Obstetricians and Gynecologists, and the American College of Chest Physicians offer recommendations based on low-grade evidence, which are sometimes controversial. The most recent guidelines of the American Society of Hematology (2018) suggest (with a very low certainty of evidence) primary LMWH prophylaxis in pregnant women with antithrombin deficiency only if they have a positive family history of venous thromboembolism.

Added value of this study

To our knowledge, this is the largest cohort of pregnant women with antithrombin deficiency that has been reported to date, and adds information to the already available evidence on pregnancy-associated risk of venous thromboembolism. Our data suggest that women with antithrombin deficiency have a high risk of venous thromboembolism during pregnancy and puerperium, which is highest in those with a positive family history of the condition but, in contrast to the information reported in some guidelines, is still relevant in those with a negative family history. Additionally, we observed for the first time that antithrombin-deficient women have an increased risk of late placenta-mediated obstetrical complications, despite the use of LMWH prophylaxis.

Implications of all the available evidence

LMWH nearly halved the risk of pregnancy-associated venous thromboembolism in women with antithrombin deficiency, but a third of those receiving therapeutic doses had a recurrence. Alternative approaches, such as higher LMWH doses, monitoring anti-factor Xa activity, or the use of antithrombin concentrates should be considered in future studies. Our results support routine primary LMWH prophylaxis for prevention of pregnancy-associated venous thromboembolism, not only in women with a positive family history of venous thromboembolism, but also in those with a negative family history of the condition. If the increased risk of late obstetrical complications in women receiving LMWH is confirmed, it should be taken into account when prescribing antithrombotic prophylaxis in women with an antithrombin deficiency. Future studies are warranted to elucidate the pathogenesis of late obstetrical complications to identify women who could benefit from LMWH without harm.

in the haemostatic balance are likely to further increase the risk of venous thromboembolism in women with inherited thrombophilia. Family studies of women with antithrombin deficiency showed an overall absolute risk of pregnancy-related venous thromboembolism of 16·6% (95% CI 0·0–45·1%), varying between 7·3% (1·8–15·6%) antepartum and 11·1% (3·7–21·0%) postpartum.[5] Women with thrombophilia might also have an increased risk of obstetrical complications owing to the impairment of the placental circulation.[6–9]

Low molecular weight heparin (LMWH) is the anticoagulant of choice in pregnancy for the prevention and treatment of venous thromboembolism and is also considered (with less robust evidence) to be useful in preventing obstetrical complications.[10,11] Although several studies have assessed the risk of pregnancy-related venous thromboembolism and obstetrical complications in women with the most common thrombophilia abnormalities—ie, the G1691A substitution in the factor V gene (factor V Leiden) and the G20210A substitution in the prothrombin gene[12]—data on women with a severe form of thrombophilia as inherited antithrombin deficiency are scarce. Different guidelines offer controversial recommendations for the management of antithrombin deficiency with low-grade evidence.[11,13–15] For example, the guidelines of the American Society of Hematology suggest primary antepartum LMWH prophylaxis, but only when a positive family history of venous thromboembolism is present.[16] Moreover, the optimal dosing of LMWH prophylaxis in pregnancy is not established and is particularly relevant for antithrombin-deficient women, considering that antithrombin is a cofactor of heparin for the inhibition of activated coagulation factors X and II. The aims of this study were to evaluate the risk of pregnancy-related venous thromboembolism, and assess obstetrical outcomes and the efficacy of LMWH in a large cohort of women diagnosed with inherited type I antithrombin deficiency.

Methods

Study design and participants

This single-centre, retrospective cohort study was done at the Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy. We included women who were referred to the Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre between Jan 1, 1980, and Jan 1, 2018, for a thrombophilia work-up, diagnosed with type I antithrombin deficiency, and who had remained pregnant at least once in their life. First-degree and second-degree relatives of patients diagnosed with antithrombin deficiency were invited to the centre for antithrombin testing, and women with type I antithrombin deficiency who met the inclusion criteria were also included. Women with type II antithrombin deficiency were excluded to reduce the heterogeneity of the cohort and also because we do not perform molecular characterisation routinely.

The study was approved by the Ethics Committee of our Hospital (Milano Area 2) and written informed consent was obtained by study participants.

Procedures

At the time of the first referral, data on previous thrombotic events, family history of venous thromboembolism, obstetrical history, and therapies during pregnancy and puerperium (defined as the 6 weeks after delivery) were collected from medical records. All women were invited to contact us for symptoms suggestive of thrombosis at any site on the body, and women of childbearing age were also invited to return at the beginning of a new pregnancy to be prescribed LMWH to be started during the first gestational weeks. A letter for the general practitioner and the gynecologist containing contact information of the centre and the invitation to refer the patient to the centre at the beginning of a future pregnancy, was given to all women of childbearing age. Additionally, women who did not regularly visit the centre were contacted by yearly telephone calls. Finally, all the women included in this study were invited to the Center between July and October, 2018, if their last visit or contact was before January, 2018, for their clinical records to beupdated.

Women who had become pregnant before the diagnosis of antithrombin deficiency did not receive antithrombotic prophylaxis, whereas those who became pregnant after the diagnosis received LMWH started at the time of the first obstetric ultrasound at 7–10 gestational weeks. Women without a personal history of venous thromboembolism (asymptomatic) or those with previous venous thromboembolism (symptomatic) who had discontinued anticoagulant therapy before pregnancy onset received intermediate prophylactic doses of LMWH (40 mg once daily [od] or 60 mg od if bodyweight >60 kg). Women receiving oral anticoagulant therapy or those asymptomatic but considered at a particularly high thrombotic risk (eg, with thrombophilia abnormalities other than antithrombin deficiency) received therapeutic doses of LMWH (bodyweight-adjusted dose twice per day). All women had the prescription so that they could continue LMWH prophylaxis during the puerperium and, if on anticoagulant therapy, to resume it soon after delivery at obstetrician discretion. There is little guidance on the use of antithrombin concentrates in pregnancy,[17] at delivery, and during puerperium. There is also great uncertainty regarding which women might benefit from antithrombin concentrate and when to administer the concentrate. For these reasons, and considering the uncertainty of the cost–benefit ratio, we do not routinely give antithrombin concentrate, as stated in a consensus paper of experts of the Italian Society for Haemostasis and Thrombosis.[18]

Blood samples for thrombophilia testing were collected and tested according to laboratory methods listed in the appendix (p 1).

See Online for appendix

Venous thromboembolism included proximal deep vein thrombosis of the limbs and pulmonary embolism and thrombosis of the cerebral, splanchnic, and superficial of the lower limbs (any extension). Only objectively diagnosed venous thromboembolism events that occurred during pregnancy or puerperium were recorded (eg, compression ultrasound or venography for deep vein thrombosis or superficial vein thrombosis, lung V/Q scan or CT angiography for pulmonary embolism, CT angiography or MRI for cerebral or abdominal vein thrombosis). A positive family history of venous thromboembolism was defined as when at least one first-degree or second-degree relative had presented with the condition. Pregnancy outcomes included full-term pregnancies, miscarriages, late obstetrical complications (preterm delivery; small for gestational age newborns; preeclampsia, eclampsia, HELLP syndrome; placental abruption, stillbirth), and terminations (voluntary abortions) according to their definitions (appendix p 2).

Women were encouraged to come to our hospital at the time of delivery, but they were free to choose the obstetrician and hospital. We provided a letter with suggestions on antepartum, peripartum, and postpartum management and also offered a 24 h on-call assistance.

Statistical analysis

Median and IQRs described continuous variables. Counts and percentages or mean and SDs were used for demographic and discrete variables. Each pregnancy was considered a separate episode, because the same woman might have had more than one pregnancy with or without venous thromboembolism during the study period. The risk of venous thromboembolism during pregnancy or puerperium, and pregnancy outcomes, were expressed as risk proportions with 95% CIs. To evaluate the effect of LMWH in puerperium, the risk of venous thromboembolism was calculated excluding

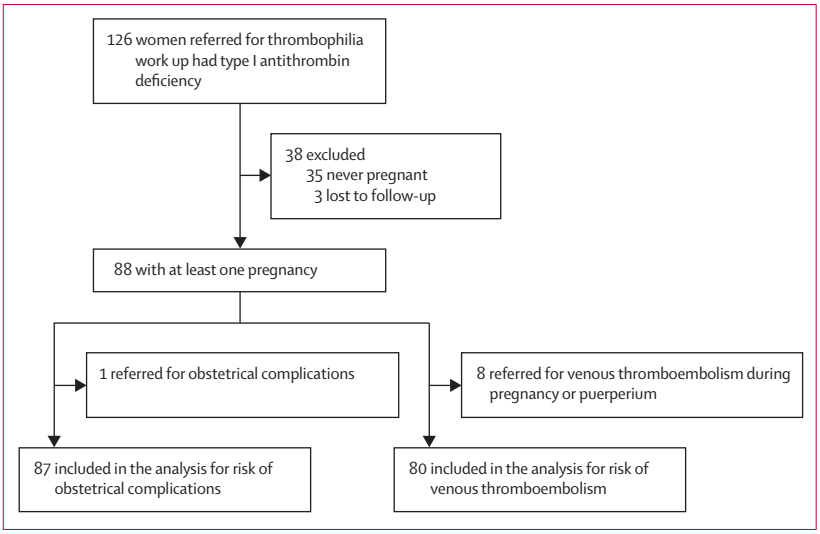

Figure: **Trial profile**

women who had pregnancy-related venous thromboembolism and those who resumed oral anticoagulant therapy after delivery. Comparisons between pregnant women who receive LMWH and those who did not and between symptomatic or asymptomatic women were done, both for venous thromboembolism and obstetrical complications, calculating relative risks (RR) with their 95% CIs. Pregnancies initiated without LMWH prophylaxis, then complicated by venous thromboembolism and treated with LMWH were included in the analysis of both pregnancies with and without LMWH. Women referred for thrombosis during pregnancy were excluded from the analysis of the risk of pregnancy-related venous thromboembolism, and women referred for obstetrical complications from the analysis of the risk of obstetrical complications. Stratification analysis considered the previous history of venous thromboembolism and the use of LMWH during pregnancy. Sensitivity analysis was done on probands (to avoid possible distortions from a mixed cohort), women with antithrombin concentration below 60 IU/dL,[17] and women without additional thrombophilia abnormalities. An additional sensitivity analysis of the risk of obstetrical complications was done in pregnancies that had occurred after the year 2000 (when the association between thrombophilia and obstetrical complications was first addressed). A mixed-effects logistic regression was done on probands only to take into account the within-patient correlation in the frame of observations within cluster (repeated measures). We applied a model considering treatment as fixed effect and controlling for woman and pregnancies in the same woman variability. The results are reported in term of odds ratio (OR) and 95% CIs were calculated with R software. We used Fisher's exact test to compare groups on binary variables.

All analyses were done with SPSS (release 25.0) and R (lmer in the lme4 package, version 3.6.1).

	Women with type I antithrombin deficiency with at least one pregnancy (n=88)
Probands	57
Relatives	31
Number of families	70
Number of relatives per probands	0·28*
Pregnancies	219
Age at diagnosis of antithrombin deficiency, years	40 (30–50)
Age at first thrombosis, years	29 (22–40)
Age at first pregnancy, years	26 (22–31)
Body-mass index, kg/m²	23 (20–26)
Antithrombin activity, %	61 (50–71)
Antithrombin antigen, %	65 (48-73)
Index venous thromboembolism†	
None	16 (28%)
Cerebral vein thrombosis	5 (9%)
Retinal vein thrombosis	2 (4%)
Deep vein thrombosis	24 (42%)
Pulmonary embolism	2 (4%)
Pulmonary embolism and deep vein thrombosis	3 (5%)
Superficial vein thrombosis	4 (7%)
Ischaemic stroke	1 (2%)
Other thrombophilia abnormalities	
Heterozygous FVL	6 (7%)
Heterozygous prothrombin G20210A mutation	2 (2%)
Homozygous prothrombin G20210A mutation	1 (1%)
Heterozygous FVL and heterozygous prothrombin G20210A mutation	1 (1%)
Heterozygous FVL and lupus anticoagulant at low titre in one test	1 (1%)
Lupus anticoagulant at low titre in two tests	1 (1%)

Data are median (IQR) or n (%), unless otherwise specified. FVL=factor V Leiden. *Number of relatives of probands included in the study (n=16) divided by the number of probands (n=57). †Percentages calculated from number of probands.

Table 1: **Baseline characteristics**

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

126 women referred for a thrombophilia work-up between Jan 1, 1980, and Jan 1, 2018, had type I antithrombin deficiency. 35 of these women were never pregnant and three were lost to follow-up. Eight women were referred to the centre for venous thromboembolism occurring during pregnancy or puerperium, and one was referred for obstetrical complication. Thus, 80 (63%) women were included in the analysis of the risk of pregnancy-related

	Pregnancies in women treated with LMWH (n=43)		Pregnancies in women who did not receive LMWH (n= 146)		RR (95% CI)	p value
	N	Risk proportion (95% CI)	N	Risk proportion (95% CI)		
Deep vein thrombosis	2	4·7% (1·3–15·5)	12	8·2% (4·8–13·8)	0·6 (0·1–2·4)	0·74
Deep and superficial vein thrombosis	3*	7·0% (1·8–17·8)	17†	11·6% (7·2–17·6)	0·6 (0·2–1·9)	0·57

LMWH=low-molecular-weight heparin. RR=relative risk. *All were recurrences that occurred with therapeutic doses of LMWH: one deep vein thrombosis in the puerperium (after a previous deep vein thrombosis in the first trimester of the same pregnancy); one deep vein thrombosis in the first trimester (after a previous deep vein thrombosis during oral contraceptive use and a previous spontaneous cerebral vein thrombosis); one superficial vein thrombosis in the second trimester (after a previous pregnancy-related deep vein thrombosis). †Four events were recurrences: three in the same woman (two superficial and one deep vein thrombosis in three different pregnancies), and one deep vein thrombosis after two previous spontaneous deep vein thrombosis in another woman. The remaining were all first events: three deep vein thrombosis in the first trimester, one deep vein thrombosis in the second trimester, two superficial vein thrombosis in the third trimester; and five deep vein thrombosis, one cerebral thrombosis, and one superficial vein thrombosis in the puerperium.

Table 2: **Risk of thrombosis during pregnancy and puerperium with or without LMWH**

venous thromboembolism and 87 (69%) in analysis of risk of obstetrical complications (figure). General characteristics of the study population are presented in table 1. None of the women had comorbidities predisposing to obstetrical complications. The 88 women included in the study belonged to 70 different families. 57 were probands (45 without relatives in the study and 12 with 16 relatives included in the study). Additionally, 15 female relatives of 13 male probands were included. 80 women had 189 pregnancies, 43 whilst receiving LMWH (32 prophylactic and 11 full therapeutic doses) and 146 without LMWH. 20 new venous thromboembolism events occurred during pregnancy (n=12) or puerperium (n=8), with a risk proportion of 10·6% (95% CI 6·8–15·6). During pregnancy, five venous thromboembolism events occurred in the first trimester (four deep vein thrombosis and one superficial vein thrombosis), four in the second (three deep vein thrombosis and one superficial vein thrombosis), and three in the third trimester (all superficial vein thrombosis). During puerperium, six deep vein thrombosis, one cerebral, and one superficial vein thrombosis were observed. Two events (cerebral and superficial vein thrombosis) happened on the second day after delivery and the remaining ones after the tenth day. Two women with deep vein thrombsosis delivered by cesarean section. Considering only deep vein thrombosis, the venous thromboembolism risk proportion was 4·1% (95% CI 0·9–8·7) in pregnancies in women who did not receive LMWH (six of 146) and 2·3% (95% CI 0·4–12·1) in pregnancies in women treated with LMWH (one of 43); 4·3% (95% CI 1·8–8·7) in puerperia in those who did not receive LMWH (six of 140) and 3·1% (95% CI 0·6–15·7) in puerperia in those who received LMWH (one of 32). Two deep vein thrombosis events of the lower limbs occurred in those treated with LMWH (one in pregnancy and one in puerperium), 11 deep vein thrombosis events plus one cerebral vein thrombosis occurred in women who did not receive LMWH (six in pregnancy and five deep vein thrombosis plus one cerebral in puerperium) with a RR of 0·6 (95% CI 0·1–2·4, p=0·74; table 2). Three superficial vein thrombosis events (7%) occurred in pregnancies in women treated with LMWH and 17 (12%) in those who did not receive treatment, with a similar RR of 0·6 (95% CI 0·2–1·9, p=0·57; table 2). The three superficial vein thrombosis events had occurred during treatment with therapeutic doses of LMWH and were recurrences. Venous thromboembolism was not observed in pregnancies with prophylactic doses of LMWH.

Overall, the incidence of pregnancy-related venous thromboembolism was higher in symptomatic (seven [22%] of 32) than in asymptomatic pregnancies (13 [8%] of 157) with a RR of 2·6 (95% CI 1·1–6·1; p=0·051). Among symptomatic women, there were three venous thromboembolism events (two deep vein thrombosis and one superficial vein thrombosis) in 16 pregnancies with LMWH (19%) and four (one deep vein thrombosis and three superficial vein thrombosis) in 16 pregnancies without (25%). Among asymptomatic women there were no venous thromboembolism events in 27 pregnancies with LMWH and 13 events (ten deep vein thrombosis, two superficial vein thrombosis, and one cerebral vein thrombosis) in 130 pregnancies without LMWH (10%). In pregnancies without LMWH, the risk of venous thromboembolism was higher in symptomatic than asymptomatic women (RR 2·5, 95% CI 0·9–6·7; p=0·094). 48 asymptomatic women had a positive family history of venous thromboembolism, and 20 asymptomatic women had a negative family history. In women with a positive family history of venous thromboembolism, no events of venous thromboembolism were observed in 16 pregnancies with LMWH, and 11 events (eight deep vein thrombosis, one cerebral vein, and two superficial vein thrombosis) in 93 pregnancies without LMWH (12%). In women with a negative family history, no events of venous thromboembolism were observed in 11 pregnancies with LMWH and two events of deep vein thrombosis in 37 pregnancies without LMWH (5%). The risk of venous thromboembolism without LMWH was 5·4% (95% CI 0·9–16·7) in women with a negative family history of venous thromboembolism, and 11·8% (6·4–19·6) in those with a positive family history of venous thromboembolism. Neither arterial thrombosis nor bleeding was observed in all 189 pregnancies. 24 patients who were asymptomatic probands had a

	Pregnancies in women treated with LMWH (n=48)		Pregnancies in women who did not receive LMWH (n=170)		RR (95% CI)	p value
	N	Risk proportion (95% CI)	N	Risk proportion (95% CI)		
Full term	28	62·2% (47·5–75·4)	120	74·5% (67·4–80·8)	0·8 (0·7–1·1)	0·13
Miscarriage	6	13·3% (5·6–25·7)	32	19·9% (14·3–26·6)	0·7 (0·3–1·5)	0·39
Late obstetrical complications	11	24·4% (13·6–38·5)	9	5·6% (2·8–10·0)	4·4 (1·9–9·9)	0·0006
Terminations	3	6·3% (1·6–16·1)	9	5·3% (2·6–9·5)	1·2 (0·3–4·2)	0·73

LMWH=low-molecular-weight heparin. RR=relative risk.

Table 3: **Pregnancy outcomes with or without LMWH**

	Pregnancies in women with previous venous thromboembolism (n=45)				Pregnancies in women without previous venous thromboembolism (n=173)			
	Treated with LMWH (n=21)	Did not receive LMWH (n=24)	RR (95% CI)	p value	Treated with LMWH (n=27)	Did not receive LMWH (n=146)	RR (95% CI)	p value
Full term	11/18 (61%)	13/18 (72%)	0·8 (0·5–1·3)	0·72	17/27 (63%)	107/143 (75%)	0·8 (0·6–1·1)	0·24
Miscarriage	4/18 (22%)	3/18 (17%)	1·3 (0·3–5·1)	1·0	2/27 (7%)	29/143 (20%)	0·4 (0·1–1·4)	0·17
Late obstetrical complications	3/18 (17%)*	2/18 (11%)†	1·5 (0·3–7·9)	1·0	8/27 (30%)‡	7/143 (5%)§	6·1 (2·4–15·3)	0·0004
Terminations	3/21 (14%)	6/24 (25%)	0·6 (0·2–2·0)	0·47	0	3/146 (2%)	..	..

LMWH=low-molecular-weight heparin. RR=relative risk. *One stillbirth, one small-for-gestational-age newborn, and one preeclampsia. †One stillbirth and one preterm delivery. ‡Two small-for-gestational-age newborns (one with preterm delivery), four preterm deliveries (two with premature rupture of membrane), and two placental abruption. §Three stillbirths (two with preeclampsia), two preeclampsia (with preterm deliveries), and two small-for-gestational-age newborns (one with preterm delivery).

Table 4: **Pregnancy outcomes in women receiving or not receiving antithrombotic prophylaxis stratified by personal history of venous thromboembolism**

positive family history and 14 patients a negative family history. Among patients who were asymptomatic probands, no event was observed in five pregnancies with LMWH, and four events of deep vein thrombosis and one event of cerebral vein thrombosis was observed in 36 pregnancies without LMWH (14%). Among patients with a negative family history, no events of venous thromboembolism were observed in 11 pregnancies with LMWH and one event of deep vein thrombosis in 21 pregnancies without LMWH (5%).

Pregnancy outcome was evaluated in 87 women with 218 pregnancies (all spontaneous conceptions), with the prevalence of outcomes calculated according to total number of pregnancies, excluding terminations. A mean of 0·29 (SD 0·37) obstetrical complications per woman (0·14 [0·31] for late obstetrical complication) was observed. Overall, there were 58 obstetrical complications (28%; 38 [18%] miscarriages and 20 [10%] late obstetrical complications) and 148 (72%) full term of 206 pregnancies. 17 complications (38%) occurred in 45 pregnancies with LMWH (35 prophylactic and 10 therapeutic doses) and 41 (25%) in 161 pregnancies without LMWH. Full term pregnancies, miscarriages, and terminations had similar risk proportions, but late obstetrical complications were more frequent in pregnancies with LMWH than in those without (RR 4·4 95% CI 1·9–9·9; p=0·0006; table 3). This difference was observed only in asymptomatic women but disappeared in symptomatic patients (table 4). Terminations were more frequent in women with previous venous thromboembolism than in those without (nine of 45 *vs* three of 173; RR 11·5 95% CI 3·3–40·9; p<0·0001). The two women with low-titre lupus anticoagulant were maintained in the analyses and both had two full-term pregnancies (only one with LMWH). A family history of venous thromboembolism did not influence the obstetrical outcome. 79 women were included in the analysis of both outcomes, and we did a separate analysis with similar results to those obtained in the primary assessment (appendix p 3). Regarding patients who were probands, two events (one deep vein thrombosis and one superficial vein thrombosis) occurred in 31 pregnancies in those treated with LMWH and ten events (seven deep vein thrombosis and three superficial vein thrombosis) in 67 pregnancies in women who did not receive LMWH. The RR of pregnancy-associated deep vein thrombosis was 0·4 (95% CI 0·1–1·9; p=0·32). Late obstetrical complications occurred in nine of 36 pregnancies with LMWH and in eight of 91 without, with an RR of 2·8 (95% CI 1·2–6·8; p=0·016). The mixed-effects logistic regression showed an OR for deep vein thrombosis of 0·3 (95% CI 0·0–2·4, p=0·25) and for late obstetrical complications 5·9 (0·9–39·2; p=0·066), associated with LMWH use.

Considering only women at particularly high risk of thrombosis because of antithrombin levels below 60 IU/dL, three (11%) events (two deep vein thrombosis and one superficial vein thrombosis) occurred in 27 pregnancies in women who received LMWH and

11 (16%) events (eight deep vein thrombosis and three superficial vein thrombosis) in 68 pregnancies in women who did not receive LMWH (RR 0·7, 95% CI 0·2–2·3; p=0·75). Eight (23%) pregnancies in 35 women treated with LMWH and six (7%) in 86 women who did not receive LMWH were complicated, (RR 3·2, 95% CI 1·2–8·6; p=0·024).

Considering only women with antithrombin deficiency and no additional thrombophilia abnormalities, 68 women were analysed for the risk of venous thromboembolism and 75 for risk of obstetrical complications. Two (5%) deep vein thrombosis events occurred in 40 pregnancies in women treated with LMWH and nine (8%; eight deep vein thrombosis plus one superficial vein thrombosis) in 119 women who did not receive LMWH (RR 1·7, 95% CI 0·1–2·9 p=0·58). Late obstetrical complications occurred in 11 of 45 pregnancies with LMWH and in seven of 143 without LMWH (RR 4·9, 95% CI 2·0–11·9; p=0·0001).

Considering only pregnancies after the year 2000, when the association between thrombophilia an obstetrical complications was first addressed, the risk of late obstetrical complications was 2·9 (95% CI 0·7–11·0; p=0·14) with three (13%) complications in 23 pregnancies in women treated with LMWH and five (5%) in 108 women who did not receive LMWH.

Discussion

To our knowledge, this is the largest cohort study of women with type I antithrombin deficiency investigating the risk of pregnancy-associated or puerperium-associated venous thromboembolism and the risk of obstetrical complications. We observed a moderate risk reduction of venous thromboembolism in patients receiving LMWH. The three events observed in pregnancies with LMWH were recurrences of previous cases of the condition that had occurred during a previous pregnancy in two women and during the intake of an oral contraceptive in another, thus confirming the increased risk of recurrent venous thromboembolism during pregnancy after a previous hormone-associated event.[19–21] Moreover, there was a 10% risk of venous thromboembolism in pregnancies of asymptomatic women without LMWH prophylaxis. Among them, the risk of venous thromboembolism was doubled in women with a positive family history of venous thromboembolism, but was still relevant in those with negative history (5%), as shown in unselected women with severe thrombophilia.[22] Furthermore, pregnancies with LMWH had a 4·4 relative risk of late placenta-mediated obstetrical complications compared with the pregnancies without LMWH, and the relative risk in asymptomatic women was 6·1. Finally, the prevalence of terminations was about 10-times higher in women with previous venous thromboembolism than in those without, notwithstanding that our women were informed on the potential benefits and safety of LMWH treatment during pregnancy. Sensitivity analyses and the mixed-effects logistic regression done to control for possible confounders and distortion showed similar risk estimates to the main analysis.

Because of the rarity of antithrombin deficiency, controlled trials on the use of LMWH in pregnancy are scarce and data on antithrombotic prophylaxis in asymptomatic women are limited to a few retrospective cohort or case-control studies. A review of these studies reported an 11·6% incidence of venous thromboembolism in patients without LMWH prophylaxis (similar to our estimate) pooling together three cohort studies, and a 6-fold increased risk of first occurrence of venous thromboembolism pooling together four case-control studies.[23] A family study including a small sample of women with antithrombin deficiency who did not receive LMWH during pregnancy showed a 14·8% incidence of venous thromboembolism in asymptomatic women and a 60% incidence of recurrence.[24] These frequencies in our study were lower (10% and 25%, respectively), but still high. The difference can be attributed to the clustering effect of the family study and to our sample size, which was three-times larger. Women with a previous venous thromboembolism and those with thrombophilia also have an increased risk of obstetrical complications, in particular late fetal loss, but data on women with antithrombin deficiencies are scarce.[8,9,21,25,26] A high risk of pregnancy loss was reported in homozygous carriers of type II antithrombin deficiency (mutation p.Leu131Phe). Despite antithrombotic prophylaxis, only a third of these patients gave birth to a live infant at the end of their pregnancies.[27] In our study, the incidence of late obstetrical complications and miscarriage in asymptomatic women without LMWH was similar to that of the general population.[28] However, LMWH appears to be associated with a reduced risk of miscarriage but with an increased risk of late complications. These figures did not change after controlling the analysis for women and pregnancies variability. These findings are difficult to explain and should be interpreted with caution because of the relatively small number of patients. Heparin influences all stages of implantation through several mechanisms that are not fully understood. For example, it prevents hypoxic-induced apoptosis modulating the expression of the heparin binding epidermal-growth factor, which has a fundamental role in the early stages of placentation. Perhaps antithrombin deficient women, having less antithrombin-heparin complexes, have more circulating heparin available to induce the expression of the growth factor, with the result of preventing miscarriage.[29] This theoretical benefit is lost after the first trimester, when the prevention of apoptosis is no longer important. The efficacy of LMWH prophylaxis in preventing pregnancy-associated venous thromboembolism, but not obstetrical complications, suggests that the two diseases have different pathological mechanisms, particularly in antithrombin deficient women, and more studies are warranted to elucidate their molecular pathways.

Alternative approaches, such as adjusted LMWH doses or the use of antithrombin concentrates should be considered in the frame of future studies.[17,30]

In addition to the relatively large sample size, strengths of our study include the homogenous prophylactic regimen, because LMWH was started at predetermined doses since the first gestational weeks, and the collection of objective documentation of venous thromboembolism. However, some limitations need to be discussed. Firstly, the absence of a control group (women without thrombophilia) does not allow for calculation of the absolute risk difference of venous thromboembolism and obstetrical complications. Secondly, data concerning pregnancies that had occurred before the diagnosis of antithrombin deficiency, and particularly when the association between thrombophilia and obstetrical complications was not yet established, might have been collected less consistently. This potential inconsistency in data collection might have led to an underestimation of the risk of obstetrical complications in pregnancies without LMWH prophylaxis, but the sensitivity analysis done on pregnancies that had occurred after the year 2000 (when thrombophilia screening was largely implemented) showed results similar to those of the whole cohort. Thirdly, because the venous thromboembolism events observed in pregnancies with LMWH were all recurrences, the poor preventive efficacy of LMWH might be attributable to the therapeutic doses.

In conclusion, our data suggest that women with type I antithrombin deficiency have not only a high risk of venous thromboembolism during pregnancy and puerperium, but also a high risk of late placenta-mediated obstetrical complications. Intermediate doses of LMWH prophylaxis reduced the risk of venous thromboembolism by 40%, but the full therapeutic doses used in women with previous cases of venous thromboembolism were not sufficient to prevent recurrences. Our results support routine LMWH prophylaxis for prevention of venous thromboembolism in pregnant women with antithrombin deficiency, even in those with a negative family history of venous thromboembolism, which differs from other recommendations.[16]

Contributors

MA and IM contributed equally to design the study and develop the manuscript, drafting and revising the text, tables, and figure. MA and PB did the statistical analysis. FG, AA, PB, MCa, IM, and FP assessed patients for eligibility, collected data, and critically revised the manuscript. CN and MCl did the laboratory tests. All authors approved the final manuscript for submission.

Declaration of interests

CN reports consulting fees from Instrumental Laboratory, Roche, Novo Nordisk, and Sobi outside of the submitted work. AA reports non-financial support from Bayer and Roche and honoraria from Janssen outside of the submitted work. MCa reports non-financial support from Novo Nordisk and Novartis outside of the submitted work. FP reports advisory fees from Bioverativ, Roche, Sanofi, Takeda, and Sobi outside of the submitted work. IM reports personal and non-financial support from Bayer and Roche outside of the submitted work. All other authors declare no competing interests.

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