



How to Manage Venous Thromboembolism Risk during Pregnancy in Patients with Inherited Antithrombin Deficiency?

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Abstract

Inherited antithrombin deficiency (ATD) is associated with a high risk of venous thromboembolic complications. Association of ATD with other conditions such as pregnancy obviously increases thromboembolic risk and may require anticoagulant therapy for prevention. Although there are several/heterogenous international guidelines regarding thromboprophylaxis in pregnant patients with ATD, data on anticoagulant prophylaxis in this context are scarce in the literature. Thus, this situation remains a challenge both in the antepartum period and during delivery. Physicians from the French Society of Thrombosis and Haemostasis (SFTH) performed a review of the literature to suggest propositions regarding the management of thrombosis prevention based on anticoagulation and antithrombin substitution in ATD pregnant women. In this review, after reporting the thrombotic risk associated with ATD, the indication of anticoagulant therapy, its dosing regimen and monitoring, and the indication of antithrombin concentrates during pregnancy and the postpartum period are discussed as well as peripartum management. Finally, this work confirms the complex management of thrombotic prevention in pregnant patients with ATD. Indeed, it requires to take into account a multiplicity of features cited in our propositions that will hopefully provide some help in this field. This work also highlights the importance of multidisciplinary discussions for pregnant women with ATD who should be counseled in an expert center including hematologist, obstetrician, and anesthetist to optimize their management.

Keywords

- ▶ pregnancy
- ▶ antithrombin deficiency
- ▶ venous thrombosis
- ▶ thromboprophylaxis

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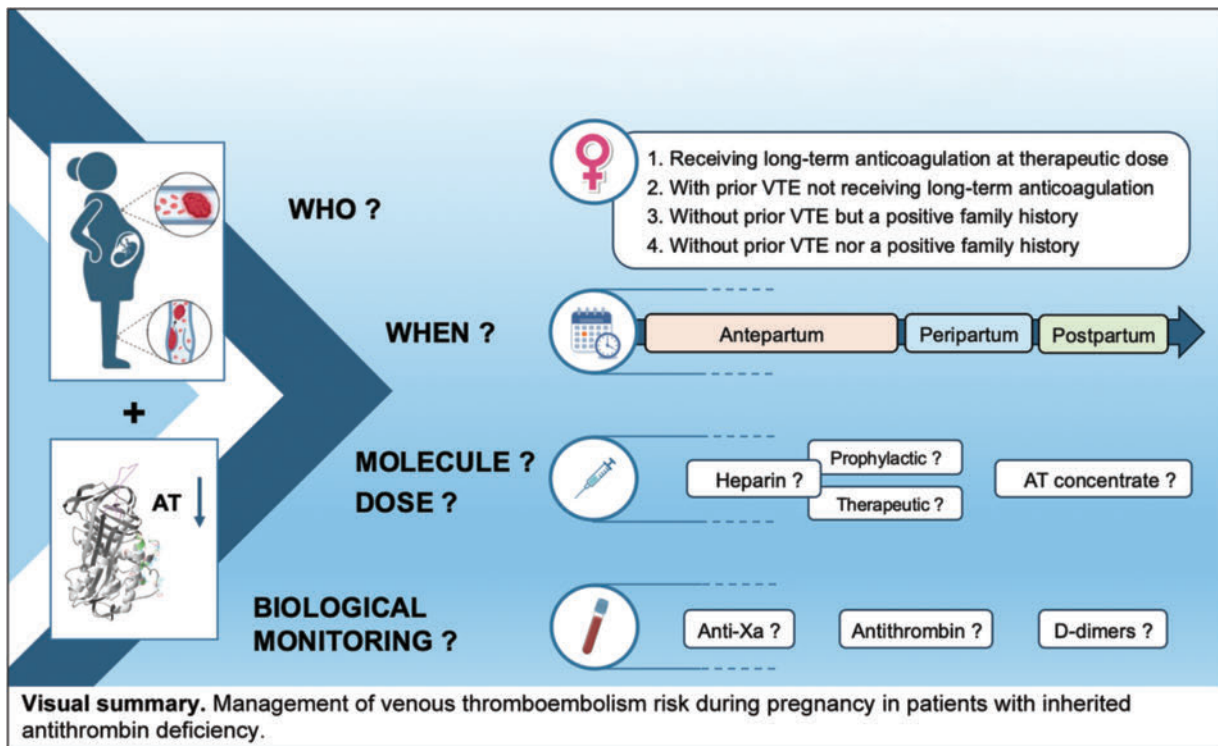
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Introduction

The Burden of VTE during Pregnancy

Venous thromboembolism (VTE) is the fourth leading cause of maternal death, with a maternal mortality rate of 1.0 per 100,000 live births according to the latest report from the confidential national survey on maternal deaths in France.¹ About 35% of VTE cases are considered preventable, indicating the need for accurate risk assessment and appropriate thromboprophylaxis during pregnancy and postpartum.¹

Pregnancy induces a hypercoagulable state, characterized by increased fibrinogen, reduced fibrinolytic activity, elevated coagulation factors II, VII, VIII, and X, decreased free protein S, and acquired resistance to activated protein C.² Venous stasis, especially in the second and third trimesters, and reduced physical activity further elevate thromboembolic risk.³ This heightened risk spans the entire pregnancy and extends up to 12 weeks postpartum,⁴ with deep vein thrombosis (DVT) primarily affecting the left leg before delivery and pulmonary embolism (PE) more common after delivery.⁵

The incidence of VTE in pregnancy is 0.76 to 1.72 per 1,000 pregnancies, 4 times higher than in non-pregnant women of the same age (relative risk 4.29, 95% confidence interval [CI] 3.49–5.22).^{6,7} To provide a clearer understanding of the risk of VTE during pregnancy, which is likely overestimated by the medical community, it is necessary to compare it with the incidence of VTE in the general population. Several cohort studies have estimated the incidence of VTE to be between 0.90 and 1.83 per 1,000 persons, with age being a significant risk factor. The risk increases by a factor of 1.7 (95% CI 1.5–2.0) every 10 years after the age of 55.^{8–10}

Therefore, the risk of VTE in pregnant women is comparable to that of individuals over 50 years old, contradicting the common belief that pregnant women have a higher thromboembolic risk than elderly individuals.^{8–10}

Major additional risk factors for VTE during pregnancy and postpartum include a personal history of VTE (odds ratio [OR] 24.8, 95% CI 17.1–36.0) and inherited thrombophilia (OR 51.8, 95% CI 38.7–69.2).⁶ These OR, derived from retrospective data, are imprecise due to administrative database limitations. Antiphospholipid syndrome also presents significant risk (OR 15.8, 95% CI 10.9–22.8).⁶ Other additional risk factors include maternal age, family history of VTE, certain chronic conditions, and pregnancy-specific factors like multiple gestations, cesarean delivery, and postpartum complications.^{6,11} Among inherited thrombophilias, antithrombin deficiency (ATD) is associated with the highest absolute risk of VTE at 7.3% (95% CI 1.8–15.6%) during pregnancy and 11.1% (95% CI 3.7–21.0%) during the postpartum period, whereas protein C or S deficiencies and homozygous factor V Leiden mutation absolute risks of VTE were estimated respectively at 3.2% (95% CI 0.6–8.2%), 0.9% (95% CI 0.0–3.7%), and 2.8% (95% CI 0.0–8.6%) during pregnancy and at 5.4% (95% CI 0.9–13.8%), 4.2% (95% CI 0.7–9.4%), and 2.8% (95% CI 0.0–8.8%) during the postpartum period.¹² Another meta-analysis reported an 11.6% incidence of VTE in patients without low-molecular-weight heparin (LMWH) prophylaxis pooling together three cohort studies, and a 6-fold increased risk of first recurrence of VTE pooling together four case-control studies.¹³ ATD is indeed responsible for major risk of thromboembolic events. Its prevalence ranges between approximately 0.02 and 0.2% in the general population¹⁴ and between 1 and 5% in VTE patients.¹⁵ The relative

risk of first thromboembolic event in ATD patients has been estimated as 15 times higher than in the general population and the risk of recurrence 4 times higher, based on an observational study.¹⁶ However, this study did not consider the type of ATD. Inherited ATD is mostly due to genetic variations in the gene coding AT, *SERPINC1*,¹⁷ and can be either quantitative (type I) or qualitative (type II). The clinical phenotype is quite heterogeneous depending on ATD type and even on the genetic variant.¹⁸ A precise characterization of the type of ATD combining classical plasma exploration with genetic analysis of *SERPINC1* is thus important, especially for type II deficiencies.¹⁹ In inherited ATD, 60% of VTE events appear to be unprovoked and 40% are secondary to a transient risk factor such as pregnancy.^{20–22} Despite guidelines on VTE prophylaxis in pregnant women, the management of such patients are highly variable including in highly specialized center.

On behalf of the French Society of Thrombosis and Haemostasis (SFTH), we analyzed the current available data on the thrombotic risk induced by inherited ATD, and the management of thromboprophylaxis and AT substitution in the specific situation of the pregnancy and postpartum periods. The objective of this manuscript was to formulate suggestions to help physicians to prevent venous thromboembolism.

Material and Methods

In May 2023, the Thrombosis, Anticoagulant, and Antiplatelet Subcommittee of the SFTH established a multidisciplinary panel of 12 French experts to address the management of VTE risk during pregnancy in patients with ATD. The panel included specialists in hemostasis (M.L., C.J., F.M., G.M., M.C., P.V., S.P., T.N., MacL.), obstetrics (S.L., M.H.), and anesthesiology (L.T.).

To define the key clinical questions, we followed the chronological course of pregnancy, from antepartum to postpartum including the peripartum period. The discussion focused on anticoagulation management: which patients should receive anticoagulation, when to initiate and discontinue therapy, and what dosing strategies to use. We also addressed the relevance of biological monitoring and the role of antithrombin concentrates in this specific population. All these questions were addressed based on the following possible clinical scenarios:

- Women on long-term anticoagulation
- Women with prior VTE without long-term anticoagulation
- Asymptomatic women with a family history of VTE
- Asymptomatic women with no family history of VTE

Individual members of the panel were assigned to a chapter and reported their formulated propositions. The literature search was carried out on MEDLINE using the following keywords: “antithrombin deficiency” OR “antithrombin” OR “thrombophilia” AND “pregnancy” OR “peripartum” OR “preeclampsia” OR “pregnancy loss” AND “antithrombotic treatment” OR “thromboembolism prophylaxis.” The search was limited to humans and articles

published in English or French. For the chapter dealing with the thrombotic risk associated with inherited ATD during pregnancy, studies were included only if ATD was genetically characterized and sufficient data were available. Data on the age at pregnancy, type of ATD, and personal and familial thrombosis histories were collected. We excluded from this review placental vascular complications induced by inherited ATD.

The different questions to be addressed and suggested answers to be provided were debated in nine meetings including the whole panel of experts, according to each expert practice and literature issues. Suggestions were considered approved on the condition that all authors reached full agreement. Though, both suggestions and texts were approved by all experts, the coordinators of the TITAN subcommittee (Prof. Pierre Morange, Dr. Isabelle Gouin-Thibault and Dr Emmanuel De Maistre) and the president of the SFTH (Prof. Chloé James).

Overview of the Relevant Literature on the Risk of Inherited ATD According to the Subtype

Inherited ATD can be either quantitative or qualitative. Several qualitative subtypes have been described depending on the origin of the functional defect. AT inhibits all serine proteases of the coagulation pathway, mainly thrombin (FIIa) and activated factor X (FXa), after recognition of its reactive site (RS). Binding of heparan sulfate and heparin to AT at the heparin binding site (HBS), a region rich in positive amino acids, favors the exposition of the RS to serine proteases, accelerating AT activity by around 1,000-fold. Qualitative deficiency can be linked to a variant affecting the reactive site (type II RS), impairing binding of glycosaminoglycan to AT (type II HBS), or finally, inducing a conformational instability of the protein affecting its functionality +/- quantity (pleiotropic effect, type II PE).¹⁷ Type II HBS ATD is usually reported to be less thrombogenic than other types. This is also the case for Cambridge II variant, which only moderately impairs anti-FIIa activity.^{18,23} However, some variants associated with type II HBS ATD still present a significant risk of VTE in a heterozygous state.^{18,24} Variants with mild effect on AT, usually type II HBS ATD, have also been observed in a homozygous state, where they are usually associated with a higher risk of thrombosis and young age.²⁵ The genetic status is thus important to determine.

Because ATD is a rare condition, data derive largely from retrospective cohorts and case control studies but confirm the increased risk of thrombosis for ATD patients in the context of pregnancy as mentioned in the introduction. In one study involving 25 ATD women with at least one pregnancy not receiving prophylaxis, VTE occurred mostly during the first (6 events) and second (9 events) trimesters of pregnancy.²⁰ De Stefano et al found that most events occurred postpartum.²⁶ High variability in reported risks of VTE among the studies can be explained by the heterogeneity of inclusion criteria. Several factors may indeed contribute to thrombosis risk, such as the type of deficiency, the existence of personal history of VTE, and the prophylaxis regimen applied. A positive family history of VTE (defined as

having at least one first-degree or second-degree relatives who has experienced a thromboembolic complication) has been associated with a higher risk of VTE in women not treated with LMWH at 11.8% (95% CI 6.4–19.6) versus 5.4% (95% CI 0.9–16.7) in women with a negative family history of VTE.²⁷ The addition of single or multiple mild thrombophilia defects might also increase the risk of VTE.^{28,29} Finally, variable definitions of ATD are used in the studies and the type of ATD is rarely defined. Abbattista et al recently confirmed the high risk of first or recurrent VTE during pregnancy for type I ATD.²⁷ But the risks associated with type II ATD have been less studied. Kovac et al³⁰ reported that all types of ATD were strong risk factors for pregnancy-related VTE, except type II heterozygous HBS defects. In untreated pregnancies, the highest incidence of VTE was observed in women carriers of type I ATD. In the treated pregnancies (LMWH/AT concentrate), homozygous type II HBS (Budapest 3 variant) was associated with the highest risk of VTE (43%) and stroke (14%).³⁰ This study included a small number of patients ($n=28$) and type II HBS were all due to the same variant, AT Budapest 3.

We thus performed an extensive literature search to collect information on pregnancy-related complications in ATD women. Because of the difficulty to characterize type II

ATD and thrombosis risk variation according to the variant, only data on genetically characterized ATD were collected. This data collection was not intended to compare the risk of thrombosis based on ATD types, first, because these data primarily come from case reports and, second, due to the heterogeneity of the contexts concerning anticoagulation treatment during pregnancy, as well as personal and familial thrombotic histories. Among the 760 studies proposed using specific keywords, 31 studies were selected (►Fig. 1). Individual data from 103 patients were finally collected (individual data in ►Supplementary Table S1, available in the online version). Pregnancy-related thrombotic complications according to the type of ATD are presented in ►Table 1. All homozygous ATD reported in the literature were due to the Budapest 3 variant. Therefore, all other ATD cases were due to variants present in a heterozygous state. Thrombotic complications during pregnancy have been reported for all types of ATD except heterozygous Budapest 3 variant. Some patients presented thrombotic complications despite receiving anticoagulation in type I and type II RS and homozygous type II HBS ATD, highlighting the risk of thrombosis in these groups. Thrombotic complications were observed mainly in antepartum and in the absence of anticoagulant treatment or AT concentrate, except for homozygous ATD patients where

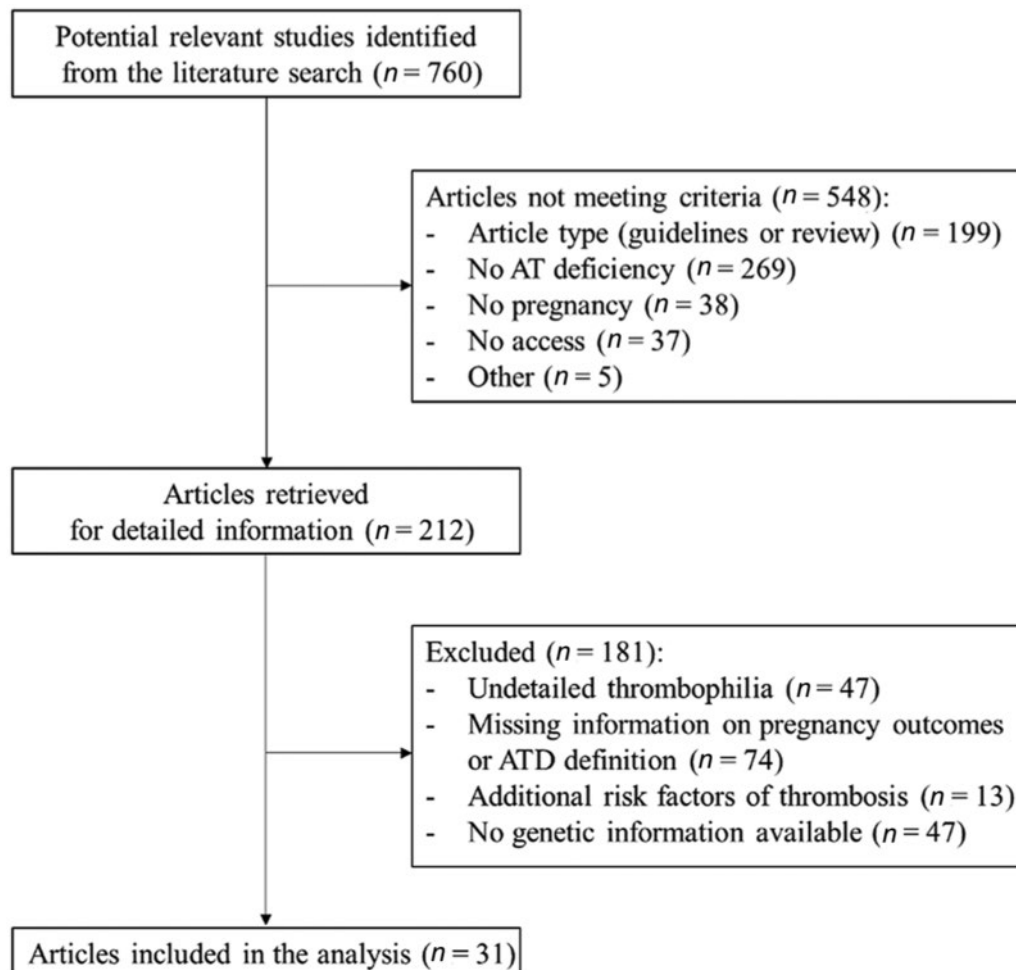


Fig. 1 Search strategy for articles on pregnancy outcomes in women with genetically characterized inherited antithrombin deficiency.

Table 1 Clinical presentation of pregnancy complications in relation to the type of ATD

	Type I	Type II HBS	Type II HBS	Type II HBS	Type II RS	Type II PE (pleiotropic)
	Htz	Hmz (Budapest 3)	Htz (Budapest 3)	Htz (Other variants)	Htz	Htz
Number of patients, <i>n</i>	47 ^a	17	10	10	11	8
Number of variants, <i>n</i>	31	1	1	5	5	5
Number of pregnancies, <i>n</i>	70	59 ^b	17	16	18	10
Under treatment from beginning, <i>n</i> (%)	28	23	ND	6	6	1
With maternal complications, <i>n</i> (%)	39 (55)	13 (24)	0 (0)	3 (19)	5 (28)	9 (90)
Type of maternal complication						
DVT or PE, <i>n</i>	31	11	0	2	5	6
DVT (atypical localization), <i>n</i>	8	2	0	1	0	1
VTE without precision, <i>n</i>	0	0	0	0	0	2
Time period of complication						
Antepartum	26	4	0	3	5	6
Puerperium/postpartum/postabortum ^d	13	9	0	0	0	1
Events under treatment, <i>n</i>	10	8	0	0	4	0
Antepartum	8/17/1 ^c	0/4/0 ^c	0	0/1/2 ^c	1/4/0 ^c	0/3/3 ^c
Postpartum	2/7/4 ^c	8/1/0 ^c	0	0	0	0/0/1 ^c

Abbreviations: ATD, antithrombin deficiency; DVT, deep venous thrombosis; HBS, heparin binding site; HELLP, hemolysis, elevated liver enzymes, low platelet count syndrome; Hmz, homozygous; Htz, heterozygous; ND, not documented; PE, pulmonary embolism; VTE, venous thromboembolism.

Notes: ^aNine patients are related: One of them experienced thrombosis in antepartum and six of them in the puerperium.

^bFour patients had six or more pregnancies.

^cAnticoagulant and/or AT concentrate at the time of complication: yes/no/ND.

^dPostpartum >22 weeks of gestation, postabortum <22 weeks of gestation.

postpartum events were also frequent, even if anticoagulant and/or AT concentrate were administered. Postpartum events were also observed in type II PE ATD. Clinical presentation of thrombosis was usually classical, mainly lower limb DVT or PE, but atypical localizations were also reported.

Obstetrical Issues

Managing anticoagulated patients requires multidisciplinary care due to the implications for epidural analgesia and childbirth management.

Term and Route of Delivery

Most deliveries occur between 39 and 41 weeks, with a median duration of 40 weeks and 2 days.³¹ In France, 7.0% of women give birth prematurely (<37 weeks), 17.8% after 41 weeks, and 25.8% undergo labor induction.³² Cesarean sections account for 21.4% of deliveries, of which 3.2% are performed in emergency before labor.³² These figures highlight the unpredictability of labor onset and delivery mode in attempted vaginal births. Although labor induction or planned cesareans can help schedule delivery, spontaneous labor may still occur earlier than expected.

Induction of Labor

Induction of labor does not increase perinatal risk or cesarean section rates in low-risk nulliparous women.³³ Induced labor lasts about 6 hours longer than spontaneous labor.³³ The benefit/risk ratio of induction, especially in patients with prior cesareans, must be carefully evaluated due to increased uterine rupture risk.^{34,35}

Methods of induction generally depend on cervical assessment (Bishop score).³⁶

- Favorable (mature) cervix: Oxytocin infusion or amniotomy, typically resulting in delivery within 24 hours.
- Unfavorable (immature) cervix: Cervical ripening with prostaglandins or balloon catheter, potentially leading to delivery within 48 hours.

Analgesia during Labor

In France, 83% of women use epidural analgesia, which facilitates non-painful instrumental assistance and cesarean sections without general anesthesia.³² Epidurals also allow immediate postpartum hemorrhage management.^{37,38} Alternatives include patient-controlled analgesia (PCA) with synthetic opioids. Cesarean sections can also be

performed with spinal or general anesthesia if epidural is contraindicated. Although epidural analgesia is the standard technique for managing labor pain with minimal side effects, it is not mandatory or essential. Some women may choose not to have it, or it may be medically contraindicated.³⁹

Anticoagulant Prophylaxis during Antepartum and Postpartum Periods

Is Anticoagulant Prophylaxis Required in the Antepartum Period?

The rarity of the ATD does not allow for a randomized clinical trial. Recommendations are based on historical cohort studies and case-control studies. The results of these studies are generally biased by the familial context of the ATD diagnosis. It is therefore difficult to conclude regarding the individual risk of VTE in the context of ATD without considering the existence of a positive family history.

Yet, several scientific societies have proposed recommendations regarding the prevention of VTE during pregnancy in AT deficient patients: the American College of Chest Physician (ACCP),⁴⁰ Society of Obstetricians and Gynecologists of Canada (SOGC),⁴¹ Royal College of Obstetricians and Gynaecologists (RCOG),⁴² American College of Obstetricians and Gynecologists (ACOG),⁴³ American Society of Hematology (ASH),⁴⁴ and the working group on women's health of the Society of Thrombosis and Haemostasis (GTH)⁴⁵ (► **Table 2**). When considering their recommendations, four clinical situations can be globally considered for the assessment of thrombotic risk during pregnancy:

- Women receiving long-term anticoagulation at therapeutic dose.
- Women with a prior VTE, whether unprovoked or occurring in a hormonal context (such as estrogen therapy or pregnancy), or provoked by a transient risk factor (excluding estrogen therapy or pregnancy) and not receiving long-term anticoagulation.
- Women without prior VTE but a positive family history.
- Women without prior VTE nor a positive family history.

A consensus exists for women receiving long-term anticoagulation to receive therapeutic dose throughout pregnancy.

All recommendations propose thromboprophylaxis with anticoagulant therapy from the first trimester if there is a personal history of unprovoked VTE or hormonal situation-associated VTE. For patients with a history of provoked VTE outside hormonal context, thromboprophylaxis with anticoagulants in the antepartum period is generally indicated throughout pregnancy, except for the ASH.⁴⁴

Regarding asymptomatic patients, for all four recommendations supporting thromboprophylaxis with anticoagulant treatment in the case of family history of VTE, it should be prescribed from the first trimester. In the absence of a family history, while the ASH advises against preventive anticoagulation during the antepartum period,⁴⁴ the SOGC, RCOG, and ACOG recommend prophylaxis throughout pregnancy.^{41–43} It should be noted that for the RCOG recommendations, anticoagulation from the first trimester should be

considered for all women with ATD regardless of whether they have a family history of VTE.⁴²

Scores have been developed to assess thrombotic risk during pregnancy. Among them, the STRATHEGE score includes ATD as a major risk factor leading to systematic preventive anticoagulation throughout pregnancy and postpartum.¹¹

When analyzing the literature, one systematic review,¹³ one meta-analysis,¹² and two retrospective studies^{27,46} include a significant number of patients supporting the suggestion for anticoagulant therapy during the antepartum period.

In a systematic review, Rhéaume et al¹³ suggest that asymptomatic women with ATD and a family history have an increased risk of pregnancy-associated VTE compared with women without ATD which, according to the authors, should justify ante- and postpartum thromboprophylaxis. Similarly, Croles et al,¹² in their meta-analysis, conclude that antepartum thromboprophylaxis should be considered in women with ATD and a family history of VTE.

In a single-center, retrospective study, Bramham et al⁴⁶ described the outcomes of 18 pregnancies occurring between 1996 and 2011 in 11 women with ATD. The authors classified patients as low-risk (family screening) or high-risk women (previous VTE). For the low-risk women, antepartum weight-adapted thromboprophylaxis was administered throughout the pregnancy while for the high-risk pregnancies, therapeutic anticoagulation was prescribed. Considering the 18 pregnancies, 4 were complicated by VTE and among them, two low-risk patients had VTE in the absence of thromboprophylaxis, one high-risk (previous PE) woman had a VTE in the presence of inadequate thromboprophylaxis and one high-risk patient had VTE during temporarily stopping injections.

More recently, a single-center historical cohort study reported the risk of VTE associated with type I ATD.²⁷ This study included 80 pregnant women between 1980 and 2018. Since diagnosis of ATD was known, patients received antithrombotic prophylaxis from the first ultrasound (7–10 weeks of pregnancy). When considering only deep vein thrombosis, the authors reported one episode of VTE in 43 (2.3%) pregnancies in women with LMWH prophylaxis, and six episodes in 146 (4.1%) pregnancies in women without prophylaxis. The authors observed a similar number of thrombotic episodes during the postpartum period. Nine episodes of VTE in 93 (10%) pregnancies occurred in patients with a family history of VTE in the absence of thromboprophylaxis. The thrombotic complication rate was 5% in the absence of family history (2/37 pregnancies). They concluded as in the preceding studies that if VTE risk is high in women with positive family history of VTE, the risk is still relevant for those without family history and thromboprophylaxis should be considered in these women.

Considering our literature review on genetically characterized ATD (► **Supplementary Table S1**, available in the online version), there is not enough data available about personal and family history for patients with type II RS, type II PE, and type II HBS ATD (except homozygous Budapest 3 type II HBS). Among homozygous Budapest 3 patients with

Table 2 International guideline recommendations for thromboprophylaxis in women with ATD considering the dose of low-molecular-weight heparin (LMWH) and dose regimens of LMWH

History	Risk period: AP vs. PP	ACCP, 2012	SOGC, 2014	RCOG, 2015	ACOG, 2018	ASH, 2018	GTH, 2020	SFTH, 2025
Women receiving long-term anticoagulation	AP	Adjusted dose or 75% of a therapeutic dose	Therapeutic dose	50 or 75% of therapeutic dose	Therapeutic dose	Therapeutic dose	Therapeutic dose	Therapeutic dose
	PP							
Women with a prior VTE not receiving long-term anticoagulation	AP	Prophylactic or intermediate dose	Intermediate or therapeutic dose	50 or 75% of therapeutic dose	Prophylactic, intermediate dose, or adjusted dose	Anticoagulant prophylaxis in case of unprovoked VTE or associated with a hormonal risk factor	50–75% of therapeutic dose	Prophylactic dose but in some cases and considering additional risk factors, therapeutic dose could be discussed
	PP							
Women without prior VTE but a positive family history	AP	–	Prophylactic dose	Not specified	Prophylactic dose	Prophylactic dose	Prophylactic dose	Prophylactic dose
	PP							
Women without prior VTE nor a positive family history	AP	–	Prophylactic dose	Not specified	Prophylactic dose	–	Prophylactic dose	Prophylactic dose if anticoagulation is decided in AP (systematic in PP)
	PP							
Dose regimens of LMWH								
LMWH	Prophylactic dose			Intermediate dose	Therapeutic dose			
Enoxaparin	4.000 UI/day			100 UI/kg or 2 × 50 UI/kg per day	2 × 100 UI/kg per day			
Tinzaparin	4.500 UI/day				175 UI/kg/day			
Dalteparin	5.000 UI/day			100–150 UI/kg per day or 2 × 50–75 UI/kg per day	200 UI/kg/day the first month then 150 UI/kg/day			
Nadroparin	2.850 UI/day				171 UI/kg/day			

Abbreviations: ACCP, American College of Chest Physician; ACOG, American College of Obstetricians and Gynecologists; AP, antepartum; ASH, American Society of Hematology; ATD, antithrombin deficiency; PP, postpartum; RCOG, Royal College of Obstetricians and Gynaecologists; SFTH, French Society on Thrombosis and Haemostasis; SOGC, Society of Obstetricians and Gynecologists of Canada; VTE, venous thromboembolism.

Note: All therapeutic or prophylactic anticoagulations in the antepartum period are initiated at the first trimester.

personal history of thrombosis ($n = 10$), 8 out of 25 (32%) pregnancies presented with thrombotic complications, even under anticoagulant treatment, while in patients without or with no documented personal history of thrombosis ($n = 7$), 5 out of 34 (15%) pregnancies presented with thrombotic complications. Information about family history is too scarce in this group of patients to be relevant. In addition, we collected data from 70 pregnancies of 47 patients with type I ATD. Among the 28 patients with family history of VTE, 23 (61%) pregnancies presented with thrombotic complications in the 38 pregnancies reported in this group, and only 3 patients with thrombotic complications while pregnant had personal history of thrombosis. Besides, among 19 patients with type I ATD and no or not documented family history of thrombosis, 16 out of 32 pregnancies (50%) presented with thrombosis. Thrombotic events appeared with or without anticoagulant treatment (► **Table 1**).

In summary, there is no consensus regarding the indication for systematic anticoagulation during pregnancy in cases of asymptomatic patients with ATD. However, this indication is widely accepted by various learned societies and supported by the published single-center historical cohort studies in case of positive familial history. We note a thrombotic complication rate greater than 1% in the absence of anticoagulation, which corresponds to the threshold considered by certain recommendations to indicate preventive anticoagulant treatment. Outside of family studies, the literature is scarce, making it more difficult to estimate thrombotic risk in the absence of a family history. One retrospective study including only type I ATD estimated a thrombotic risk at 5% in the absence of family history, which seems in favor of preventive anticoagulation in the antepartum period.

Since thrombotic risk remains constant during pregnancy, if patients are deemed at risk and require preventive anticoagulation, various recommendations and protocols advocate for anticoagulation from the first trimester.

SFTH Proposal

Is Anticoagulant Prophylaxis Required in the Antepartum Period?

- In case of long-term anticoagulation, switch to LMWH.
- In case of a prior VTE without long-term anticoagulation, it is suggested to start anticoagulation from the start of pregnancy.
- In asymptomatic patients with a family history of VTE, it is suggested to start anticoagulation from the start of pregnancy.
- In asymptomatic patients with no family history of VTE, decision of LMWH treatment has to be evaluated after discussion with an expert center. Indeed, the published data do not allow us to propose systematic anticoagulant treatment to prevent first VTE. Individual risk assessment should consider family history, type of ATD (and causal variation), and the presence of associated VTE risk factors.

- If anticoagulation is required, it should be started at the first trimester.

When Anticoagulant Therapy is Required: What Dose?

When thromboprophylaxis is indicated, appropriate dosage must be determined. In reviewing the literature, different situations must be distinguished.

Women Receiving Long-term Anticoagulation at Therapeutic Dose

Seven pregnancies in seven patients on long-term anticoagulation were reported in the literature: three had type I ATD, two had homozygous type II HBS ATD, and for two patients the type of deficiency was not specified.^{47–53} All patients had been anticoagulated at a therapeutic dose from the start of pregnancy except one, who received high-risk prophylactic anticoagulation combined with AT supplementation (homozygous type II HBS).⁵³ However, two thrombotic complications were reported in two patients with type I ATD despite receiving heparin at therapeutic dose.^{51,52}

All expert recommendations currently agree that it is recommended to continue anticoagulation at a therapeutic dose during pregnancy in patients already on long-term anticoagulation regardless of the underlying thrombophilia. This recommendation should therefore also apply in the context of ATD. However, the risk of thrombotic recurrence may persist in certain patients warranting discussion of its association with AT supplementation in specific cases (refer to the chapter “Antithrombin Concentrate Substitution” below).

Women with a Prior VTE not Receiving Long-term Anticoagulation

In the literature, 18 pregnancies were reported in 13 patients with personal history of VTE.^{54–56} In most cases, neither the type of ATD nor the long-term preconception anticoagulant treatment was clearly specified. In most pregnancies (14/18), coming from the same paper, patients received thromboprophylaxis at therapeutic dose or even supra-therapeutic dose (adapted to anti-Xa activity).⁵⁶ Two thrombotic complications during pregnancy have been reported in these situations.⁵⁶

Four other pregnancies were managed by initiating anticoagulant treatment at a prophylactic dose from the first trimester of pregnancy, including one associated with AT supplementation.^{54,55} An ischemic stroke was reported in a patient with homozygous type II HBS deficiency and two VTEs occurred during two pregnancies in a patient with unspecified type deficiency.^{54,55} The pregnancy, for which anticoagulation was initiated at a prophylactic dose with AT supplementation, was not complicated by thrombotic events.⁵⁴

Recommendations from guidelines are particularly heterogeneous on this issue. They suggest anticoagulation at either prophylactic, intermediate (or 50 to 75%), or 100% therapeutic dose. Given the lack of demonstrated benefit of the intermediate dose over the prophylactic dose (as shown in the Highlow study),⁵⁷ and considering that the *peripartum* management of patients on an intermediate dose mirrors that of those on therapeutic dosing—due to precautionary

measures and limited data—we advise against the use of an intermediate dose.

Because these cases are rare, there are few data to conclude on the need for therapeutic dose in this context, but previous data tend to suggest that preventive dose prophylaxis alone could not be sufficient. Individual risk assessment is required in this context to assess the global risk or VTE recurrence during pregnancy.

Women without any History of VTE but with a Positive Family History of VTE

This situation concerns patients for whom only a familial history of VTE was described. In the literature, 12 pregnancies in eight patients have been reported: three patients with type I ATD, two with homozygous type II HBS, and three unspecified.^{56,58,59} The thrombotic risk was prevented with prophylactic dose for four pregnancies, among which one also received AT concentrate,⁵⁸ intermediate doses of anticoagulation for two pregnancies,⁵⁶ and finally therapeutic or supra-therapeutic dose (adapted to the anti-Xa) for six pregnancies.^{56,59} A single thrombotic complication was reported during the pregnancy of a patient with type I deficiency on prophylactic dose of heparin.⁵⁸

Most recommendations suggest a thromboprophylaxis with a prophylactic dose and one team states that intermediate dose could be an option in this situation. There is no consensual attitude and case-by-case support will be necessary. In the case of prophylactic anticoagulation, associated AT supplementation may be discussed according to the procedures described in certain cases (refer to the chapter “Antithrombin Concentrate Substitution” below).

SFTH Proposal

When Anticoagulant Therapy is Required: What Dose?

- In case of long-term anticoagulation, therapeutic dose of anticoagulant should be continued throughout pregnancy.
- In case of a prior VTE without long-term anticoagulation, we suggest prophylactic dose of anticoagulant. Therapeutic dose could be suggested considering individual risk assessment taking into account family history, type of ATD (and causal variation), and the presence of associated VTE risk factors.
- In asymptomatic patients with a family history of VTE, we suggest prophylactic dose of anticoagulant. Therapeutic dose could be suggested considering individual risk assessment taking into account family history, type of ATD (and causal variation), and the presence of associated VTE risk factors.
- In asymptomatic patients with no family history of VTE, for whom anticoagulation is decided, we suggest prophylactic dose of anticoagulant.
- We suggest against using intermediate dose of anticoagulant.

Is Anticoagulant Treatment Required in the Postpartum Period?

In the postpartum period, recommendations suggest anticoagulation ranging from prophylactic to therapeutic dose in

case of a personal history of VTE, whether it occurred in a hormonal situation, associated with transient risk factors (outside hormonal context), or not, for a duration of 6 weeks for most cases. Considering asymptomatic patients with ATD, recommendations differ depending on whether there is a family history of VTE or not. Most recommend at least thromboprophylaxis in the presence of a family history of VTE. The use of LMWH at prophylactic dose for a duration of 6 weeks is specified for the SOGC,⁴¹ RCOG,⁴² and ACCP.⁴⁰ In the absence of a family history, recommendations from the ACCP and ASH differ from the others as they do not propose systematic use of prophylactic anticoagulation.

Recommendations from the French National College of Obstetricians and Gynecologists (CNGOF) for clinical practice in the postpartum period suggest adapting thrombotic risk prevention to associated risk factors.⁶⁰ The French National College of Obstetricians and Gynecologists states that ATD confers a risk of >20 (adjusted odds ratio) and this justifies the initiation of a preventive anticoagulation for a duration of 6 weeks, especially after a cesarean section.⁶⁰

SFTH Proposal

Is Anticoagulant Treatment Required in the Postpartum Period?

- In patients receiving long-term anticoagulation, therapeutic anticoagulant should be continued.
- In patients with a prior VTE not receiving long-term anticoagulation, anticoagulation for a duration of 6 to 12 weeks should be proposed, according to obstetrical and personal risk factors. In some cases, and considering additional risk factors, therapeutic dose could be discussed.
- In asymptomatic patients with a family history of VTE, anticoagulation is offered for a period of 6 to 12 weeks according to obstetrical and personal risk factors.
- In asymptomatic patients with no family history of VTE, we propose a systematic prophylactic anticoagulation for a period of 6 weeks.

Anticoagulant Therapy Monitoring

Anti-Xa Monitoring of LMWH

Heparin and its derivatives are parenteral indirect anticoagulants that bind to a region rich in positive charges of AT through a pentasaccharide motif and amplify the inhibition of factor Xa (FXa).⁶¹ Measurement of anti-FXa activity (anti-Xa) inhibitory function of heparins is used when LMWH monitoring is required. The principle of anti-Xa assay is based on heparin's inhibition of FXa through AT present in patient's plasma or exogenous AT depending on the commercial assay used.^{62,63} Supplementation by exogenous AT can lead to an overestimation of the *in vivo* activity of heparins,^{64,65} in particular in patients with ATD. However, how this relates to the true anticoagulant effect *in vivo* in a patient with ATD is largely unknown. To allow interpretation of anti-Xa levels when using LMWH at therapeutic doses, samples should be taken 3 to 4 hours after the most recent

administration in the case of twice-daily dosage and 4 to 6 hours after once-daily dosage.^{63,66}

To Monitor or not LMWH Anti-Xa during Pregnancy in Patients with ATD

Most patients treated with prophylactic or therapeutic dose of LMWH do not require anti-Xa monitoring because the anticoagulant activity of body weight-adjusted doses of LMWH is highly predictable, and a favorable safety profile without monitoring was demonstrated in clinical trials.⁶⁷

When using LMWH, monitoring of anti-Xa levels is not recommended in routine practice, given uncertainties regarding the relationship between these variables and clinical ends of bleeding or thrombosis and regarding the accuracy and reliability of the measurements. Unlike unfractionated heparin (UFH) anti-Xa, LMWH anti-Xa activity does not correlate strongly with therapeutic anticoagulation.^{67,68} Furthermore, inter-assay and inter-laboratory variability in anti-Xa measurements have been described in non-pregnant and pregnant patients who were treated with therapeutic doses of LMWH, and the validity of using peak anti-Xa levels as a marker of anticoagulant activity has been questioned.^{69,70}

However, the physiological changes in maternal metabolism have led to discussions on optimal LMWH dosing strategy and possible need for monitoring. During physiological pregnancy, there is a time course plasma volume expansion and an increased clearance by glomerular filtration.^{71,72} However, the discrepancies during pregnancy in the pharmacokinetic parameters observed in the literature can be mainly attributed to the different study designs (mostly observational), dosing regimens, and indications for heparin in the study population (therapeutic versus prophylactic administration).⁷² Lower C_{max} values were observed during pregnancy, even with higher doses.⁷² Only two studies showed a statistically significant higher clearance of LMWH during pregnancy.^{73,74} In a prospective study, Aleidan et al observed that a recommended therapeutic range of 0.6 to 1.0 IU/mL was achieved in only half of the pregnant women compared to 75% in the non-pregnant women.⁷⁵ Furthermore, studies with a dose increase design of LMWH (therapeutic or prophylactic) showed an increase in the C_{max} of anti-Xa levels.^{76,77} Recent studies have shown that, as pregnancy progresses, there is a decrease in peak anti-Xa levels and an increase in trough anti-Xa levels when LMWH is administered once or twice daily, without any clinical complications.^{78,79} It was also described that up to 74 to 91% of pregnant women treated with LMWH have sub-therapeutic trough anti-Xa levels, and that a 10 to 20% increased dose is often required to achieve target anti-Xa levels.⁸⁰ Currently, no clinical endpoint studies have demonstrated an increase in efficacy and safety outcomes, such as VTE recurrence or bleeding risk, when using anti-Xa monitoring with optimal therapeutic range, and consecutive dose adjustment performed.^{81,82}

In the various studies reporting the use of therapeutic-dose LMWH during pregnancy, it is not made clear which weight of the woman is considered when calculating the dose of LMWH; this is generally the weight at the time of the

VTE or the weight at the start of pregnancy as recommended.⁸³ Furthermore, literature about anti-Xa monitoring is confusing with studies mixing patients treated during pregnancy (with or without ATD) with prophylactic, intermediate, or therapeutic doses. In a recent systematic review, Kjaergaard et al⁶² included 33 studies (4 RCTs and 29 cohort studies) of pregnant patients (including very few patients with ATD).⁶² No meta-analysis was conducted due to high heterogeneity between the studies. They observed that prophylactic dosing strategies employing weight-based dose, fixed dose, or anti-Xa-adjusted LMWH dose performing equal in effectiveness and safety. In pregnant women with VTE or high thromboembolic risk, therapeutic weight-adjusted LMWH and weight plus anti-Xa-adjusted LMWH provided similar results in terms of effectiveness and safety. Based on the results of this systematic review,⁶² current evidence does not support the need for anti-Xa monitoring when using LMWH as thromboprophylaxis or treatment during pregnancy (without mechanical heart valve). Nonetheless, the need for anti-Xa monitoring in pregnant women with ATD was not in the scope of the study.

Monitoring of LMWH with anti-Xa activity in pregnancy is controversial because there is an inadequate evidence base to know what levels are appropriate, assays are variable with high inter-assay variability, laboratory monitoring for outpatients is not easy particularly at peak levels, and there is a lack of clinical trials to validate appropriate anti-Xa levels in pregnancy.

In patients with ATD (outside the setting of pregnancy), it was shown that anti-Xa measurements after spiking of LMWH or UFH are clearly correlated with AT activity.⁸⁴ Mean anti-Xa levels were about 35% lower than expected in ATD patients as compared to controls, and 76 to 95% of ATD patients had levels that would be classified as “subtherapeutic” in clinical setting.⁸⁴

The 2019 European Society of Cardiology Guidelines⁸⁵ recommend weight-based therapeutic-dose LMWH in pregnant women with acute VTE and suggest reserving anti-Xa monitoring for specific high-risk circumstances such as recurrent VTE, renal impairment, and extremes of body weight. Also, the American College of Chest Physicians guideline recommends weight-based LMWH doses and states that use of anti-Xa monitoring remains controversial.⁸⁶ In 2018, the ASH guidelines⁴⁴ and in 2019, the French guidelines^{83,87} suggest against monitoring with anti-Xa in pregnant women with acute VTE, which is also in line with the RCOG, which recommends against routine monitoring with anti-Xa in pregnant women with acute VTE except in those with extremes of body weight (<50 and >90 kg), or with other complicating factors (e.g., renal impairment or recurrent VTE). Anti-Xa monitoring of therapeutic doses of LMWH is controversial in pregnancy, with even less known in women with ATD. The RCOG recommends monitoring with anti-Xa in pregnant women with ATD and prior thrombophilia-associated VTE event. In a monocentric retrospective English study of 18 pregnancies in 11 women with ATD, Bramham et al⁴⁶ identified 5 pregnancies considered at high risk (previous VTE). For these women, anti-Xa monitoring

was performed at least monthly, and every 2 weeks if there was a dosage adjustment, with the aim of maintaining trough levels above 0.1 IU/mL and peak levels (4 hours post injection) between 0.5 and 1.0 IU/mL. Among them, one (20.0%) had complication of VTE (sagittal sinus thrombosis) in a setting of inadequate thromboprophylaxis. No data were available concerning anti-Xa levels and thrombotic events. Furthermore, there was no correlation between AT levels and outcomes in all pregnancies reported. Moreover, anti-Xa monitoring in pregnant women supplemented by AT, for acute VTE or not, and treated with LMWH is even less known.

To the best of our knowledge, during LMWH therapy, LMWH resistance should not be defined by the failure to achieve a specified anti-Xa level despite the use of an appropriate dose of heparin.⁸⁸ In pregnant patients with ATD, LMWH resistance should be suspected only in the presence of recurrent VTE, extension of existing thrombosis, or a new episode of VTE despite therapeutic-dose LMWH (weight-adjusted), and not by a failure to achieve target anti-Xa levels.

SFTH Proposal

To Monitor or not LMWH Anti-Xa during Pregnancy in Patients with ATD

- We suggest against routine monitoring of anti-Xa levels to adjust LMWH at therapeutic dose, except for preventing overdosing and subsequent bleeding risk in specific patient populations, such as those with extreme body weight and renal impairment.

Is There Indication for D-dimer Level Evaluation during Pregnancy?

D-dimer level measurement is used for the exclusion of thrombotic event, to estimate the risk of venous thromboembolism recurrence, and is included in the ISTH algorithm for the diagnosis of disseminated intravascular coagulation.⁸⁹

It is well known that D-dimer level increases during pregnancy with a significant rise between the first, second, and third trimesters. In the cohort of Wang et al⁹⁰ including 1,343 pregnant women, D-dimer levels above the threshold of 500 µg/L were observed respectively in 15, 71, and 96% during the first, second, and third trimesters.⁹¹ In 102 pregnant women, D-dimer levels in the first trimester ranged from 169 to 1,202 mg/L, from 393 to 3,258 mg/L in the second trimester, and from 551 to 3,333 mg/L in the third trimester.⁹²

In a context of suspected PE, D-dimer measurements are used in algorithm and associated with a pre-test of low/intermediate or unlikely clinical probability. Modified or unmodified D-dimer thresholds in the context of pregnancy are proposed and make it possible to exclude a VTE in order to limit the use of imaging in this context.⁹³ Out of 510 women suspected of PE (12 excluded), the YEARS algorithm made it possible to avoid 195 pulmonary CT angiograms.⁹³ The yield of this algorithm is greater in the first (exclusion in 65% of cases) than in the third trimester (exclusion in 32%). It is noticeable that in this study, known thrombophilia was reported for 14 (28%) without any further description. Other similar studies are detailed in Wauthier et al's 2023 review.⁹¹

D-dimer level measurement can thus be used as an exclusion criterion in case of PE suspicion in pregnant women while no study is available to support the use of D-dimer in other contexts.

SFTH Proposal

Is There Indication for D-dimer Level Evaluation during Pregnancy?

- There is no indication for evaluating D-dimer level during pregnancy apart from a suspicion of PE.

Antithrombin Concentrate Substitution

Which AT Concentrates can be Used in this Setting?

Two types of AT concentrates are currently available, plasma-derived and recombinant concentrates. Both are approved for prophylaxis, but only plasma-derived AT (pdAT) is indicated in the context of acute VTE.⁹⁴ Recombinant concentrates are not available in Europe⁹⁵ and are not recommended during pregnancy. Recombinant concentrate half-life is shorter (10 hours) than that of plasma-derived products (average 1.5 to 3 days, 55 +/- 14 hours, depending on the clinical situation and whether or not heparin therapy is used).^{94,96}

Which Dose of AT Should be Used?

One international unit of AT is equal to the quantity of AT found in 1 mL of normal plasma. Administration of 1 IU/kg will increase circulating levels by around 2% in inherited ATD and without a thromboembolic event. The number of IU/kg to administer initially can be based on the formula:

$$\text{Plasma-derived AT} = (120\% (1) - \text{baseline AT activity level}) \times \text{body weight (kg)} / 1.4^{52}$$

- (1) According to product monographs; "120%" could be replaced with desired AT level in percentage.

In the case of a maintenance dose, 60% of the initial bolus should be injected every 24 hours. AT levels can be monitored, sampled 20 minutes after injection (to calculate the recovery rate) and at least 12 hours after injection.⁹⁴

What is the Place of AT Concentrates in the Context of Pregnant Women with Inherited ATD during Antepartum and Postpartum

In the absence of randomized clinical trials and large observational studies to guide the management of women with inherited ATD in pregnancy, there is limited guidance on the appropriate role of AT concentrates during pregnancy (antepartum, peripartum, and postpartum).^{47,97} It is also uncertain who would benefit from AT replacement therapy and when to infuse them. The safety data for neonatal outcomes in case of AT replacement is reassuring. No fetal adverse effects have been reported in animal or human studies with pdAT concentrate. It is not the case for recombinant products. However, there have been no neonatal adverse effects reported in the 22 infants born from mothers who received ATryn. Administration of AT concentrates does not have to be

systematic.⁹⁸ Besides personal and familial thrombotic history, cost–benefit considerations should be taken into account.

The three main indications for AT concentrate substitution in pregnant women are (i) development of VTE despite therapeutic anticoagulant, (ii) the peripartum period when anticoagulant therapy has been withheld for delivery, and (iii) when anticoagulants are contraindicated (bleeding, surgery, etc.).

Antepartum

In a pregnant patient who develops a VTE during pregnancy despite a therapeutic dose of LMWH, two options might be discussed: (i) increasing the dose of LMWH or (ii) starting substitution with AT concentrate. This has to be discussed with clinician from specialized centers. Among the different studies, AT concentrate substitution in this situation seems to be the preferred option and was associated with favorable outcomes.^{46,52,99} When AT concentrate substitution is decided, a loading dose of 50 UI/kg (target between 80 and 120%) is administered followed by maintenance doses every 48 to 72 h to reach a trough level of >60% until delivery.^{46,52,58,97} There is no standardization in the duration of the regimen of replacement therapy.^{51,52} Case reports mention punctual or pregnancy-long duration of treatment.⁵²

Some suggest that AT substitution could be discussed in pregnant women with a history of VTE during a first pregnancy despite a well-managed therapeutic dose of LMWH. In this situation, the decision to prescribe AT concentrates could take into account the severity of the deficiency (type, causal variant), other associated thrombophilia, and other additional risk factors (age, obesity, comorbidities, etc.).⁵¹

At least systematic AT concentrate substitution along with therapeutic anticoagulation should be discussed in homozygote type II HBS associated with high risk of VTE.

SFTH Proposal

AT Concentrates in Pregnant Women with Inherited ATD during Antepartum

- Decision of AT substitution must be evaluated after discussion with an expert center including hematologist, obstetrician, and anesthetist.
- In patients who develop VTE during pregnancy despite well-managed therapeutic dose of LMWH, we suggest AT concentrate substitution.
- In patients with a history of VTE during a first pregnancy despite well-managed therapeutic dose of LMWH, the decision to prescribe AT concentrates could take into account the severity of the mutation, other associated thrombophilia, and other additional risk factors (age, obesity, comorbidities).
- In patients with homozygous type II HBS, systematic AT concentrate substitution should be systematically discussed.

Postpartum

AT concentrate substitution used for peripartum alone should be discontinued when prophylactic or therapeutic

anticoagulation has been restarted after delivery. Some authors consider that AT substitution could be continued for more than a few days after delivery^{52,99} or before INR is in therapeutic range when VKA therapy was introduced.⁹⁵

It should be maintained in patients who received AT concentrate during antepartum, until the end of LMWH treatment.

Otherwise, AT substitution could be introduced in the postpartum period when anticoagulant treatment has to be withheld, e.g., in case of bleeding, surgery, or in patients who develop a VTE during pregnancy despite a therapeutic dose of LMWH if heparin is still used for VTE treatment.

Surgery and Pregnancy

AT concentrates could be administered in cases with high risk of bleeding (anticoagulation is desired but contraindicated). Protocol might start the day before surgery to the postoperative period, until the thrombotic risk (according to the procedure) ceases or the anticoagulation is restarted.^{47,94,99}

Homozygous Type II HBS

Literature is conflicting regarding this subtype of ATD. Some authors suggest substitution at 34 weeks gestation, others in the peripartum or just after delivery, and some only suggest substitution in the postpartum period. The combined use of prophylactic treatment and substitution yields variable outcomes depending on the patient, and neither fully prevents the risk of VTE nor the risk of fetal loss.⁵³ Alguet et al¹⁰⁰ reported two live births in the absence of substitution (one on LMWH alone and one on VKA). Kovac et al³⁰ showed that the HBS homozygous Budapest 3 group, despite anticoagulant treatment, had the lowest live birth rate (28.5% compared with 100% for type I). Complications included fetal death, intrauterine growth restriction, fetal loss, and placental abruption. Kovac et al also reported arterial events in this subtype.³⁰ In the case of homozygous type II HBS, substitution with AT concentrate along with LMWH is recommended.¹⁰¹ In this type of homozygous ATD, the benefit of using heparin therapy alone seems low. Therapeutic choice arises between treatment with LMWH combined with AT substitution throughout the pregnancy or warfarin in the second and third trimesters.

Despite these general experts' opinions, each case should be individualized, and physicians are advised to contact an expert center.

Peripartum Management of Anticoagulant Therapy and Antithrombin Concentrate Substitution

Management of Anticoagulant Therapy

The scenarios encountered with peripartum anticoagulation can be categorized into three distinct situations, assuming that LMWH is the preferred anticoagulant during pregnancy.

1. Prophylactic LMWH (low-dose LMWH: enoxaparin ≤ 4,000 UI or dalteparin 5,000 UI in one subcutaneous injection per day or enoxaparin 3,000 UI in two subcutaneous injections per day):

According to the latest international recommendations from the Society of Obstetric Anesthesia and Perinatology published in 2018, epidural analgesia is possible 12 hours after the last injection.¹⁰²

Data from the HIGHLOW trial⁵⁷ show that 82% of women with unplanned childbirth (spontaneous labor or emergency cesarean) and 93% with planned delivery (induction or planned cesarean) were eligible for epidural analgesia (interval between last injection and delivery >24 h for intermediate-dose LMWH, >12 h for low-dose LMWH).¹⁰³ This indicates that most women on prophylactic dose of LMWH can access epidural analgesia, and thus, prophylactic dose of LMWH does not typically necessitate artificial labor induction for epidural access. Similar time intervals should theoretically be respected for insertion and for removal of an epidural catheter (12 h)¹⁰⁴ although some teams authorize resumption of anticoagulation at least 4 hours after catheter removal.¹⁰² The risk of severe postpartum hemorrhage does not appear to be increased in the event of delivery under preventive anticoagulation.^{105,106}

2. Therapeutic dose of LMWH (high-dose LMWH: enoxaparin 1 mg/kg or dalteparin 120 UI/kg in two subcutaneous injections per day or enoxaparin 1.5 mg/kg or dalteparin 200 units/kg in one subcutaneous injection per day):

According to the same recommendations, epidural analgesia requires a 24-hour wait after the last injection.¹⁰² This 24-hour delay for epidural eligibility explains why only 61% of women with unplanned deliveries (spontaneous labor or emergency cesarean) and 81% with planned deliveries (induction or planned cesarean) could benefit from an epidural analgesia.¹⁰³ Thus, induction of labor may be justified for epidural access if two conditions are met:

- a. No obstetric contraindications exist, and the risks of induction do not outweigh the benefits of epidural access.
- b. An anticoagulation window of 48 to 72 hours is allowed, considering the induction process can take up to 48 hours in case of unfavorable cervix. Cervical monitoring at the end of pregnancy can help determine a favorable time for induction with favorable cervix, minimizing the anticoagulation window to 48 hours.

Similar time intervals should theoretically be respected for insertion and for removal of an epidural catheter (24 hours)¹⁰⁴ although some teams authorize resumption of anticoagulation at least 4 hours after catheter removal.¹⁰²

Although the data are limited, the risk of severe postpartum hemorrhage does not appear to be increased in patients receiving therapeutic dose of LMWH.¹⁰⁷

3. Therapeutic doses of LMWH and major thromboembolic risk without possible anticoagulation window:

This scenario typically applies to patients with mechanical heart valves on long-term anticoagulation or recently diagnosed with PE. For these patients, the peripartum

strategy must be pre-planned with the obstetrician, anesthesiologist, and relevant specialists. If no anticoagulation window is possible, labor induction for epidural analgesia is not recommended unless obstetrically indicated. Spontaneous labor and faster delivery are preferred.

A summary of management of anticoagulant therapy and delivery is addressed in ► **Supplementary Data S2** (available in the online version).

The Place of AT Concentrate Substitution

As mentioned in the previous section, anticoagulant therapy (prophylactic or therapeutic dose) should be stopped before delivery, which exposes patients to thromboembolic risk. Unfortunately, and although the literature focuses on both antenatal and postpartum cares, there are few studies considering the peripartum period. Recommendations are based on personal experience⁹⁵ or studies including very few patients^{46,51,97} and systematic substitution with AT concentrates is recommended regardless of antenatal antithrombotic therapy without proven benefits on the thromboembolic risk. At her center, Pabinger⁹⁵ systematically replaces all patients with AT in cases of type I, type II RS, and homozygous type II HBS ATD patients. When ATD type is unknown, it is proposed to systematically replace with AT, considering AT level (<60%), personal and family history of thrombosis.^{95,97} Although limited data are available in the literature—since case reports usually do not report AT trough levels during the peripartum period in patients receiving AT supplementation—the objective is most often to maintain AT levels between 70 and 20%.^{46–48,51,55,95,108–110} Although it is accepted that the initial AT injection is 50 IU/kg, the subsequent management of AT substitution until delivery is very poorly documented. Bramham et al⁴⁶ stated that systematic injection of 50 UI/kg 12 hours after the initial one has to be administered if labor lasts >12 hours. For other authors, injection is only required when AT level measured 12 hours after the previous injection is <70%.⁴⁷ In ► **Fig. 2**, we propose an algorithm of AT substitution considering the different situations of peripartum and delivery. In this algorithm, systematic substitution with 50 UI/kg is administered when anticoagulant treatment is stopped. AT level is evaluated each 12 hours⁵² during labor and before delivery. AT concentrate is re-administered only if the AT level is below 70%. Given that artificial labor induction may require a phase of cervical ripening, AT substitution should be considered 12 to 24 hours after the last LMWH injection (depending on the dose of LMWH) at the point of continuing labor induction with oxytocin administration or artificial rupture of membranes, or at the onset of labor (cervical dilation ≥4 cm). These timings are based on the recommended delay between the last LMWH injection and the eligibility for epidural analgesia.¹⁰² If there is a contraindication to epidural analgesia, labor pain management can be provided at any time using patient-controlled analgesia with synthetic opioids, either until delivery or while waiting for the necessary time interval. In the case of an indication for cesarean delivery, the criteria for access to spinal anesthesia regarding

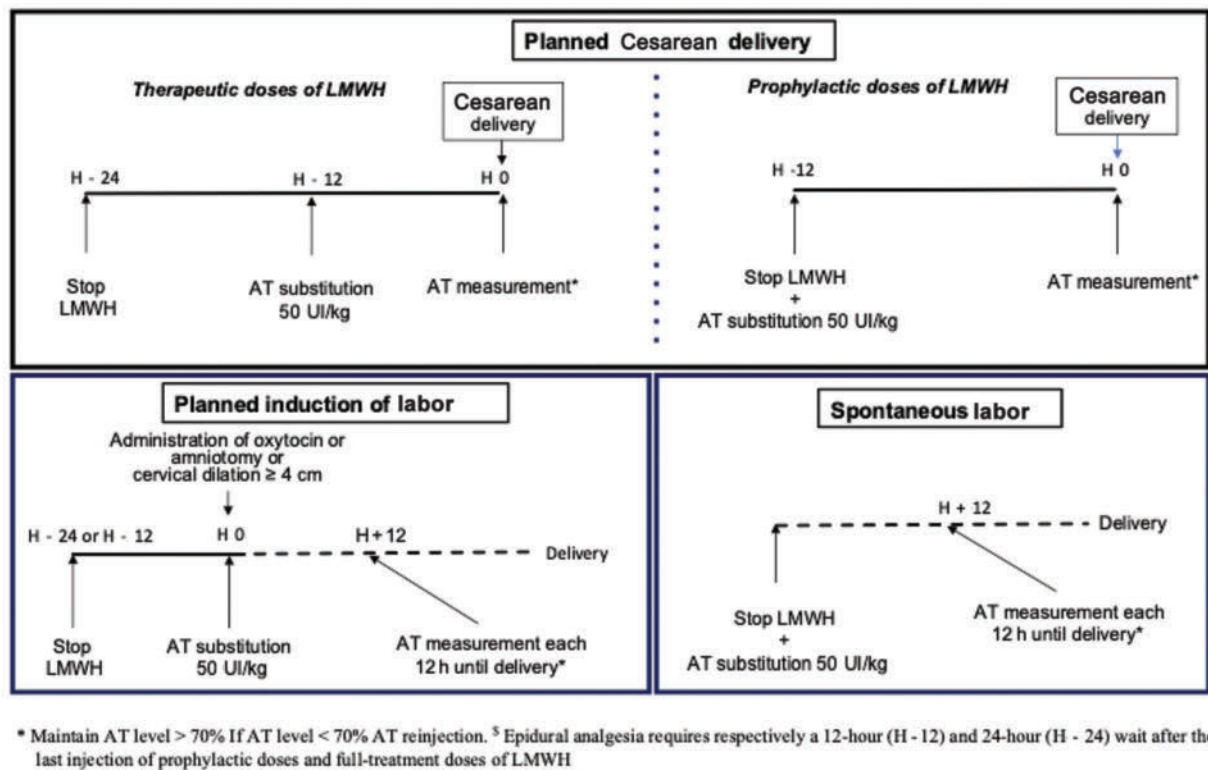


Fig. 2 Proposal of antithrombin substitution during peripartum in patients with inherited antithrombin deficiency. LMWH, low-molecular-weight heparin.

anticoagulation with heparin are identical to those described for epidural analgesia. If neither epidural nor spinal anesthesia is feasible, a cesarean section will have to be performed under general anesthesia.

SFTH Proposal

AT Concentrate Substitution during Peripartum

- A multidisciplinary approach, including hematologist, obstetrician, and anesthetist, should be systematically considered to elaborate a protocol for the peripartum period.
- AT concentrates should be proposed in ATD patients.
- We suggest maintaining trough AT level at least at 70% during peripartum period. ► **Fig. 2** suggests the time and the dose of AT concentrate substitution during peripartum.

Conclusion

The thromboembolic risk during pregnancy in patients with ATD is significantly high. However, this risk depends on both the patient's personal and family VTE history, additional thromboembolic risk factors, and the type of ATD, thereby justifying an individualized thromboprophylaxis throughout pregnancy.

The aim of this TITAN group, on behalf of the French Society of Thrombosis and Haemostasis, was to harmonize the management of pregnant women with ATD, by setting up a national multidisciplinary consultation meeting to provide personalized recommendations for each of these patients.

Although anticoagulant treatment is systematically prescribed at some point during pregnancy, its regimen depends on the patient's history and associated risk factors. It is noteworthy, therapeutic regimen adapted to weight does not require any monitoring by anti-Xa activity and D-dimer dosage. Peripartum management is challenging in patients with antepartum anticoagulation, as anticoagulant therapy must be discontinued, and antithrombin concentrate is systematically administered to restore hemostatic balance. Finally, administration of anticoagulant treatment in postpartum period is quite consensual; however, the choice of the dosage necessitates further considerations.

Hence, this rare clinical situation associated with a high risk of thrombosis clearly needs a multidisciplinary approach involving obstetricians, anesthetists, and hematologists.

Conflict of Interest

N.G. discloses consulting fees or travel awards by Bayer, Bristol-Myers Squibb/Pfizer, LEO-Pharma, LFB, Werfen, and Stago Diagnostica. L.S. reports receiving lecture fees from Norgine, and lecture and consulting fees from Ferring Pharmaceuticals, GlaxoSmithKline, Pfizer, Organon, and Bayer. N.T. discloses consulting fees from Sanofi and Viatris.

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