Thrombosis Research 157 (2017) 41–45

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Management of hereditary antithrombin deficiency in pregnancy

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ARTICLE INFO

Article history:
Received 4 February 2017
Received in revised form 1 May 2017
Accepted 20 May 2017
Available online 24 May 2017

ABSTRACT

Antithrombin (AT) deficiency is a high-risk thrombophilia and a rare condition. Despite full anticoagulation during pregnancy and the postpartum period, women with AT deficiency may still be vulnerable to developing venous thromboembolism (VTE), including fatal events. There is limited guidance on the management of AT deficiency in pregnancy, including the role of AT concentrates. Following a comprehensive review of the state of the art with respect to recommendations and guidelines, our expert panel in maternal-fetal medicine, hematology and basic science reached consensus on key issues in the recognition and management of AT deficiency in pregnancy. This paper summarizes the state of the art and summarizes what we believe are best practices with special emphasis on a multidisciplinary approach involving obstetrics and hematology in the care of women with AT deficiency.

1. Introduction

Antithrombin (AT) deficiency is a high-risk thrombophilia and an uncommon disorder. AT inhibits all the serine proteases of the coagulation system (including thrombin, factors Xa, and IXa and, to a lesser extent, factors XIa and XIIa as well as kallikrein and plasmin), with its function accelerated by heparin and by heparan sulfate proteoglycans expressed on the vascular endothelium [1]. Deficiency of AT significantly increases the risk of VTE, typically deep-vein thrombosis or pulmonary embolism. The estimated prevalence of AT deficiency varies widely, with estimates between 1:500 and 1:5000. This broad range reflects the difficulties in ascertaining the true prevalence of a relatively uncommon disorder with different subtypes. Of the various inherited thrombophilias, with the possible exception of homozygous and compound heterozygous conditions, AT deficiency carries the highest risk of VTE, with an estimated 20-fold increased risk of a first VTE. In penetrant families, the estimated risk of thrombosis is approximately 50%, whereas with heterozygosity for factor V Leiden, the lifetime risk is 5%. In patients with AT deficiency and a history of prior VTE or a family history of VTE, the additional risk factors of surgery, immobilization, and pregnancy further increase the risk of VTE and warrant consideration of prophylaxis, not only with anticoagulation, but also with AT concentrates. It is estimated that about 60% of the thrombotic events in individuals with AT deficiency are actually provoked by such high-risk situations [2–5].

Despite full anticoagulation during pregnancy and the postpartum period, women with AT deficiency may still be vulnerable to developing venous thromboembolism (VTE), including fatal events. Prophylaxis with AT concentrates can potentially reduce this risk in high-risk situations, including pregnancy. Additionally, in the event of acute VTE and/or heparin resistance, AT replacement therapy can be used along with heparin. In rare circumstances, a pregnant woman with AT deficiency may receive AT concentrates as an outpatient along with anticoagulation [2,6].

There is limited guidance on the management of AT deficiency in pregnancy, including the appropriate role of AT concentrates, and little evidence on which to base clinical decisions. In the absence of randomized clinical trials and large observational studies to guide management of women with inherited antithrombin deficiency in pregnancy, we

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http://dx.doi.org/10.1016/j.thromres.2017.05.017
0049-3848/

convened a panel of experts to interpret the available and relevant medical literature and to weigh in with practical considerations.

2. Materials and methods

On October 16, 2015, the Foundation for Women and Girls with Blood Disorders convened a panel of experts in the fields of basic science, hematology and maternal-fetal medicine, hematology to address the challenges in the management of women with inherited AT deficiency in pregnancy. The purpose of the meeting was:

1. To convene experts in the fields of obstetrics & gynecology and hematology, who are knowledgeable in AT deficiency and women's blood disorders.
2. To review the state of the art with respect to recommendations and guidelines concerning the management of AT deficiency during pregnancy.
3. To examine the full range of options, both published and practiced, with respect to diagnosing and caring for women with AT deficiency during pregnancy.
4. To describe and underscore for healthcare providers the intersection of obstetrics and hematology in the optimal care of women with AT deficiency.
5. To reach agreement on the best practices for diagnosis and management of women with AT deficiency during pregnancy.
6. To develop a report and disseminate the results to practicing physicians.

To facilitate consensus on best practices for diagnosis and management of AT deficiency in pregnancy, the agenda was planned in advance by the Foundation and two members of the group, who also served as leaders and facilitators. One of the leaders also served as note-taker. Furthermore, the meeting was recorded. Individual members of the panel were assigned, according to their background and expertise, to review the available and relevant medical literature and summarize it for the group. The available and relevant medical literature specific to pregnancy included, but was not limited to, a current review on the diagnosis and management of hereditary antithrombin deficiency [2], two systematic reviews of pregnancy-related VTE risk and risk of adverse pregnancy outcome in women with AT deficiency [7,8], a systematic review of the safety of low-molecular-weight heparin (LMWH) in pregnancy [9], two single arm, open label clinical trials of AT concentrates in pregnancy [10,11], and multiple (small) case series of AT deficiency in pregnancy [12–15]. Presentations included 1) the establishment or confirmation of the laboratory diagnosis of AT deficiency, 2) the epidemiology of AT deficiency in pregnancy, 3) hematologic considerations and 4) maternal-fetal medicine considerations. The existing systematic reviews were incorporated. At the conclusion of the presentations, the experts were asked to weigh in on pre-selected questions relating to 1) the establishment of the diagnosis, 2) the involvement of specialists, 2) stratification of treatment according to risk factors, 3) concerns about bleeding, and 4) fetal surveillance. Various responses to the questions were considered until consensus was reached. Ample time was allowed for each question. For every question, consensus was reached without the need for a formal vote.

Table 1
Conditions that can result in acquired AT deficiency.

Medical conditions	Mechanism of decrease in antithrombin levels
Acute thrombosis	Increased consumption
Disseminated intravascular coagulation	
Surgery	
Sepsis	
Inflammatory bowel disease	
Systemic inflammation	
Liver failure	Decreased synthesis
Malnutrition	
Nephrotic syndrome	Increased excretion

3. Results

3.1. Summary of the relevant literature with respect to establishment or confirmation of the laboratory diagnosis of AT deficiency

Establishment of the diagnosis of AT deficiency begins with measurement of AT activity [16,17]. The laboratory assay of AT activity is usually performed using an amidolytic assay. Excess thrombin or Xa is added to patient platelet-poor plasma and residual thrombin activity, which is inversely proportional to AT activity, measured using a chromogenic substrate. Heparin cofactor (HC) II inhibits thrombin but not Xa. Elevated levels of HCII can falsely increase measured AT activity, and thus assays have been optimized using a Xa-based assay, protease inhibitors, and/or bovine thrombin, which are not inhibited by HCII. This measure of activity may not detect all type II variants, some of which may require special laboratory evaluation in a reference center. Two categories of congenital AT deficiency have been described, Type I and Type II [17]. Type I AT deficiency is due to a quantitative deficiency in AT, with a concordant decrease in antigen and activity. In type II AT deficiency, the antigen level is usually normal but a measure of activity is decreased. These deficiencies are due to mutations in the reactive site (IIa), heparin-binding site (IIb), or near the region of the reactive loop (IIc). Types I and IIa are most clearly associated with an increased thrombotic risk [18].

Many factors can affect AT assays, and given that inherited AT deficiency is rare, a low AT level is most commonly due to an acquired condition or analytic variable [16](Table 1). For that reason, inherited deficiency should be confirmed by repeat testing and family studies. Medications that affect AT levels are shown in Table 2. In addition, assays can be affected by hemolysis, lipemia, a high hematocrit (>55%), and a clotted sample. In addition latex immunoassays are affected by high levels of rheumatoid factor or paraproteins. The most common treatment and medical conditions resulting in low AT levels include unfractionated heparin infusions, massive thrombosis, and disseminated intravascular coagulation. In general, patients should not be tested for inherited AT deficiency during hospitalization, acute illness or while on anticoagulation. Oral contraceptives and estrogens may result in a modest decrease in AT levels [19]. There is also a modest decrease in AT levels during pregnancy, with further decrease at the time of delivery [20]. Levels return to baseline by 72 h postpartum [20].

3.2. Summary of the epidemiology of AT deficiency in pregnancy

AT deficiency is associated with an increased risk of pregnancy-associated VTE, with the risk estimates for antepartum and postpartum VTE ranging from 3 to 47.7%, with the higher risk estimates derived from older retrospective family studies that did not necessarily require objective confirmation of VTE, sometimes used probands who had already suffered VTE, and may have inadvertently involved families with more than one (as yet undiscovered) thrombophilia [12,21–26]. The methodologically stronger studies, including more recent retrospective and

Table 2
Medications that affect AT levels.

Medication	Effect on antithrombin level	
	Decrease	Increase
Heparin	✓	
L-Asparaginase	✓	
Hormonal contraceptives	✓	
Warfarin		✓
Direct thrombin inhibitors	✓ (falsely with thrombin-based AT assay)	
Direct Xa inhibitors	✓ (falsely with Xa-based AT assay)	

prospective family cohort studies, suggest that the risk lies somewhere between 3 and 17.7%, with half of these events expected to occur antepartum and half postpartum [12,25,26]. This is a very broad range, and even these studies still have methodologic limitations, including variable definitions of AT deficiency. Of note, the odds of VTE in pregnancy, based on a systematic review of case control studies (which would not necessarily have enrolled patients with a positive family history of VTE) [7], are 4.69 (95% confidence interval 1.30, 16.96); which would lead to an absolute risk estimate for both antepartum and postpartum VTE of 0.5%, assuming a baseline risk of VTE with pregnancy of 1.2/1000 [27].

3.3. Summary of hematologic considerations

Two recent publications based on the clinical studies that led to the approval of both the plasma-derived AT concentrate [10] and the recombinant AT concentrate (rhAT) [11] have provided insight into indications and dosing of AT concentrates for the prevention and treatment of VTE during pregnancy in women with AT deficiency. For the plasma-derived concentrate, 6 women with hereditary AT deficiency who had VTE during pregnancy were dosed according to a weight-based protocol and were treated concomitantly with anticoagulation. None experienced recurrent thrombosis while receiving treatment with AT concentrate [10]. For the recombinant concentrate, 21 women with hereditary AT deficiency, a personal or family history of VTE, and documented AT activity levels ≤60% of normal were treated at the time of delivery. Evaluation of the pharmacokinetic data from this study revealed a higher clearance and volume of distribution for rhAT in pregnant versus nonpregnant patients. Two postpartum VTE occurred in women who were no longer receiving rhAT and were on prophylactic (as opposed to therapeutic) anticoagulation [11]. The dosing regimens are summarized in Table 3. A limitation of both of these studies is that the number of subjects was small and there was no control arm.

3.4. Summary of maternal - fetal considerations

AT deficiency poses risks to the fetus as well as the mother. In theory, in a high-risk thrombophilia like AT deficiency, thrombosis of the uterine or intervillous circulation could contribute to fetal hypoperfusion independent of whether or not the fetus carried a mutation for AT deficiency. Initial studies suggested that thrombophilias, in general, might be important contributing factors to adverse pregnancy outcome. The initial studies, however, were predominately case-control in design. The thrombophilias that were significant in initial studies were factor V Leiden, the prothrombin gene mutation and protein S deficiency, perhaps because only these thrombophilias were frequent enough to allow reasonable statistical power. Prospective cohort studies have suggested that these thrombophilias are probably not major factors in determining whether someone will or will not suffer adverse pregnancy outcome.

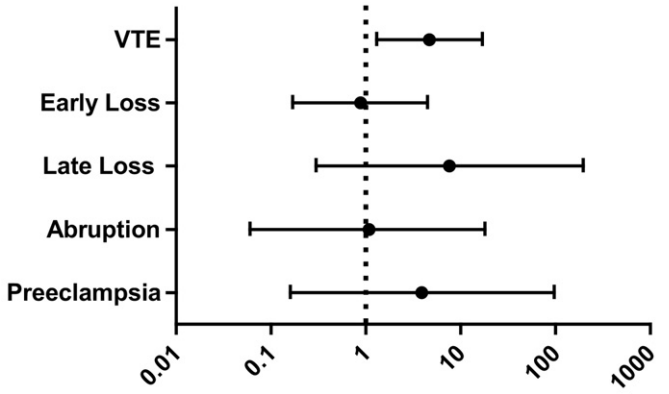

Fig. 1. Odds of adverse pregnancy outcome(based on single studies with one or two cases). Adapted from Robertson et al., Br J Haematol. [7].

In most studies, AT deficient cases have been analyzed along with these other thrombophilias, e.g., factor V Leiden, making it impossible to appreciate AT deficiency's unique contribution to adverse pregnancy outcome. In one systematic review [7], which included one study for each of the following adverse outcomes - early loss, late loss, abruption and preeclampsia - there was no evidence of these conditions being associated with AT deficiency (See Fig. 1). However, there are four subsequent case series that suggest otherwise, especially among women who did not receive thromboprophylaxis. In a report of an unspecified number of pregnancies among 12 women, there were no fetal losses in the women who received thromboprophylaxis, but 63% among those who did not [12]. In another report of 18 pregnancies, there was a difference in the rate of fetal growth restriction in those pregnancies treated with thromboprophylaxis versus those not so treated (27% versus 50%), as well as a difference in the rate of stillbirth (0% versus 50%) [13]. In another report of 18 pregnancies among 7 women, 25% had a growth restricted fetus, and the fetal loss rate was 33%. Two out of 6 of the fetal losses were late losses, and all occurred in women who did not receive thromboprophylaxis [14]. In a recent study of 18 pregnancies among 11 women with AT deficiency, patients with no prior VTE received enoxaparin 40 mg daily until 16 weeks gestation and 40 mg twice daily thereafter. Patients with prior VTE initially received intermediate dose enoxaparin (1 mg/kg) once daily, increased to twice daily at 16 weeks with anti-Xa monitored dosing. Thromboprophylaxis was stopped at initiation of labor or 12 h prior to cesarean and 50 IU/kg antithrombin concentrate was given. Thromboprophylaxis was restarted after delivery. Median gestation was 39 weeks and median birth-weight was 2995 g, but 35% of infants were small for gestational age ($p = 0.01$) [[15].] In these recent case series, fetal loss may have been increased among women who did not receive thromboprophylaxis, but the rate of fetal growth restriction and small for gestational age infants were significantly increased independent of thromboprophylaxis.

Table 3
Dosing of AT concentrates for the treatment and prevention of VTE during pregnancy in women with AT deficiency. [10,11].

	Plasma derived AT concentrate ($n = 6$ women with AT deficiency who had VTE during pregnancy)(10)	Recombinant AT concentrate (rhAT) ($n = 21$ with AT deficiency, personal or family history of VTE and AT level ≤ 60 IU/dL(11)
Loading dose during acute treatment of VTE	54–62 units/kg	
Maintenance dose during acute treatment of VTE	50%–100% of the loading dose for 3–10 days	
Loading dose for delivery	46–50 units/kg	IU/kg = (100 - the pretreatment AT level in %) /1.25 administered as bolus over 15 min
Maintenance dose peripartum	50%–75% of the loading dose for 5–7 days	IU/kg/h = (100 - pretreatment AT level in %) /5.43 administered as a continuous dose
Thrombotic events	None	None during treatment with AT concentrate. 2 with postpartum VTE while on prophylactic (as opposed to therapeutic) anticoagulation.

4. Our Consensus on the management of hereditary antithrombin deficiency in pregnancy

The group members achieved consensus on the following best practices for correct diagnosis and optimal management of women with AT deficiency during pregnancy. Except where noted below, these recommendations are based on expert opinion (the opinion of the experts who participated.)

4.1. Establishment of the diagnosis

The establishment of the diagnosis is critical. Clinicians should recognize that a patient is unlikely to have AT deficiency unless she has a first degree relative with a history of VTE occurring less than the age of 50 and in the absence of strong risk factors, like surgery, cancer and immobilization. Testing should start with a chromogenic AT activity assay, taking care to avoid testing in the setting of acute illness, acute thrombosis, or during heparin treatment. Given that AT deficiency is uncommon and that laboratory test results may require expert interpretation, patients suspected of having AT deficiency based either on family history or initial AT activity testing should be seen by a hemostasis/thrombosis expert for confirmation of the diagnosis. (Based on expert opinion.)

4.2. Role of specialists

Antithrombin (AT) deficiency is a high-risk thrombophilia and a rare condition. Management of AT deficiency in pregnancy requires consultation with a hemostasis thrombosis expert and with maternal-fetal medicine. AT concentrates should be prescribed and administered under the direction of a hemostasis/thrombosis expert. Maternal-fetal medicine should be consulted during the pregnancy and in anticipation of delivery. In advance of delivery, the patient should have the opportunity to meet with a member of the anesthesia team . (Based on expert opinion.)

4.3. Stratification of treatment

Treatment during pregnancy should be stratified according to the presence of acute VTE and according to the presence of risks factors, including personal history of VTE, family history of VTE, and requirement for long-term anticoagulation.

4.3.1. Acute VTE

AT concentrates can be used to normalize AT levels for women with AT deficiency who have current VTE or recurrent VTE despite anticoagulation. (Based on two single arm, open label clinical trials of AT concentrates in pregnancy.[7,8].

4.3.2. History of VTE and on long-term anticoagulation

These women should receive full-dose LMWH during pregnancy and the postpartum period. There are no data to support routine monitoring of anti-Xa levels, but if monitoring is performed for adequacy of dosing (such as in morbid obesity, unusual weight gain or recurrent thrombosis), the dose of LMWH should not be reduced below weight-based dosing. If monitoring is performed to ensure against excess anticoagulation (such as in renal insufficiency or bleeding), the dose of LMWH may be reduced. Heparin-induced thrombocytopenia is rare with LMWH treatment; routine platelet screening is not indicated. Because of the less consistent anticoagulation provided by subcutaneous unfractionated heparin (UFH), patients should not be converted to UFH unless it is intravenous (IV) UFH and the patient is being monitored in the hospital. (Based on a systematic review of the safety of LMWH in pregnancy (9) and expert opinion.)

AT concentrates are a treatment option when anticoagulation is withheld in potentially high-risk settings such as bleeding, surgery or other invasive procedure, miscarriage, and childbirth. Both plasma-derived and recombinant AT concentrates are well tolerated, with minimal adverse reactions, and pose an extremely low risk for transmission of infectious agents. (Based on two single arm, open label clinical trials of AT concentrates in pregnancy(7, 8) and expert opinion.)

4.3.3. Patients with a history of VTE not on long-term anticoagulation

Due to the therapeutic implications, confirmation of the diagnosis is critical. If the diagnosis is confirmed, and AT activity is <60%, the patient should be treated like the patient with a history of VTE on long-term anticoagulation. The patient should receive full-dose LMWH during pregnancy and the postpartum period. AT concentrates are a treatment option when anticoagulation is withheld in all potentially high-risk settings such as bleeding, surgery, and childbirth. (Based on expert opinion.)

4.3.4. Patients with AT activity <60% and no personal history of VTE, but with a family history of VTE

In this situation, a range of options can be considered from prophylactic to full anticoagulation, depending on the patient's other risk factors, her family history, and her preferences. Whether or not to prescribe AT concentrates in this situation is a matter of clinical judgment, but a hemostasis/thrombosis expert should be consulted. Anticoagulant treatment should be continued for at least 6 weeks postpartum. (Based on expert opinion.)

4.3.5. Patients with AT activity <60%, no personal history of VTE, and no family history of VTE

In this situation, a range of options can be considered from observation to prophylactic anticoagulation depending on the patient's other risk factors and her preferences. It is unlikely AT concentrates would be prescribed in this situation unless AT activity is very low (< 40%), but a hemostasis/thrombosis expert should be consulted. If prophylactic anticoagulation is prescribed, it should be prescribed for at least 6 weeks postpartum. (Based on expert opinion.)

4.4. Concerns about bleeding

Because of concerns about bleeding in a patient on anticoagulation and receiving AT concentrates, the patient should have the opportunity to meet with a member of the anesthesia team in advance of delivery. The anesthesiologist should be aware that in the absence of heparin, antithrombin is NOT a therapeutic anticoagulant. AT concentrates' anticoagulant properties are merely physiologic. AT concentrates are administered to restore normal AT levels. Therefore, AT concentrates are not a contraindication to regional anesthesia.

There is a paucity of evidence regarding appropriate and effective management of obstetric bleeding, e.g., postpartum hemorrhage, in women with AT deficiency. Generally, the full range of management strategies can be implemented such as administration of uterotonics, repair of lacerations and incisions, balloon tamponade, compression sutures, administration of blood products and avoidance of nonsteroidal anti-inflammatory drugs. Use of tranexamic acid may be considered as it has not been shown to increase the risk of thrombosis in other settings [28]. Anticoagulants should be resumed as soon as hemostasis is assured and after discussion among participating specialists. (Based on expert opinion.)

4.5. Fetal surveillance

A plan for fetal surveillance should be implemented based on the patient's other obstetrical risk factors and the fact that AT deficiency is a high-risk thrombophilia and that there are some reports of an increased risk of fetal growth restriction. At a minimum, a plan for fetal surveillance should include serial ultrasounds for fetal growth. Were fetal growth restriction to develop, appropriate fetal surveillance for

fetal growth restriction should be implemented. (Based on expert opinion.)

5. Discussion

The recommendations presented in this paper are intended as a guide for clinicians caring for pregnant women with AT deficiency. A strength of the recommendations is their derivation from a review of the current existing medical literature and the input of the experts. A limitation is their derivation from limited data. During the proceedings that culminated in the recommendations, several additional areas were identified that were deemed worthy of consideration in the optimal management of AT deficiency in pregnancy, but were outside the scope of this expert panel's consensus discussions. These areas include the:

- Role of genetic testing in the diagnosis of AT deficiency
- Risks of thrombosis associated with type II AT deficiency
- Optimal prophylactic anticoagulant dosing
- Optimal target AT level
- Feasibility of ambulatory administration of AT concentrates
- Cost-benefit ratio of various treatments

As they stand, the recommendations are focused on optimizing the management and treatment of AT deficiency in pregnancy remains of clinical importance due to the life-threatening nature of the condition to both the mother and fetus. Both the obstetrical and hematological aspects of the condition necessitate a multidisciplinary approach to management involving hemostasis/thrombosis experts and maternal-fetal medicine specialists. Confirmation of the diagnosis is critical, as is the stratification of treatment after diagnosis. Besides consideration of anticoagulation and AT concentrates to mitigate the increased risk of thrombosis, management during pregnancy requires consideration of the potential bleeding risks to the mother and possible risks of adverse fetal outcome.

Potential conflicts of interest with respect to the content of this paper:

Andra H. James, MD, MPH - none.

Shannon M. Bates, MDCM, MSc, FRCPC - salary support through the Eli Lilly Canada/ May Cohen Chair in Women's Health.

Kenneth A. Bauer, MD - consultation for Janssen Pharmaceuticals and Boehringer Ingelheim.

Ware Branch, MD - none.

Kenneth Mann, PhD – consultation for Haematologic Technologies, Stago.

and Vascular Solutions.

Michael Paidas, MD – research funding from rEVO Biologics, Inc.

Neil Silverman, MD - none.

Barbara A. Konkle, MD – none.

Acknowledgment

Support for the meeting was provided by an unrestricted grant to the Foundation for Women and Girls with Blood Disorders by Grifols, Inc.

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