

# Management of Antithrombin Deficiency in Pregnancy

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## Abstract

Antithrombin (AT) deficiency is a high-risk thrombophilia and a rare condition. The risk of venous thromboembolism (VTE) is increased in AT-deficient women during pregnancy and the postpartum period and is especially high in women with a prior history of VTE. A thorough assessment of VTE risk is recommended in pregnant AT-deficient women, comprising the degree and type of AT deficiency, genetic mutations, personal and family history, and additional preexisting or pregnancy-specific risk factors. Due to a lack of adequate study data, there is limited guidance on the management of AT deficiency in pregnancy, including the need for prophylactic anticoagulation, the appropriate dose of low-molecular-weight heparin (LMWH), and the role of AT substitution. LMWH is the medication of choice for the pharmacological prophylaxis and treatment of VTE in pregnancy. Patients with a history of VTE should receive full-dose LMWH during pregnancy and the postpartum period. AT concentrates are a treatment option when anticoagulation is withheld in potentially high-risk events such as childbirth, bleeding, or surgery and in cases of acute VTE despite the use of therapeutic dose anticoagulation. Women with AT deficiency should be counseled at specialized centers for coagulation disorders or vascular medicine, and close cooperation between obstetricians and anesthesiologists is warranted before delivery and during the peripartum period.

## Keywords

- ▶ antithrombin deficiency
- ▶ heparin
- ▶ anti-Xa monitoring
- ▶ antithrombin concentrate
- ▶ pregnancy

## Introduction

Antithrombin (AT) is the key regulator of coagulation by inhibiting procoagulant serine proteases such as thrombin and activated (a) factor (F) X, FIXa, FXIIa, and FVIIa when in complex with tissue factor. AT is synthesized in the liver and has a half-life of 2 to 3 days.<sup>1</sup> Two distinct domains on the molecule are primarily involved in the mechanism of the inhibitory function of AT: a pentasaccharide binding site and an active reaction center. The activity of AT is greatly

accelerated in the presence of heparin or heparan sulfate, which contain specific pentasaccharide sequences. The presence of heparin leads to a conformational change, the reactive site is exposed, and the target protease is then cleaved by the scissile bond of the reactive site and captured by the inhibitor.<sup>2</sup>

AT deficiency is considered the most clinically severe deficiency of a natural anticoagulant and was the first major thrombophilia described by Egeberg in 1965.<sup>3</sup> Usually, it is diagnosed when the plasma anticoagulant activity is less

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than 80% of the normal activity (or the lower limit of the assay's reference range). Hereditary AT deficiency is a rare cause of congenital thrombophilia, occurs in 0.02 to 0.07% of the general population, and is found in 1 to 5% of patients with venous thromboembolism (VTE).<sup>4,5</sup> A meta-analysis of case-control and cohort studies showed an increased risk of first VTE in AT-deficient individuals (odds ratio [OR]: 16.3, 95% confidence interval [CI]: 9.9–26.7) compared with controls. This risk was substantially higher than that in subjects with protein S or protein C deficiency (ORs: 5.4 and 7.5, respectively).<sup>6</sup> Patients with AT deficiency mainly present with deep vein thrombosis (DVT) and pulmonary embolism (PE), whereas the cerebral sinus and abdominal veins are rarely affected.<sup>7–11</sup> Arterial thrombosis is not characteristic of AT deficiency, but cases of it have been reported.<sup>12,13</sup>

AT deficiency is transmitted as an autosomal disorder, and the penetrance is very high, with more than 50% of individuals experiencing a thromboembolic event before the age of 50 years.<sup>14</sup> Patients with AT deficiency show notable clinical heterogeneity depending on environmental risk factors, the type of deficiency, and genetic factors.<sup>15</sup>

The *SERPINC1* gene that encodes AT comprises seven exons and six introns and is located on the long arm of chromosome 1. To date, more than 350 mutations in the *SERPINC1* gene that cause AT deficiency have been described, comprising missense mutations, frame-shift deletions, nonsense mutations, insertions, and deletions.<sup>16</sup> Mutations impair protein synthesis and/or function.

There are two types of AT deficiency. Type I deficiency is a quantitative defect and leads to a parallel reduction in the level of AT activity and antigen in the plasma. Type II is a qualitative defect characterized by the presence of a variant AT protein that is secreted in normal amounts but with impaired function. Type II deficiencies are classified into three subtypes: mutations affecting the reactive site (type IIa) in which the defects disrupt the enzyme-inhibitor interaction; heparin binding site (HBS) defects resulting in the defective binding of heparin to AT (type IIb); and a pleiotropic group of mutations near the reactive loop leading to decreased AT levels (type IIc). Eighty percent of AT-deficient individuals with thromboembolic events exhibit a type I deficiency. Patients with type I and type IIa/IIc deficiencies display a significantly more severe phenotype with a higher risk for thromboembolism than individuals with heterozygous HBS mutations.<sup>17,18</sup> Affected individuals are generally heterozygous because the homozygous state exhibits a minimal chance of survival. The only individuals with homozygous AT deficiency carry mutations in the HBS. In individuals with homozygous type IIb/HBS AT Budapest 3 deficiency, neonatal and early childhood thrombosis is common, and affected individuals develop thrombotic events at a younger age (median age: 21 years; range: 3–68 years) and have a higher risk of thrombosis than heterozygous individuals.<sup>19,20</sup>

An exact diagnosis of AT deficiency is of clinical relevance to estimate the thrombogenic risk and to provide the most appropriate management for VTE prophylaxis and treatment. A full diagnostic workup comprises functional and

antigenic AT assays and further genetic testing. Van Cott et al suggested an algorithm for interpreting AT activity results in the diagnosis of hereditary AT deficiency.<sup>21</sup> The two types of AT deficiency can be distinguished based on activity and antigen assays. The first-line test for the diagnosis of AT deficiency is a functional assay that detects both type I and II deficiencies. Routine diagnostic AT assays are predominantly chromogenic assays that measure AT inhibition of FIIa or FXa in the presence of heparin. If a low activity level is repeatedly observed, an immunological test can be considered to differ between type I and type II deficiency. AT type I deficiency is characterized by low AT activity and antigen levels, whereas low activity and normal antigen levels are typical for AT type II deficiency. In the latter case, further testing might be necessary to distinguish between HBS variants and other type II variants. It is important to rule out the presence of a direct oral anticoagulant (DOAC) and full-dose heparin therapy and to consider the acquired causes for AT deficiency. Full-dose heparin or low-molecular-weight heparin (LMWH) can cause mild decreases in AT during the first days after initiation due to consumption.<sup>22</sup> Direct FXa inhibitors may increase FXa-based assay results and therefore falsely elevate the test results, whereas the results of thrombin-based tests remain unaffected.<sup>23</sup> In contrast, direct thrombin inhibitors are able to falsely elevate thrombin-based tests, but not Xa-based results.<sup>24</sup> Thus, the intake of DOACs should be paused for 48 to 72 hours before testing. Alternatively, laboratory tests can be performed during DOAC therapy when adding an activated charcoal-based product (e.g., DOAC-Stop, DOAC-Remove) to adsorb DOACs from plasma samples.<sup>25</sup> As thrombotic risk seems to depend on the type of AT deficiency, genetic testing should be performed in selected patients.<sup>21</sup>

It is important to emphasize that acquired etiologies for decreased AT are more common than hereditary AT deficiencies. AT activity can be reduced in several clinical scenarios, such as impaired liver function, increased protein consumption (e.g., surgery, acute thromboembolism, disseminated intravascular coagulation, pregnancy), protein loss (e.g., nephrotic syndrome, protein-losing enteropathy), the drug-induced depletion of AT (e.g., heparin, L-asparaginase, estrogen therapy), and extracorporeal circulation.<sup>26,27</sup> Thus, in the case of low AT, testing should be repeated to confirm the diagnosis, and preanalytical errors and acquired causes should be excluded.

### AT Deficiency and the Risk of Pregnancy-Associated VTE

Pregnancy and the postpartum period are well-known risk factors for thromboembolic events in a woman's life. Generally, pregnant women have a fivefold higher risk for VTE than nonpregnant women.<sup>28</sup> The risk is the highest in the first postpartum weeks and remains elevated for up to 12 weeks postpartum.<sup>29,30</sup> Many risk factors are responsible for the increased VTE risk in pregnancy and the puerperium. Pregnancy-related physiological changes comprise a hypercoagulable state due to an increase in coagulation factors (e.g., FVIII, fibrinogen, von Willebrand factor), a decrease in

physiologic anticoagulants (manifested mainly by a reduction in free protein S), progesterone-induced venous dilatation, and compression of the iliac veins and the inferior vena cava by the gravid uterus. Additionally, preexisting risk factors (e.g., comorbidities, obesity [body mass index (BMI) > 30 kg/m<sup>2</sup>], age [> 35 years], positive family history of VTE), pregnancy-related risk factors (e.g., caesarean section, postpartum infection), and further transient risk factors contribute to VTE risk. In particular, a personal history of VTE and/or hereditary thrombophilia are the main factors that contribute to an increased VTE risk in pregnancy and the puerperium.<sup>31</sup>

Women with AT deficiency experiencing pregnancy and delivery are at high risk of maternal VTE and other obstetric complications, such as embryo–fetal losses.<sup>32,33</sup>

Conard et al reported on the incidence of VTE in pregnant women with deficiencies in AT, protein S, or protein C. In their study, 7 of 50 (14%; 95% CI: 8–28%) women with AT deficiency developed DVT during pregnancy, compared with 0.2% of women in the general population. The VTE risk was higher in the postpartum period than during pregnancy (11/39, 28%, 95% CI: 30–36%).<sup>34</sup> A few years later, De Stefano et al showed that approximately 37% of women with AT deficiency developed VTE during pregnancy and the postpartum period, with most events occurring in the postpartum period.<sup>35</sup> In these early reports, the very high risk of pregnancy-associated VTE in women with inhibitor deficiencies, including many patients with a history of VTE and episodes of VTE, was not objectively confirmed.<sup>36</sup> The review by Robertson et al focused on thrombophilic defects and the occurrence of VTE and obstetric complications in pregnant women. Based on three studies, an OR of 4.69 (95% CI: 1.3–16.96) for VTE was calculated in pregnant women with AT deficiency.<sup>37</sup> The ORs from this study were used to calculate absolute risk estimates of pregnancy-associated VTE in women with inherited thrombophilia according to the American College of Chest Physicians' (ACCP) 2012 guidelines.<sup>38</sup> The observed or estimated absolute risk of VTE in AT-deficient women in the ante- and postpartum periods was 3.0% (95% CI: 0.08–15.8) in family studies and 0.7% (95% CI: 0.2–2.4) in nonfamily studies. In a recent review, Croles et al examined the relative and absolute risks of hereditary thrombophilia on VTE associated with pregnancy. The authors included case–control studies, cohort studies, and observational studies on pregnancy-associated VTE. The total number of pregnancies reported was 41,297, of which 5,994 were in women with thrombophilia. For women with AT, protein C, and protein S deficiencies, only family studies were available.<sup>39</sup> Bayesian statistics were used for a meta-analysis of the relative risks and absolute risks of pregnancy-associated VTE in women with thrombophilia. The highest absolute risk of pregnancy-associated VTE was found in AT-deficient women. The absolute risk of VTE in the antepartum and postpartum periods was 7.3 (95% CI: 1.8–15.6) and 11.1 (95% CI: 3.7–21.0), respectively.

Because AT deficiency is rare in the general population and in pregnant women, risk estimates are uncertain. Most studies have analyzed only a small number of cases or were

cohort studies including family members. The risk of VTE in individuals with AT deficiency is difficult to predict and varies according to the deficiency subtype and the genetic defect. In observational studies with nonpregnant patients, a dose–response effect has been demonstrated insofar that decreasing activity levels of AT are associated with an increased risk of VTE.<sup>40,41</sup> A substantial reduction in AT levels is generally present if AT activity is less than 60%.<sup>42,43</sup> Additionally, the VTE risk increases in cases of a positive family history and in combination with other preexisting or pregnancy-related risk factors.

## Case Report (Part 1)

A 28-year-old woman developed PE while using a combined hormonal contraceptive. Her family history was positive regarding VTE: her father was diagnosed with recurrent VTE with the first thromboembolic event at the age of 35 years, and her sister was diagnosed with PE at the age of 20 years. Thrombophilia testing revealed AT levels of 57% in an FXa-based assay and 60% in a FIIa-based chromogenic AT activity assay (reference range: 79–111 and 83–118, respectively). In addition, AT antigen levels were similarly reduced, and a type 1 deficiency was diagnosed. Genetic testing showed a heterozygous nonsense mutation in exon 5 (SERPINC1 gene). Anticoagulation with a vitamin-K antagonist (phenprocoumon) was initiated and was switched to a DOAC (rivaroxaban at a dosage of 20 mg once daily) a few years later at the request of the patient. At the age of 34 years, the patient came to seek advice regarding pregnancy. Her body weight (bw) was 85 kg. She had no comorbidities, and, besides anticoagulation therapy, took no other medication. The patient was informed about the increased risk of VTE during pregnancy and the postpartum period and the potential teratogenic effects of the DOAC. As the patient had a regular monthly menstrual cycle and clearly understood the increased risk of miscarriage and embryopathy if the DOAC was continued after the sixth week of gestation (i.e., ≥ 14 days after the first missed day of the expected menses), we recommended the continuation of DOAC therapy and a switch to a weight-adjusted therapeutic-dose of LMWH as soon as a pregnancy was confirmed. This strategy was in agreement with the recently published recommendations of the Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH) that addressed thromboprophylaxis for women with thrombophilia.<sup>31</sup>

## Management of AT Deficiency in Pregnancy

To date, there are no randomized controlled trials on the use of LMWH for AT deficiency in pregnancy. There is also uncertainty concerning the appropriate dose of LMWH. This is especially relevant for AT-deficient patients, as AT is a cofactor of heparin for the inhibition of activated coagulation FX and FII. Furthermore, there is controversy concerning the need for monitoring anti-Xa levels during anticoagulation and during the use of AT concentrates.

A retrospective multicenter clinical analysis of more than 1,000 patients with pregnancy-associated VTE or severe pregnancy complications in three different German university hospitals was performed by Rogenhofer et al.<sup>32</sup> Patients were screened for hereditary and acquired thrombophilia. A total of 18 pregnancies in seven AT-deficient patients were identified. Five patients were diagnosed with a heterozygous mutation, and one patient was diagnosed with a homozygous missense mutation (type HBS). Genetic testing was not performed for one patient. Because the thrombophilic disorder was not known at the time of pregnancy, anticoagulation with different types of LMWH (enoxaparin, tinzaparin, nadroparin, dalteparin) or fondaparinux was not applied for more than half of the pregnancies. No prophylactic anticoagulation was administered in 10 pregnancies. VTE occurred in three of the ten pregnancies during pregnancy or the postpartum period. LMWH without AT substitution was administered for three pregnancies. In two pregnancies, LMWH was given in a weight-adjusted prophylactic dosage, and VTE occurred at the end of the first trimester. In three pregnancies without a prior or current VTE, prophylactic AT replacement was initiated during the first trimester concomitant to LMWH, and no VTE was documented during pregnancy or the postpartum period. Immediately after the diagnosis of VTE, substitution with AT was started for two pregnancies, and AT concentrates were administered for two pregnancies with VTE after 34 weeks of gestation and peripartum. Several adverse pregnancy outcomes were registered, including one newborn delivered at 25 weeks of gestation, two losses at 21 and 28 weeks of gestation and four early miscarriages. The monitoring of anti-Xa levels and bleeding complications were not reported. The authors of this study concluded that patients with the substitution of AT in addition to LMWH showed the best maternal and neonatal outcomes. However, it should be critically noted that only very few patients received this treatment.

### Risk Stratification and Thromboprophylaxis Management Protocols

Bramham et al reported on a retrospective, single-center observational study that assessed thrombotic events and pregnancy outcomes in women with established AT deficiency.<sup>44</sup> In contrast to the previously mentioned study, these patients were treated according to a standard protocol. Women at low risk, defined as having no previous VTE, were prescribed enoxaparin or dalteparin in high-risk prophylactic doses with a dose adjustment for women with a bw greater than 90 kg. The doses were increased from a once daily application to a twice daily application after 16 weeks of gestation. High-risk patients, defined as those with a positive history of VTE, were started on a half-therapeutic dose of enoxaparin once daily. The dose was increased after 16 weeks of gestation to a twice daily application and adjusted according to the anti-Xa levels (targeted peak level of 0.5–1.0 IU/mL). LMWH was withheld at the initiation of labor or 12 hours prior to an elective caesarean section. AT concentrates were given to low- and high-risk patients at a dose of 50 IU/kg at the initiation of labor to achieve an

empirical estimated AT activity target of 100%. LMWH was restarted 24 hours postdelivery in the low-risk group and as soon as active bleeding was stopped in the high-risk group. Altogether, 18 pregnancies in 11 patients were reported. Four pregnancies (22%) were complicated by VTE. One woman presented with index thrombosis in pregnancy, two women developed VTE while not taking the prescribed thromboprophylaxis, and one woman had VTE in the presence of inadequate thromboprophylaxis despite being in a high-risk situation. Seventeen pregnancies were successful. The bleeding risk was not increased during pregnancy or the peri-/postpartum period.

The largest and most recent cohort study of women with AT type I deficiency investigating the risk of pregnancy- or puerperium-associated VTE and the risk of obstetrical complications was published by Abbattista et al in 2020.<sup>33</sup> In this single-center study, 80 women were included in the analysis of the risk of pregnancy-associated VTE and 87 were included in the analysis of the risk of obstetrical complications. Notably, women who became pregnant before the diagnosis of AT deficiency did not receive thromboprophylaxis during pregnancy. However, women for whom pregnancy occurred after the diagnosis were treated with LMWH according to a standard protocol. Women without a personal history of VTE or those with previous VTE who had stopped anticoagulation therapy before pregnancy received prophylactic doses of LMWH (4,000 IU once daily or 6,000 IU for women with a bw > 60 kg). Women on anticoagulant therapy or those without prior VTE who were considered at a particularly high thrombotic risk received therapeutic doses of LMWH. The measurement of anti-Xa levels to guide anticoagulation was not performed. AT concentrates were not routinely given. When compared with women without LMWH prophylaxis, a nonsignificant risk reduction of VTE was observed in patients receiving LMWH: three VTE events occurred in 43 pregnancies in women treated with LMWH (7.0%, 95% CI: 1.8–7.8) who previously suffered from hormone-associated VTE, and 17 events occurred in 146 pregnancies in women who did not receive LMWH (11.6%, 95% CI: 7.2–17; RR: 0.6, 95% CI: 0.2–1.9;  $p=0.57$ ). In asymptomatic women with a negative family history of VTE, the VTE risk without anticoagulation was 5.4% (95% CI: 0.9–16.7), whereas in asymptomatic women with a positive family history, the VTE risk was 11.8% (95% CI: 6.4–10.6). The authors concluded that women with AT deficiency are at high VTE risk during pregnancy. The VTE risk was highest in asymptomatic women with a positive family history but was also not negligible in women with a negative family history.

In summary, these cohort studies show that there is no standardized approach on how to manage pregnant women with AT deficiency. In the studies by Bramham et al and Abbattista et al, the inclusion criteria concerning low- and high-risk patients were completely different, and varying doses of LMWH were applied in the low-risk group. High-risk patients were uniformly treated with therapeutic doses of LMWH beyond the 16th week of gestation in both studies.



### Monitoring of anti-Xa Levels during Anticoagulation with LMWH

With a focus on achieving adequate anticoagulation in pregnant women with severe AT deficiency who received LMWH, Pearson-Stuttard et al conducted a multicenter case series.<sup>45</sup> Severe AT deficiency was defined as an AT level less than 55% (irrespective of prior VTE) or an AT level less than 80% with a personal history of VTE. Thirteen of 18 women had a personal history of VTE. All 18 women included in the study were treated with LMWH (enoxaparin, dalteparin, or tinzaparin) during their 27 pregnancies, and anticoagulation was adapted according to anti-Xa levels. Anti-Xa activity was measured 3 to 4 hours post-dose aiming for a target peak level of 0.5 to 1.0 IU/mL. To achieve the target peak, daily doses between 10.000 and 36.000 IU of LMWH were needed, according to an average daily dose (normalized per kg of bw) of 299 IU/kg. Two women (11%) experienced VTE despite anticoagulation, and all pregnancies ended in live births. This study illustrates that high doses of LMWH are needed to achieve therapeutic anti-Xa levels. Remarkably, the dose of LMWH did not correlate with the severity of AT deficiency. According to the authors, the use of LMWH was safe during pregnancy with no reported bleeding complications. However, two postpartum hemorrhages occurred immediately after vaginal delivery, with blood losses of 600 and 900 mL, respectively.

Croles et al spiked plasma samples from 34 AT-deficient subjects and 17 family controls with unfractionated heparin and LMWH, aiming to reach an anti-Xa activity of 0.8 IU/mL.<sup>46</sup> Reduced AT activity was associated with significantly reduced anti-Xa levels. Thus, standard doses of heparin may lead to undertreatment in AT-deficient patients. Notably, the standardization of anti-Xa assays across laboratories is poor. An overestimation of the *in vivo* heparin activity is possible when exogenous AT is added to anti-Xa assays.<sup>47</sup> There is no evidence on the target peak and trough levels, and clinical trials to validate appropriate anti-Xa levels are lacking.

### Use of Antithrombin Concentrate

James et al reported on six pregnant women with AT deficiency who experienced VTE during pregnancy and were treated with a plasma-derived AT concentrate in a clinical trial.<sup>48</sup> All women received AT concentrates for the time of delivery or termination of pregnancies (two cases). Two of the patients received AT concentrates only in the peripartum period. AT concentrates were initiated for two patients with acute VTE, as IV heparin treatment failed to reach the targeted activated partial thromboplastin time, and treatment with AT concentrates and anticoagulation was maintained until the peripartum period. In one woman, treatment with an AT concentrate was started due to recurrent PE while being treated with heparin, and in another patient, an AT concentrate was initiated due to acute DVT and laboratory signs of disseminated intravascular coagulation. No VTE occurred while patients were receiving treatment with AT concentrates.

A further study was performed by Paidas et al using a recombinant AT concentrate.<sup>49</sup> Twenty-one pregnant women with documented AT levels less than 60% and a personal or family history of VTE were enrolled in the trial and treated at the time of delivery. Two patients on prophylactic anticoagulation who were no longer receiving AT concentrates developed postpartum VTE.<sup>49</sup> Refaei et al summarized cases with the use of AT concentrates.<sup>50</sup> AT concentrates were mainly applied for the treatment of acute VTE in pregnancy that occurred predominantly despite therapeutic anticoagulation ( $n = 23$ ) and for prophylaxis during pregnancy and the peri- and postpartum period in addition to LMWH ( $n = 10$ ). When an AT concentrate was used for treatment, concomitant anticoagulation with heparin was provided, and therapeutic doses were predominantly administered. In the majority of cases, AT concentrates were withheld after delivery.

Notably, four plasma-derived AT concentrates (Atenativ [Octapharma], Kybernin [Behring], Anbinex [Grifols], AT III NF [Takeda]) are approved in Germany for use in patients with inherited AT deficiencies to prevent thrombotic complications during or following pregnancy or surgical procedures. No recombinant AT concentrate is currently available in Germany.

In summary, there are only scarce data on the use of AT concentrates. The majority of the data are derived from case reports or small case series.

### What is known from the current guidelines on this topic?

In the last decade, several international guidelines have been published on VTE risk assessment and the evaluation of VTE prophylaxis during pregnancy and the postpartum period.<sup>31,38,51–54</sup> The most recent recommendations on this topic were summarized in a position paper published by the GTH Working Group in Women's Health in 2020.<sup>31</sup> When evaluating antithrombotic prophylaxis during pregnancy, three different situations must be distinguished:

- Women with no personal history of VTE but have known thrombophilia with a positive/negative family history of VTE.
- Women with a personal history of VTE (provoked by a transient risk factor vs. associated with exogenous estrogen, pregnancy, or unprovoked VTE) who are no longer on antithrombotic therapy.
- Women with a personal history of VTE on long-term anticoagulation.

In all women, a VTE risk assessment should be performed, preferably before pregnancy or in early pregnancy. It should be repeated in situations that increase VTE risks during pregnancy (e.g., hospitalization, immobilization), before or after delivery. In general, the decision for or against pharmacological thromboprophylaxis must be made on an individual basis, weighing the risk of VTE against the risk of adverse side effects such as severe bleeding complications. According to the current guidelines, the absolute VTE risk must exceed 1 to 5% before a benefit of thromboprophylaxis

can be expected. Briefly, all guidelines recommend pharmacologic VTE prophylaxis for the postpartum period in women with prior VTE. Pharmacologic VTE prophylaxis is recommended for all women in the antepartum period in the case of prior VTE in the context of exogenous estrogen, pregnancy, or unprovoked VTE, irrespective of an underlying thrombophilia. In asymptomatic women, the recommendations on pharmacologic VTE prophylaxis differ according to the underlying thrombophilia and a positive family history. An overview of these recommendations is presented in the position paper of the GTH.<sup>31</sup> Heparins do not cross the placental barrier and do not pass into breast milk in significant amounts and are therefore the pharmacological agents of choice for the prophylaxis and treatment of VTE during pregnancy and the postpartum period.<sup>38,51,53,55,56</sup> If pharmacologic prophylaxis is indicated, it is usually initiated in the first trimester and continued for at least 6 weeks postpartum.

Moreover, the current guidelines also differ in the assessment of VTE risk in women with AT deficiency. AT deficiency is considered high risk by the guidelines of the American College of Obstetricians and Gynecologists (ACOG), the Royal College of Obstetricians and Gynaecologists (RCOG), the Society of Obstetricians and Gynaecologists of Canada (SCOG), and the GTH in cases of severe deficiency (i.e., < 60%). As mentioned earlier, the VTE risk of patients with AT deficiency is hard to predict and depends on the degree of the deficiency, the type of AT deficiency, the family history, and other intraindividual or pregnancy-related risk factors. Of note, these specific and essential risk factors are not included in the current guidelines. ▶Table 1 summarizes the recommendations for thromboprophylaxis in women

with previous VTE and AT deficiency. The recommendations for thromboprophylaxis in women with no prior VTE but with a known AT deficiency are summarized in ▶Table 2. As presented in ▶Table 3, the guidelines differ in their recommendations on the appropriate dose of LMWH for AT deficiency. According to the RCOG and GTH guidelines, monitoring of anti-Xa activity may be performed to guide prophylaxis or treatment with LMWH. Only the authors of the RCOG guidelines point to the assessment of AT replacement in the peripartum period. James et al summarized the state of the art and expert opinions on the management of hereditary AT deficiency in pregnancy.<sup>57</sup> The authors emphasized a multidisciplinary approach in the care of pregnant women with AT deficiency involving obstetricians and experts in the field of coagulation disorders. The recommendations are summarized in ▶Table 4. AT concentrates can be administered prophylactically in special high-risk situations such as surgery, immobilization, and childbirth, in cases of bleeding when anticoagulation is paused and to normalize AT levels in acute VTE despite anticoagulation and should be guided under the direction of an experienced hemostaseologist or thrombosis expert. In these situations, the goal is to raise the AT activity levels to normal (i.e., 80–120%). According to Bauer et al, monitoring should be performed at least every 12 hours and before the next infusion.<sup>17</sup> The dose and frequency of AT replacement and the duration of treatment should be adapted to the clinical situation. Pabinger et al maintained trough levels of at least 70% within the first 5 days after delivery.<sup>58</sup> For further information, we refer to the German summary of product characteristics of the aforementioned approved AT concentrates in Germany.

**Table 1** International guideline recommendations for thromboprophylaxis in women with previous VTE and AT deficiency

History	Risk period: AP vs. PP	ACCP, 2012 <sup>38</sup>	SOGC, 2014 <sup>51</sup>	RCOG, 2015 <sup>53</sup>	ACOG, 2018 <sup>54</sup>	ASH, 2018 <sup>52</sup>	GTH, 2020 <sup>31</sup>
Prior VTE, provoked by a transient risk factor (unrelated to pregnancy or estrogen)	AP	–	+	+	+	–	+
	PP	All guidelines recommend postpartal pharmacologic thromboprophylaxis					
Prior VTE in the context of exogenous estrogen, pregnancy or unprovoked	AP	All guidelines recommend ante- and postpartal pharmacologic thromboprophylaxis					
	PP						

AT deficiency is considered high risk by ACOG, RCOG and SCOG and GTH in case of severe deficiency (AT deficiency < 60%). AP: antepartum, PP: postpartum, AT: antithrombin, VTE: venous thromboembolism.

**Table 2** International guideline recommendations for thromboprophylaxis in women with AT deficiency and no prior VTE.

History	Risk period: AP vs. PP	ACCP, 2012 <sup>38</sup>	SOGC, 2014 <sup>51</sup>	RCOG, 2015 <sup>53</sup>	ACOG, 2018 <sup>54</sup>	ASH, 2018 <sup>52</sup>	GTH, 2020 <sup>31</sup>
No personal history of VTE, no family history of VTE	AP	–	+	+	+	–	+
	PP	–	+	+	+	–	+
No personal history of VTE, positive family history of VTE	AP	–	+	+	+	+	+
	PP	All guidelines recommend postpartal pharmacologic thromboprophylaxis					

AT deficiency is considered high risk by ACOG, RCOG and SCOG and GTH in case of severe deficiency (AT activity < 60%). AP: antepartum, PP: postpartum, AT: antithrombin, VTE: venous thromboembolism.

**Table 3** International guideline recommendations for thromboprophylaxis in women with AT deficiency considering the dose of LMWH, monitoring of anti-Xa activity and AT replacement.

	Dose of LMWH	Monitoring of anti-Xa activity	AT concentrate
ACCP, 2012 <sup>38</sup>	<ul style="list-style-type: none"> <li>Prophylactic or intermediate dose postpartal in women without prior VTE but a positive family history</li> <li>Prophylactic or intermediate dose LMWH ante- and postpartal in women with a prior VTE (unprovoked, pregnancy- or estrogen related) not receiving long-term anticoagulation</li> <li>Adjusted-dose LMWH<sup>b</sup> or 75% of a therapeutic dose in women on long-term anticoagulation</li> </ul>	<sup>a</sup>	<sup>a</sup>
SOGC, 2014 <sup>51</sup>	<ul style="list-style-type: none"> <li>Prophylactic dose ante- and postpartal in asymptomatic women</li> <li>Intermediate or therapeutic dose ante- and postpartal in case of a previous VTE in women not previously on anticoagulation</li> <li>Therapeutic dose in patients on long-term anticoagulation</li> </ul>	<sup>a</sup>	<sup>a</sup>
RCOG, 2015 <sup>53</sup>	<ul style="list-style-type: none"> <li>Individual specialist management by experts in hemostasis and pregnancy</li> <li>Higher doses (50 or 75% of full treatment dose) of LMWH should be offered to women with a previous VTE ante- and postpartal</li> </ul>	<ul style="list-style-type: none"> <li>If measured, 4-h target peak-levels: 0.5–1.0 IU/mL<sup>c</sup></li> </ul>	<ul style="list-style-type: none"> <li>Assessment of AT replacement at the initiation of labor or prior to caesarean section</li> </ul>
ACOG, 2018 <sup>54</sup>	<ul style="list-style-type: none"> <li>Prophylactic dose in asymptomatic women ante- and postpartal</li> <li>Prophylactic, intermediate dose, or adjusted dose in case of a previous VTE in women not on long-term anticoagulation antepartal and intermediate or dose-adjusted LMWH postpartal</li> <li>Therapeutic dose in women receiving long-term anticoagulation</li> </ul>	<sup>a</sup>	<sup>a</sup>
ASH, 2018 <sup>52</sup>	<ul style="list-style-type: none"> <li>Prophylactic dose in women without a prior VTE but a positive family history ante- and postpartal</li> <li>Prophylactic dose in women with a prior VTE (unprovoked, pregnancy- or estrogen related) antepartal and either prophylactic or intermediate-dose postpartal</li> </ul>	<sup>a</sup>	<sup>a</sup>
GTH, 2020 <sup>31</sup>	<ul style="list-style-type: none"> <li>Counseling at specialized centers for coagulation disorders or vascular medicine is recommended</li> <li>Prophylactic dose in asymptomatic women</li> <li>50–75% of full therapeutic dose in women with prior VTE not on long-term anticoagulation</li> <li>Therapeutic doses in women with prior VTE, a high risk of recurrence, and on long-term anticoagulation</li> </ul>	<ul style="list-style-type: none"> <li>Monitoring of anti-Xa levels and LMWH doses adjustments may be required</li> </ul>	<sup>a</sup>

Abbreviations: AT, antithrombin; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

<sup>a</sup>there is no information on this issue in the guidelines

<sup>b</sup>definition of adjusted-dose: weight-adjusted or full-treatment doses of LMWH.

<sup>c</sup>an anti-Xa test that does not use exogenous antithrombin should be used.

**Table 4** Expert recommendation of the management of hereditary AT deficiency in pregnancy<sup>57</sup>

Issue	Recommendation
Women with acute VTE	<ul style="list-style-type: none"> <li>AT concentrates can be used to normalize antithrombin levels in current VTE or recurrent VTE despite anticoagulation</li> </ul>
Women with prior VTE on long-term anticoagulation	<ul style="list-style-type: none"> <li>Full-dose LMWH ante- and postpartal</li> <li>Anti-Xa monitoring in special situations, e.g., morbid obesity, unusual weight gain, or recurrent thrombosis</li> <li>AT replacement as a treatment option in potentially high-risk settings such as bleeding, surgery, and childbirth</li> </ul>
Women with a history of VTE not on long-term anticoagulation	<ul style="list-style-type: none"> <li>Full-dose LMWH ante- and postpartal</li> <li>AT replacement as a treatment option in potentially high-risk settings such as bleeding, surgery, and childbirth</li> </ul>
Women with severe AT deficiency <sup>a</sup> with no prior VTE but a family history of VTE	<ul style="list-style-type: none"> <li>Assessment of the dose of LMWH depending on individual risk factors, family history, and patient's preference</li> <li>Individual assessment of AT replacement in high-risk situations</li> </ul>
Women with severe AT deficiency, no personal and family history of VTE	<ul style="list-style-type: none"> <li>Assessment of the need and dose of LMWH depending on individual risk factors, family history, and patient's preference</li> </ul>

Management of AT deficiency in pregnancy requires a multidisciplinary approach involving experts on maternal-fetal medicine and experts in the field of coagulation disorders. Anticoagulation should be prescribed for at least six weeks postpartum.

Abbreviations: AT, antithrombin; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

<sup>a</sup>defined as AT deficiency < 60%.

## Case Report (Part 2)

The patient became pregnant and stopped taking DOACs before the sixth week of gestation. She was immediately switched to 100 IU/kg/bw of enoxaparin twice daily. Due to the highly positive family history of VTE and prior VTE, we targeted an anti-Xa level of 0.5 to 1.0 IU/mL, measured 3 to 4 hours after the administration of enoxaparin using an anti-Xa assay without exogenous AT. To reach the targeted anti-Xa peak level, the dose was adapted gradually to a daily dose of 24,000 IU during pregnancy. The patient was counseled at the 32nd week of gestation about issues of delivery, and a caesarean section under general anesthesia was planned due to obstetrical issues. We provided a written recommendation to the obstetrician about anticoagulation and AT replacement for the peri- and postpartum periods. Lastly, LMWH was administered in a therapeutic dose 24 hours before the caesarean section. AT was replaced 12 hours before delivery at a dose of 4,000 IU to target an AT level of 100%. The dosage depended on the patient's bw, AT level, and the targeted AT level and was calculated according to the manufacturer's advice:  $\text{calculated international units} = \text{bw (98 kg)} \times (\text{targeted AT-level (100\%)} - \text{current AT-level (60\%)})$ . AT levels were measured 12 hours after application (before the caesarean section) and 12 hours after surgery and were within the targeted range (95 and 82%, respectively). Enoxaparin was initiated at an intermediate dose of 6,000 IE 12 hours after delivery and was gradually increased in the following days to reach the targeted anti-Xa peak levels. As DOACs are not recommended while breastfeeding and long-term LMWH treatment was not preferred, the patient was switched to a vitamin-K antagonist (phenprocoumon; target INR: 2–3) 10 days postpartum, while oral vitamin K supplementation was ensured as part of the regular preventive medical examination of the newborn. During pregnancy and the postpartum period, no bleeding or thromboembolic complications occurred.

## Conclusions

The VTE risk of pregnant women with AT deficiency is difficult to predict. Thus, an individual assessment for VTE risk should be performed in all women with a known AT deficiency prior to pregnancy and repeated when pregnancy is achieved and before and after delivery. In addition, the type and extent of AT deficiency, the patient and family history, and additional preexisting risk factors (e.g., age, BMI, and comorbidities) must be considered. Furthermore, specific pregnancy- and postpartum-related risk factors and patient's preferences should be taken into consideration. Pregnant women with previous VTE have an especially high risk of VTE and should therefore be treated with therapeutic-dose LMWH. The monitoring of anti-Xa levels is not recommended by most of the current guidelines but may be performed in special situations. In AT-deficient women without prior VTE but with a positive family history, LMWH prophylaxis with a dose regimen for high-risk patients is recommended at least during pregnancy and for

a minimum of 6 weeks postpartum. AT replacement should be considered in cases of acute VTE despite therapeutic anticoagulation and in situations when LMWH is generally paused (e.g., delivery, surgery, or bleeding). Due to the rarity of AT deficiency and the highly increased VTE risk, especially in patients with AT deficiencies of type I, IIa, and IIc and homozygous carriers of HBS mutations, patients should be counseled by specialists on coagulation disorders or vascular medicine. A multidisciplinary approach involving experts in maternal–fetal medicine and experts in the field of coagulation disorders is recommended with regard to delivery, and written recommendations on the use of anticoagulants and AT replacement should be provided. Data from prospective clinical trials are urgently needed to improve and standardize medical treatment in pregnant women with AT deficiency.

## Zusammenfassung

Frauen mit angeborenem Antithrombin (AT)-Mangel haben ein erhöhtes Risiko für venöse Thromboembolien (VTE) in der Schwangerschaft und im Wochenbett. Das Risiko hängt hierbei von verschiedenen Faktoren ab, die in die Risiko-Nutzenevaluation einer Antikoagulation mit einzubeziehen sind: positive Eigen- bzw. Familienanamnese für VTE, Restaktivität von AT, zugrundeliegende genetische Mutation, Patientinnen-eigene Risikofaktoren (z.B. Alter, Gewicht, Komorbiditäten) sowie Schwangerschafts-assoziierte Risikofaktoren. Die Datenlage in Bezug auf Indikationsstellung einer Antikoagulation, der adäquaten Dosis von Heparin, des Monitorings der anti-Xa Aktivität unter Heparin sowie des Einsatzes von Antithrombin-Konzentraten ist spärlich und leitet sich ausschließlich aus retrospektiven Fallbeschreibungen und Kohortenstudien ab. Bei Frauen mit VTE in der Vorgeschichte wird eine Antikoagulation mit niedermolekularem Heparin (NMH) in therapeutischer Dosierung während der Schwangerschaft und im Wochenbett durchgeführt. Frauen ohne VTE in der Vorgeschichte mit jedoch positiver Familienanamnese und / oder weiteren Risikofaktoren erhalten eine prophylaktische Antikoagulation entsprechend des Hochrisiko-Bereichs. Ein Monitoring der anti-Xa Aktivität unter Behandlung mit NMH kann in speziellen Situationen erwogen werden. Die Substitution von Antithrombin-Konzentraten wird im Rahmen einer akuten VTE, die unter therapeutischer Antikoagulation aufgetreten ist, sowie zur Geburt empfohlen. Die Geburtsplanung sollte in enger Zusammenarbeit mit den Fachbereichen Hämostaseologie / Gefäßmedizin, Anästhesie und Geburtshilfe erfolgen. Daten aus prospektiven klinischen Studien sind notwendig, um das hämostaseologische Management von schwangeren Frauen mit Antithrombin-Mangel zu verbessern.

## Conflict of Interest

Susanne Heimerl has received Payment or honoraria for presentations from Takeda Pharmaceutical and Roch. Also Support for attending meetings from Takeda Pharmaceutical and Swedish Orphan Biovitrum.



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