Management and outcome of pregnancies in women with antithrombin deficiency: a single-center experience and review of literature

Péter Ilonczai, Zsolt Oláh, Anna Selmeczi, Adrienne Kerényi, Zsuzsanna Bereczky, Róbert Póka, Ágota Schlammadinger and Zoltán Boda

Women with antithrombin (AT) deficiency have an increased risk for pregnancy-associated venous thromboembolism (VTE) and adverse pregnancy outcome. AT deficiency is a rare thrombophilia with heterogeneous genetic background. Owing to the few cases reported in the literature, management strategies of pregnancy with AT deficiency are inconsistent. Our aim was to examine the type of the genetic defect, management, maternal, and pregnancy outcome in patients with hereditary AT deficiency. Five expectant mothers with AT deficiency were followed in our center to evaluate thrombotic events, and maternal and pregnancy outcomes. AT gene sequencing was performed in all cases, and levels of AT and anti-FXa were regularly measured to guide the risk-adopted anticoagulant prophylaxis. Three mothers had homozygous type II heparin-binding site mutations and two had heterozygous type I mutations of the gene encoding AT. Two women had additional factor V Leiden heterozygous mutations. Three maternal VTEs – four healthy newborns and five pregnancy losses – were observed. The risk of patients to VTE and adverse pregnancy outcome was found to associate with the homozygous type II heparin-binding site mutation of the AT gene. High risk of maternal VTE and frequent pregnancy complications were observed to associate with AT deficiency. Our results support the need of individualized, risk-adopted anticoagulant therapy in patients with AT deficiency.

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Keywords: anticoagulant therapy, antithrombin concentrate, antithrombin deficiency, pregnancy

Introduction

Antithrombin (AT) is a natural anticoagulant and its primary action is to inhibit thrombin-mediated fibrin clot formation and generation of thrombin by FXa [1].

Antithrombin deficiency is a rare and the most thrombogenic type of thrombophilia, with a 25–50-fold increase of relative risk of venous thromboembolism (VTE) in the general population [2,1].

More than two hundred mutations of the AT gene have been identified so far [3]. Mutations can cause defects in the reactive site (type II RS), heparin-binding site (type II HBS), or can generate a pleiotropic effect (type II pulmonary embolism) [3–5]. Compared to type II RS and pulmonary embolism deficiency, the defects of the HBS are associated with a lower thrombotic diathesis and can be present in the homozygous form [2,3,6,7]. A well described type II HBS defect is known as Budapest mutation [8]. The homozygous type II mutation with low levels of antigen is associated with severe venous and arterial thrombosis, and recurrent pregnancy loss [2,6,7,9–16].

In pregnant women with thrombophilia, especially with AT deficiency, decreased activity of the anticoagulant system may lead to deteriorated placental circulation and adverse pregnancy outcome (APO) [6,17–19]. Maternal AT deficiency has an estimated six-fold increased risk of thromboembolic complications and a markedly increased risk of fetal loss [6,20,21]. An increased risk of late-pregnancy complications like preeclampsia, stillbirth, intrauterine growth restriction (IUGR), placental abruption, and hemolysis, elevated liver enzymes and low platelet count syndrome (HELLP) is also associated with patients with AT deficiency and pregnancy [6,20,22,23].

Treatment guidelines are inconsistent with regards to management of patients with AT deficiency and pregnancy [24–27]. Owing to its rarity, therapeutic approaches are mainly based on case reports published in the literature [9,11,12,21–23,28–32]. The purpose of our study was to evaluate management, and maternal and fetal outcomes in patients with heritable AT deficiency and pregnancy.
Materials and methods

Study design and setting
A retrospective observational study was performed to evaluate management, thrombotic events, maternal, and pregnancy outcomes in women with hereditary AT deficiency, managed in our center.

Study population
Between 2012 and 2014, five patients with hereditary AT deficiency and pregnancy were included. Secondary causes of AT deficiency were excluded. A written informed consent was obtained from all patients according to the rules of the local ethical committee.

Methods

Collection of data
We reviewed anamnestic data, medical history, information regarding previous pregnancies, treatment before and during pregnancy and postpartally, thrombotic events, and maternal and fetal outcome.

Thrombophilia screening
Testing for factor V Leiden mutation and FII polymorphism was performed and antiphospholipid antibodies were screened in patients with a history of a previous VTE or recurrent pregnancy loss. Protein C and S evaluations were omitted in an attempt to prevent the possibility of a false positive result.

Antithrombin gene sequencing
Collection of the clinical data involved thrombophilia screening and genetic testing of the type of inheritance. AT deficiency was confirmed by the fluorescent DNA sequencing method.

Antithrombin measurements
Antithrombin activity measurements were performed daily at the beginning of the therapy and were checked monthly throughout pregnancy. AT activity was evaluated just before (trough) and 4h after injection of (peak) enoxaparin (Clexane, Sanofi, Miskolc, Hungary). Reference ranges for the management of LMWH therapy were defined as prophylactic (0.2–0.5 IU/ml) and therapeutic (0.5–1.2 IU/ml) [25,31,34].

Anti-FXa monitoring
Measurement of the low-molecular-weight heparin (LMWH) levels was performed by using FXa and its chromogenic substrate. Anti-FXa assessments were performed daily at the beginning of therapy or in case of dose adjustment, and were regularly monthly checked throughout pregnancy [33]. Anti-FXa levels were evaluated just before (trough) and 4h after injection of (peak) enoxaparin (Clexane, Sanofi, Miskolc, Hungary). Reference ranges for the management of LMWH therapy were defined as prophylactic (0.2–0.5 IU/ml) and therapeutic (0.5–1.2 IU/ml) [25,31,34].

Management protocol
Preconceptional period
Patients who were on acenocumarol or warfarin were put on enoxaparin. Women without anticoagulant therapy were put on enoxaparin as soon as their pregnancy test became positive. In one case, anticoagulation started at the 23rd gestational week.

Gestation
Patients were checked monthly by a hemostasis-specialized hematologist in collaboration with an obstetrician experienced in management of patients with pregnancy and thrombophilia. Treatment protocol was based on the patients’ thrombotic risk, described by the family history of VTE, presence of a previous thromboembolic event, and a history of APO [24,25,27,31,33,35,36]. The type of inheritance was also taken into account; homozygous type II ‘Budapest’ AT mutation was considered as a factor resulting in a high risk for thrombotic events [6,7,9,11–16]. Combined thrombophilia, like factor V Leiden heterozygous mutation and AT deficiency, was also considered as a high risk. In case of women with low risk, 40 mg of enoxaparin was given once a day at the start; for high-risk patients, 1 mg/kg body weight of enoxaparin was prescribed twice a day in a form of a subcutaneous injection [24,31,33,35,37]. LMWH administration was guided by the measurements of anti-FXa levels, in accordance with recommendations [24,33,35]. Our aim was to reach prophylactic trough levels of anti-FXa in all cases and to achieve therapeutic peak levels of anti-FXa in women with a high thrombotic risk. If the targeted anti-FXa level was not achieved despite increased dose of enoxaparin, ATC was initiated [31,36,37]. Infusion of ATC was started at a daily dose of 30–50 IU/kg body weight [calculated from (100 – baseline activity)/1.6] to achieve 100% of activity, as there are no general recommendations or guidelines to monitor the treatment. For maintenance, ATC was administered three times per week. Trough and peak AT activity measurements were regularly performed, but in fact, ATC dosing was guided by anti-FXa activities (Table 1).

Delivery
At delivery, LMWH was withheld at least 12h before labor or cesarean section, and 30–50 IU/kg body weight of ATC was given daily for 2 consecutive days.

Postpartum period
After postdelivery bleeding ended, 1 mg/kg body weight of enoxaparin was re-administered and switched to acenocumarol or warfarin therapy. Patients with no history of
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, (gravity)</th>
<th>Parity</th>
<th>Family history of VTE</th>
<th>VTE before pregnancy</th>
<th>Risk</th>
<th>Treatment before pregnancy</th>
<th>Treatment during pregnancy</th>
<th>Treatment at delivery</th>
<th>Treatment after pregnancy</th>
<th>VTE during pregnancy</th>
<th>Pregnancy outcome</th>
<th>Maternal outcome</th>
<th>Neonatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21 [1]</td>
<td>1</td>
<td>negative</td>
<td>DVT (left iliacaval), 2005</td>
<td>Not considered</td>
<td>Acenocumarol</td>
<td>Enoxaparin 30 mg OD, from gw 6 to gw 8 enoxaparin 40 mg b.i.d. + ATC then acenocumarol</td>
<td>–</td>
<td>Acenocumarol</td>
<td>DVT at gw 7 (left iliofemoral, right iliac)</td>
<td>gw 8 miscarriage</td>
<td>Recovered</td>
<td>Fetal death</td>
</tr>
<tr>
<td>27 [2]</td>
<td></td>
<td></td>
<td>High</td>
<td>Acenocumarol</td>
<td></td>
<td>Enoxaparin 50 mg b.i.d. + ATC 2500 IU OD then 1500 IU 3tw from gw 25 to gw 30</td>
<td>LMWH was withheld 50 IU of ATC daily for two days</td>
<td>Acenocumarol</td>
<td>No</td>
<td>gw 39 induced vaginal delivery</td>
<td>Healthy</td>
<td>Healthy</td>
<td>(2840 g)</td>
</tr>
<tr>
<td>2</td>
<td>19 [1]</td>
<td>1</td>
<td>DVT</td>
<td>None</td>
<td>High</td>
<td>None</td>
<td>None</td>
<td>–</td>
<td>None</td>
<td>No</td>
<td>gw 19 miscarriage</td>
<td>Healthy</td>
<td>Fetal death</td>
</tr>
<tr>
<td>20 [2]</td>
<td></td>
<td></td>
<td>None</td>
<td>None</td>
<td>Low</td>
<td>None</td>
<td>None</td>
<td>–</td>
<td>None</td>
<td>No</td>
<td>gw 20 miscarriage</td>
<td>Healthy</td>
<td>Fetal death</td>
</tr>
<tr>
<td>21 [3]</td>
<td></td>
<td>1</td>
<td>DVT</td>
<td>None</td>
<td>Low</td>
<td>None</td>
<td>Enoxaparin 40 mg OD from gw 11 40 mg enoxaparin BID + ATC 1500 IU 2tw</td>
<td>–</td>
<td>Enoxaparin 40 mg b.i.d. for 6 weeks</td>
<td>No</td>
<td>gw 28 miscarriage</td>
<td>Healthy</td>
<td>Fetal death</td>
</tr>
<tr>
<td>22 [4]</td>
<td></td>
<td>1</td>
<td>DVT</td>
<td>None</td>
<td>Low</td>
<td>Enoxaparin 60 mg OD from gw 12 BID + ATC 2500 IU 3tw</td>
<td>LMWH was withheld 50 IU of ATC daily for two days</td>
<td>Acenocumarol</td>
<td>PE at gw 7</td>
<td>gw 32 preterm delivery, prim. caes. sec.</td>
<td>Healthy</td>
<td>Healthy</td>
<td>(1640 g)</td>
</tr>
<tr>
<td>3</td>
<td>26 [1]</td>
<td>1</td>
<td>DVT</td>
<td>None</td>
<td>Low</td>
<td>Enoxaparin 40 mg OD then BID, from gw 20 enoxaparin 60 mg BID + 1000 IU ATC 2tw, from gw 26 2000 IU 3tw</td>
<td>LMWH was withheld 50 IU of ATC daily for six weeks</td>
<td>Enoxaparin 60 mg BID for six weeks</td>
<td>No</td>
<td>gw 36 primary ces. sec.</td>
<td>Healthy</td>
<td>Healthy</td>
<td>(4140 g)</td>
</tr>
<tr>
<td>4</td>
<td>32 [1]</td>
<td>1</td>
<td>DVT (left calf), 2006</td>
<td>None</td>
<td>High</td>
<td>From gw 23 enoxaparin 80 mg BID</td>
<td>LMWH was withheld 50 IU of ATC daily for two days</td>
<td>Warfarin</td>
<td>DVT (right femoral) at gw 23</td>
<td>gw 38 primary caes. sec.</td>
<td>Recovered</td>
<td>Healthy</td>
<td>(2840 g)</td>
</tr>
<tr>
<td>5</td>
<td>21 [1]</td>
<td>0</td>
<td>DVT (bilateral iliofemoral)</td>
<td>Acenocumarol</td>
<td>High</td>
<td>From gw 6 enoxaparin 40 mg BID + 2500 IU ATC 3tw</td>
<td>LMWH was withheld 50 IU of ATC daily for six weeks</td>
<td>Acenocumarol</td>
<td>No</td>
<td>gw 13 miscarriage</td>
<td>Healthy</td>
<td>Fetal death</td>
<td>(gw 13)</td>
</tr>
</tbody>
</table>

2tw, two times weekly; 3tw, three times weekly; ATC, antithrombin concentrate; DVT, deep vein thrombosis; gw, gestational week; IU, International Unit; LMWH, low-molecular-weight heparin; mg, milligram; PE, pulmonary embolism; VTE, venous thromboembolism.
VTE received 1 mg/kg body weight of enoxaparin twice a day for 6 weeks. In case of patients with previous or gestational VTE, enoxaparin was switched to either acenocumarol or warfarin (target INR 2.0–3.0).

**Follow-up**
Patients were monthly checked for 3 more months postpartally.

**Statistical analysis**
Data are expressed as mean ± SD. Statistical analysis was done with GraphPad Prism 5 software (GraphPad Software Inc., San Diego, California, USA).

**Results**
A total of nine pregnancies of five women with hereditary AT deficiency were reviewed. The women ranged in age from 19 to 32 years [23.2 ± 4.2 (mean ± SD)]. Four of the five mothers were classified of being at high risk for a thrombotic event. History of fetal loss was found in two cases, and spontaneous abortion was observed, despite heparin prophylaxis, in one case. All patients were put on enoxaparin upon the recognition of pregnancy. Four women required ATC to reach the targeted anti-FXa effect (Table 1).

**Laboratory findings**
Three patients had homozygous type II HBS mutations (Budapest 3), two had type I heterozygous mutations of serpin peptidase inhibitor clade C1 (SERPINC1), and two patients also had an additional factor V Leiden heterozygous mutation. The patients with homozygous type II mutations had seriously decreased AT levels (12–17%). The targeted anti-FXa levels were attainable except in one noncompliant case (third pregnancy of case 3) (Table 2).

**Discrepancies from treatment protocol**
In one case, the patient was noncompliant, which resulted in no further dose change in anticoagulant therapy despite inappropriate anti-FXa effects. In another case (patient 4), LMWH was started when the patient presented with a right femoral deep vein thrombosis (DVT) and pregnancy in the 23rd gestational week. In this case, assessments were performed monthly in the local hospital due to the notable distance of the patient’s home. Results were consulted by telephone.

**Maternal outcome**
Two mothers experienced VTE during pregnancy without prophylaxis, including one nonmassive pulmonary embolism and a right femoral DVT. One patient with Budapest 3 homozygous AT mutation had a DVT despite LMWH prophylaxis. All patients recovered. With adequate anticoagulant therapy, no maternal VTE, preeclampsia, eclampsia, placental abruption, or HELLP syndrome was observed. (Table 3)
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Table 3 Characteristics of pregnancies, maternal and neonatal outcomes

<table>
<thead>
<tr>
<th>Expectant mothers</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Age at conception (years, mean ± SD)</td>
<td>20–32 (25.6 ± 4.4)</td>
</tr>
<tr>
<td>Gravity</td>
<td>9</td>
</tr>
<tr>
<td>Pregnancy loss (without treatment)</td>
<td>3 (gestational week 8th, 19th, and 20th)</td>
</tr>
<tr>
<td>Pregnancy loss (under treatment)</td>
<td>2 (gestational week 13th and 28th)</td>
</tr>
<tr>
<td>Delivery</td>
<td>4</td>
</tr>
<tr>
<td>Type of delivery</td>
<td>1 (vacuum extraction)</td>
</tr>
<tr>
<td>Induced vaginal</td>
<td></td>
</tr>
<tr>
<td>Primary Cesarean section</td>
<td>3</td>
</tr>
<tr>
<td>Gestational age (weeks, mean ± SD)</td>
<td>36 ± 3</td>
</tr>
<tr>
<td>Weight at birth (grams, mean ± SD)</td>
<td>2815 ± 1028</td>
</tr>
<tr>
<td>VTE during pregnancy</td>
<td>3</td>
</tr>
</tbody>
</table>

DVT, deep vein thrombosis; VTE, venous thromboembolism.

Neonatal outcome

Without effective anticoagulant prophylaxis, pregnancies ended with one early and two late miscarriages in cases of mothers with type II HBS AT mutations (Table 1). Under anticoagulant therapy from six gestations, four healthy babies were born – three at terminuses and one at gestational week 32. The preterm delivery was forced by the mother who denied further anticoagulant therapy. Histology of the placenta found normal structure. Two fetal losses occurred on gestational weeks 13 and 28 in cases of two mothers with homozygous type II HBS AT mutations, despite anticoagulant therapy. Histology showed normal chorionic structure in case of the early miscarriage. In contrast, examination of the placenta revealed microthromboses and placental degeneration in case of the late pregnancy loss. No IUGR or stillbirth was observed (Table 3).

Discussion

In our study, on patients with AT deficiency and pregnancy, we experienced a high rate of maternal VTE, especially in cases with homozygous type II HBS mutations. Our data are in accordance with the citations reporting that AT deficiency and pregnancy are associated with a high risk of VTE [20,22,32]. Our findings suggest that the type of AT deficiency may play an important role in creating a high-risk phenotype, as is reported in cases of homozygous type II HBS mutations [6,7,9–16], and may support the requirement of thromboprophylaxis in the prevention of maternal thrombotic complications in patients with AT deficiency [24,26,27,33].

In contrast to the literature reporting on the association of thrombophilia and the risk of a poor pregnancy outcome [20,38–40], systematic reviews found a conflicting relationship [18,41], or even failed to find an association between AT deficiency and APO [42,43]. Although AT deficiency has a known heterogeneous genetic background configuring different phenotypes, the case series did not differentiate between the types of AT deficiencies and the levels of activity from the aspect of risk of VTE and pregnancy outcomes. In one study, authors did not find a relationship between AT activity and pregnancy outcome, although the lowest AT activity was 30% [31].

In the present study, mothers with the homozygous type II HBS mutation and the lowest AT activity produced the highest rates of miscarriage and maternal VTE. These findings are in accordance with the case reports [9,10,12,16] and support the notion that AT deficiency increases the risk of placenta-mediated pregnancy complications [20,29]. Adequate anticoagulant therapy may prevent vascular lesions in the placenta caused by a high-risk thrombophilia-like AT deficiency [9,20,23,29–32,36]. Data concerning the association between late pregnancy complications and AT deficiency are contradictory [42,43]. Some authors reported a higher prevalence of AT deficiency among patients with late pregnancy complications [20], which in the present study were not observed.

Despite the fact that AT deficiency is considered as a high-risk thrombophilia, treatment guidelines recommend only antepartum and postpartum LMWH prophylaxis [25,26,33] or even just antenatal vigilance and postpartum LMWH prophylaxis in cases of AT deficiency without a history of maternal VTE [24]. These guidelines classifying AT-deficient women into high or moderately increased risk of VTE on the basis of family and personal history of VTE do not differentiate between the certain types and do not take into account the severity in the decrease of AT activity [24,25]. In contrast, many authors report on the association of high incidence of maternal thrombotic and fetal complications in cases of homozygous type II HBS AT deficiency and pregnancy with a seriously diminished AT activity [9,10,12,16]. In fact, we observed a strong association between the type and severity of AT deficiency, and the incidence of maternal and fetal complications. Our data underline the clinical importance of the distinction between type II HBS and other types of AT deficiencies, as well as between the homozygous and the heterozygous forms. Hence, when AT gene sequencing is not available, concomitant determination of progressive anti-FXa and heparin cofactor anti-FXa activities can help to diagnose the type II HBS AT deficiency and distinguish between homozygotes and heterozygotes [44].

Although current guidelines do not recommend using ATC even in high-risk patients with pregnancy requiring therapeutic anticoagulation [24–26,45], many case reports and observational studies found a better pregnancy outcome, with the use of LMWH and ATC together [20,23,29–31,35–37,46,47]. Our data support in conjunction with citations above the necessity of therapeutic anticoagulation for high-risk patients.
Our study has a number of strengths. To our knowledge, there are only two cases of homozygous type II HBS AT deficiency with successful pregnancy outcome reported until now [10,12]. This is the first study to report three expectant mothers with homozygous type II HBS AT mutations. They had two successful deliveries treated with our anticoagulant protocol. The novel aspect of our study is that a risk-adopted individualized anticoagulant protocol was used on the basis of clinical risk assessment and mutation analysis. The potential limitation of our study could be its single-center design and a relatively small number of cases due to the low prevalence of AT deficiency.

We concluded that since the risk of thromboembolism varies considerably between AT mutations, to assess patients’ perceived level of risk – beyond the familiar and personal VTE history – the type of AT deficiency and the underlying mutation should be taken into account. We found that AT deficiency is associated with a high risk of maternal VTE and frequent pregnancy complications, which support the need for risk-adopted anticoagulant therapy.

Acknowledgements
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Conflicts of interest
None declared.

References
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