

Review Article

Pregnancy complicated with deficiency of antithrombin: Review of current literature

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Abstract

Antithrombin deficiency, although the rarest thrombophilia, carries the highest risk of thromboembolism. This risk is increased especially for pregnant women due to physiological coagulation changes in pregnancy. Therefore, in cases of positive personal and/or family history of thromboembolic events as well as recurrent pregnancy loss women should be tested for antithrombin deficiency. Antithrombin deficiency is caused by numerous mutations of serpin peptidase inhibitor clade C 1 gene (SERPINC) and is classified according to antithrombin plasma activity and antigen levels into Type I (quantitative defect) and Type II (qualitative defect). Complications during pregnancy can be divided into those regarding the mother and those concerning the fetus. The main clinical manifestation of antithrombin deficiency regarding the mother is thromboembolism occurring spontaneously or recurrently during pregnancy. Numerous major gestational complications such as miscarriage, intrauterine growth restriction or fetal death, placental abruption, preeclampsia and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome can be linked to antithrombin deficiency. Close monitoring with early and adequate prophylaxis and treatment nowadays can mostly assure the positive pregnancy outcome for both mother and child. Prophylaxis/therapy with both low molecular weight heparin and antithrombin concentrate should start as soon as pregnancy is planned or at least as early as possible in pregnancy and continue until the end of the puerperium.

Introduction

Pregnancy itself represents an important risk factor for development of venous thrombosis due to the physiologically increased clotting potential and decreased fibrinolysis in pregnancy [1,2]. The risk is further augmented by thrombophilic states. Thrombophilias, hereditary or acquired, are the cause of at least 50% of cases of venous thromboembolism in pregnant women [2,3]. Out of all thrombophilias antithrombin (AT) deficiency is the rarest type, but the one with the highest risk of suffering a thromboembolic event during lifetime [4,5].

AT deficiency is uncommon hereditary thrombophilia with

the prevalence in general population of 1/2000–5000 [3,6,7]. AT deficiency is classified according to antithrombin plasma activity and antigen levels into Type I (quantitative defect) and Type II (qualitative defect) [8,9]. Thromboembolism in these patients can happen in early age and recurrently and is often life-threatening [10-12].

AT deficiency during pregnancy in literature has variable incidence, but recently the number of pregnant women with congenital AT deficiency has increased [3,5,10]. Several reports have been published about the relationship between inherited thrombophilias and adverse pregnancy outcomes [13-15]. Although the association between

More Information

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different thrombophilias and pregnancy complications is well established and confirmed, data regarding the influence of inherited AT deficiency on pregnancy outcome are still limited and controversial [16-18].

Antithrombin III belongs to a family of serine protease inhibitors and plays a role in the regulation of hemostasis [6,8]. Antithrombin is a naturally occurring anticoagulant synthesized in the liver and vascular endothelial cells. It is a 58,200-Da glycoprotein encompassing 432 amino acids in length and three disulfide bonds making a total of four possible glycosylation sites [19]. It has a circulatory half-life of approximately 2.4 days. Antithrombin has two functional domains. One binding site is for heparin and the other for thrombin/factor Xa, which contains the reactive center Arg 393 – Ser 394 [19, 20]. Binding of AT to heparin enhances the formation of protease-inhibitor complex which inactivates principally thrombin and to some extent other activated coagulation factors FIXa, FXa, and FXIIIa [7,9]. It should be noted that in the absence of AT heparin has little effect. Consequently, it can be seen that AT is one of the most important natural agents responsible for the prevention of spontaneous intravascular clot formation [18,21]. The decrease of 50% in AT activity level is sufficient to set the grounds for thrombotic state in the organism. It seems that defects in the reactive center carry the highest while in the heparin-binding site the least thrombotic risk [7,19].

Inherited and acquired at deficiency

AT is characterized by high structural flexibility that makes it vulnerable to mutations [13]. AT deficiency has autosomal dominant inheritance and the majority of patients are heterozygous [6,20]. Homozygous AT deficiency is extremely rare probably as it is mostly fatal in utero or the early neonatal period. The only documented homozygotes for AT deficiency are those that cause small defects in heparin binding site or thrombin inhibition capacity such as AT Budapest 3, AT Cambridge II or L99F [13,22,23].

The gene encoding antithrombin named SERPINC1 (serpin peptidase inhibitor clade C) is localized on the chromosome 1q23-25. It has seven exons and six introns and encompasses 13.4 kb of genomic DNA [7]. Mutations in the SERPINC1 gene cause AT deficiency [9]. Majority of mutations are point mutations and small deletions/insertions, but large scale deletions and insertions have also been detected [8]. These mutations are found throughout the gene without particular mutations hotspot. The most important for clinical manifestations are mutations occurring in the gene coding regions [13].

The first mutation linked to AT deficiency was characterized more than 30 years ago and so far the total 256 different mutations the SERPINC 1 gene have been reported with type I and type II AT deficiency [13,20]. One of the polymorphisms that are most often linked with thrombosis is

rs2227589 located 140 bp downstream of exon I in AT gene. Two polymorphisms in AT gene (PstI and rs2227589) as well as carriers of SERPINC1 786A allele seem to be positively correlated with recurrent pregnancy loss [8,9].

Based on the mutation type AT deficiency is divided into Type I and II. In Type I AT deficiency synthesis of the antithrombin molecule is decreased [1,19]. This deficiency type is more often and caused by short deletions and insertions, or single nucleotide polymorphisms in the antithrombin gene. These patients have 50% decrease in both plasma AT antigen and functional activity levels [9].

Type II antithrombin deficiency happens due to single base-pair substitutions usually in the reactive site of antithrombin (thrombin-binding site – type IIa; heparin-binding region – type IIb; mutations near the reactive loop site changing the interaction of AT with thrombin – type IIc). This leads to qualitative defects of AT [8,9,19]. These patients have normal antithrombin antigen levels, but 50% decreased plasma antithrombin functional activity. Literature data have shown that among type II deficiencies type IIb is the most prevalent while type IIa is the most thrombogenic variant [24].

Women with AT deficiency have a 50% chance of passing this disorder on to their offspring [25]. If the fetus is affected the major complications are cardiovascular or multiple thromboembolisms that can lead to adverse outcome. Careful neonatal and infantile care is needed for all children of women with AT deficiency. Fetuses and neonates affected by congenital AT deficiency should start with anticoagulant treatments as soon as the condition is confirmed [8,9].

Acquired antithrombin deficiency can result from increased excretion due to renal failure, decreased production in liver failure or accelerated consumption after severe injury/trauma or surgery [19,25-27]. Finally, pregnancy itself can be regarded as acquired AT deficiency state [27].

Clinical presentation and complications in pregnancy

Complications of AT deficiency during pregnancy can be divided into those regarding the mother and those concerning the fetus. Numerous major gestational complications such as miscarriage, intrauterine growth restriction (IUGR), intrauterine fetal death (IUFD), placental abruption, preeclampsia and hemolysis, elevated liver enzymes and low platelets syndrome (HELLP) are registered significantly more often in pregnancies of women with AT deficiency than in the general healthy population [2,15,26,28]. It is well known that gestational complications in women with thrombophilias originate in vascular lesions in the placenta [29]. The adverse effect of maternal thrombophilias on uteroplacental blood flow could impair oxygen delivery to the fetus, during pregnancy causing complications such as growth restriction, preeclampsia and placental abruption as well as during labor increasing the risk of intrapartum fetal distress [27,29].



The main clinical manifestation of AT deficiency regarding the mother is thromboembolism that can occur spontaneously or be recurrent during pregnancy [1,30,31]. Deep veins of lower extremities are the most often localization of thrombosis, although it may occur in unusual locations such as the upper extremities, mesentery, heart, intracranially [25,32,33]. Venous insufficiency and pulmonary embolism are also relatively common during pregnancy [34]. The hypercoagulable state that normally exists during pregnancy increases 4–5 times the risk of venous thromboembolism [2,29]. The incidence of pregnancy-associated venous thromboembolism is estimated at 1 in 1000 in the overall population of pregnant women [17,19]. In a pregnancy complicated with AT deficiency the risk of a thromboembolic manifestation increases from 5-10 times than in general healthy population [30]. Thrombotic risk of pregnant women with AT deficiency ranges from 30% in threaded patients to 70% in patients without adequate treatment and with previous history of thrombosis [3,6,31].

Although significantly higher prevalence of AT deficiency was found among women who had pregnancy complications, if AT deficient women received proper anticoagulant treatment the incidence of pregnancy complications reduced [11,35]. However, it was reported that 75% of pregnant women had venous thromboembolism during pregnancy despite heparin prophylaxis [25]. A history of venous thromboembolism is important predictor of venous thromboembolism during pregnancy in women with antithrombin deficiency [34]. Risk for recurrence of thromboembolism during pregnancy is 49% [7,12,34]. Recurrent thrombosis has been described to occur even during the course of a single pregnancy (in the first and later trimesters) in patients with inherited AT deficiency [12,19].

The incidence of venous thromboembolism in the puerperium is about 30% - 50%, although some authors consider that thromboembolism in AT deficient women who did not receive prophylactic therapy occurs mostly postpartum [15]. A report of antithrombin deficiency occurring in patients with preeclampsia has also been published [27,28]. The risk of thromboembolism is tenfold higher in the presence of preeclampsia or multi-fetal pregnancy [19,25]. Some, pregnant women with AT deficiency may be at risk of acute fatty liver [18].

AT deficiency can be also associated with recurrent miscarriages and infertility [6,15,36]. According to literature incidence of miscarriage seems to be twice greater in women with AT deficiency than general healthy population while the risk for fetal loss/stillbirth in these women increases five-fold [25,37]. Therefore, in case of three or more spontaneous abortions in otherwise asymptomatic women, along with more common thrombophilias AT deficiency should be considered [8,19].

Pregnancy outcomes

Studies have obtained contradictory results regarding the pregnancy outcomes of both mothers and their children [2,26,32]. Cases have been reported that due to embolism patients' death occurred quite early during pregnancy [11]. Investigations have proven that in women who did not receive prophylaxis and/or adequate therapy during pregnancy neonatal outcomes were adverse in majority of cases and only 30% of pregnancies ended up with a healthy child [15,18]. Although the risks for adverse effects are high and in some studies reported in more than 50% of patients, recently with the use of appropriate prophylaxis and treatment, majority of both mothers and their children successfully survive the pregnancy [22,23,35,37]. We presented some of the literature data regarding pregnancy course and outcome of women with AT deficiency in the table 1.

Diagnosis

The first step in AT risk assessment for both asymptomatic and symptomatic women is detailed personal medical (previous thromboembolism or numerous miscarriages) and family history [4,25]. A significant percent of AT deficient women will report having thromboembolism at an early age or the first trimester of pregnancy, which is quite unusual for other disorders [4]. Moreover, because of the autosomal dominant inheritance, women will often report thromboembolic events in at least few of the close relatives [7].

The differential diagnosis includes deficiency of protein C or S, factor V Leiden. Other hypercoagulable states such as antiphospholipid syndrome also need consideration [8,25]. If these more common types of thrombophilias are excluded testing for AT deficiency should be performed. Complete assessment of coagulation factors is clinically essential for diagnosis [4,30].

The diagnosis of AT deficiency is based on decrease in AT concentration or functional activity measured by immunologic or functional tests [19,25]. If the level of AT functional activity is reduced to 50% - 60% or less the condition is confirmed. Nevertheless, some patients can have almost adequate AT activity [5,17]. Consequently, in case of clinically suspected AT deficiency and unconvincing laboratory analyses, genetic testing of patient and family members is recommended [7].

It should be kept in mind that AT functional level can be distorted and incorrect if measured in the acute phase of venous thromboembolism [4,25]. Moreover, in relatively large proportion of cases correct diagnosis of thromboembolism during pregnancy can be delayed. Swelling and discomfort in the legs, dyspnea and tachypnea are common in pregnancy and therefore those signs could be misinterpreted [2].

Consecutive monitoring of hemostatic molecular markers must be performed throughout the pregnancy, because the half-life of blood AT levels changes according to gestational

**Table 1:** Literature data of patients with AT deficiency. In all presented cases mothers successfully survived the pregnancy.

Cases/Studies	Family history	Personal history	Treatment	Thrombotic event during pregnancy	Outcome for the child
Case 1 Brandt 1981	Sister died in the 6 th pregnancy month	Negative	Heparin + AT concentrate	Negative	Positive
Case 2 Brandt 1981	Numerous family members	Recurrent thromboembolism	Heparin + AT concentrate	Thrombosis of lower limbs and lower vena cava	Pregnancy termination
Case 3 Blondel-Hill 1992	Numerous family members	DVT in previous pregnancy	Heparin	12 th GW lower limbs DVT	Positive
Case 4 Blondel-Hill 1992	Negative	I trimester DVT previous pregnancy	Heparin	6 th GW lower limbs DVT	Positive
Case 5 Swaim 1999	Numerous family members	Negative	LMWH + AT concentrate	16 th GW lower limbs DVT	Positive
Case 6 Yamada 2001	Father and aunt	2 DVT in lower limbs at 8GW; 1x cerebral	AT concentrate	12 th GW lower limbs DVT	Positive
Case 7 Yamada 2001	Numerous family members	Negative	Heparin + AT concentrate	Lower limbs DVT; emboli postpartum	Positive
Case 8 Ozsener 2001	Negative	Negative	Surgery	36 th GW cerebral thrombosis	Positive
Case 8 Sharpe 2011	Numerous family members	Negative	LMWH	I trimester DVT; 34 th GW cerebral thrombosis	Positive
Case 9 Sabzi 2015	Negative	Previous pregnancy cardiac thrombosis	AT concentrate + surgery	I trimester cardiac thrombosis	Pregnancy termination
Case 10 Xia 2012	Sister during pregnancy	3 rd month lower limbs DVT	LMWH	Thrombi in mesenteric vein	Pregnancy termination
Case 11 Xia 2012	Father	Recurrent DVT	Warfarin/LMWH	Negative	Fetal death in 5 th month
Case 12 Kovac	Mother	Negative	Heparin/LMWH, AT concentrate	Negative	Positive
Cases 13 - 30 Rogenhofer 2014	Negative	DVT	Heparin/LMWH, AT or no therapy	3 women with lower limbs DVT	11 positive and 7 negative
Cases 31 - 48 Sabadell 2010	Negative	Negative	12 women LMWH; other 6 - no therapy	3 women with lower limbs DVT	8 positive and 10 negative
Cases 49 - 54 James 2013	Numerous family members in 5 women; 1 negative	DVT in 2 women; 4 negative	Heparin or AT concentrate	DVT in all and 3 pulmonary embolisms	4 positive and 2 negative

Legend: GW: Gestational Week; DVT: Deep Vein Thrombosis; LMWH: Low Molecular Weight Heparin; AT: Antithrombin

age [6,26]. Studies of AT levels in healthy pregnant women proved that in majority of women there are no significant changes in AT activity during each trimester or during the postpartum period [17,25]. However, in women with AT deficiency functional activity of AT gradually decreases as pregnancy progresses, reaching the lowest percent four days after delivery [6,17,26]. Reduced activity of AT also correlates with term preeclampsia, implying that women with AT deficiency need to check blood pressure and urine protein levels even more often than generally suggested [25,27,28]. If AT serum activity remains in the lower level by delayed/post-term delivery the risk for thromboembolism increases even more. This fact should be kept in mind if Caesarean Section has to be performed due to lack of natural delivery commencement before the 42nd gestational week [33].

Management

Management of AT deficiency should be considered according to pregnancy period: pre-pregnancy planning, during pregnancy, intrapartum and postpartum management [25,38]. Prophylaxis of thromboembolism is an essential therapy during pregnancy [1,39]. All women with AT deficiency should be anticoagulated with heparin throughout the whole pregnancy as their risk for thromboembolism significantly increases from first to third trimester. Moreover, women with AT deficiency should start receiving heparin prophylaxis as soon as they start planning pregnancy [18,25,29,40].

Long-term anticoagulant thromboprophylaxis is not advised unless previous venous thrombosis has occurred to avoid hemorrhage [14,19,38,39]. The standard anticoagulation is done with heparin or Warfarin to achieve referral INR of 2.0 to 3.0. and AT level from 80% to 120% [1,19]. The therapy effects are monitored with functional hemostasis tests and anti-factor Xa and the dosing is adjusted during the course of pregnancy [24,30].

Oral anticoagulants should be ceased prior to pregnancy since, due to placental permeability, they may cause both teratogenic and numerous adverse fetal effects [6,38]. Warfarin use, if necessary, must be restricted to second trimester and/or early third trimester [7,19].

Heparin is a widespread treatment for AT deficiency [16]. Although heparin is easy to use during pregnancy, a large amount of heparin alone is necessary to achieve a sufficient anticoagulant effect on AT deficiency [6,38]. Women on prolonged heparin therapy (longer than 20 weeks) should be monitored for potential adverse effects such as thrombocytopenia and decrease in bone mineral density [6]. Another potential problem is the fact that AT deficiency is the most common cause of resistance to heparin, because heparin necessitates adequate level of antithrombin to achieve anticoagulation [19].

Therefore, use of low-molecular-weight heparin (LMWH)



has become more often during pregnancy [2,40]. LMWH represents the most efficacious and safe anticoagulant modality during pregnancy as it does not cross placenta and is not secreted in breast milk. While some researchers recommend low dose administered subcutaneously (5,000 units/day), others suggest that pregnant women with AT deficiency should use LMWH at larger therapeutic doses (30,000 units/day) [25]. Still, there is a wide range of variations in LMWH dosing during pregnancy, taking into consideration previous thromboembolic history. The advantage of LMWH is decreased risk of thrombocytopenia and hemorrhagic complications as compared to heparin [21]. LMWH may be administered until the delivery without continuous laboratory monitoring. The main disadvantage of LMWH is the fact that it is a costly therapy [25].

Thus, during pregnancy AT concentrate supplementation might be preferable [6,11]. Although currently AT concentrates are not used routinely during the antepartum period, literature data imply that AT supplementation can be the most beneficial therapy because it easily maintains blood AT levels high enough to prevent thrombi and does not increase the risk of bleeding [19,25]. Some studies reported that administration of AT concentrate infusions alone ended in a favorable outcome for most women and children [14,18]. However, since AT concentrate is a blood derivative, apart from being expensive, there is a risk of viral infection transition [6]. Recently recombinant human antithrombin has been manufactured and is available for clinical use [40]. However, clinical trials on large samples of this product still need to be performed [5,19].

Conventional heparin should be withdrawn when delivery is planned or started [25,40]. After the 37th gestational week heparin dosage should be reduced 10,000–15,000 IU/day to prevent hemorrhagic complications during delivery. LMWH can generally be continued through labor [1,25,40,41]. However, successful regional anesthesia without any complications even with LMWH therapy has been reported [25].

Nevertheless, it seems preferable (safe and effective) to use AT concentrate during delivery because it reduces risks of both, bleeding and thrombosis [11,38]. AT supplementation is mostly combined with LMWH therapy 24 hours prior to delivery and bridged to oral anticoagulant in postpartum period. Dosing of AT concentrate is based on body weight and baseline AT activity. However, there are still no clear guidelines on appropriate dosing and monitoring of AT supplementation during pregnancy, or the optimal duration of this therapy postpartum [16,41].

During the immediate postpartum period, the patient may be managed with heparin [25]. Currently according to literature data it is believed that AT concentrate, combined with heparin, should be given to all women after delivery for thromboprophylaxis regardless of their thrombosis history

[40,41]. Alternatively oral anticoagulants like Warfarin can be used after delivery again, as it is not excreted in breast milk [6].

Conclusion

Antithrombin deficiency is the rarest thrombophilia, but the one with the highest risk of thromboembolism. This risk is increased even more for pregnant women due to physiological changes of coagulation occurring in pregnancy. Therefore, in cases of positive personal and/or family history of thromboembolic events as well as recurrent pregnancy loss women should be tested for AT deficiency. Close monitoring with early and adequate prophylaxis and treatment nowadays can mostly assure the positive pregnancy outcome for both mothers and their children. To achieve the best maternal as well as neonatal outcome prophylaxis/therapy with both LMWH and AT concentrate should start as soon as pregnancy is planned or at least as early as possible in pregnancy and continue until the end of the puerperium.

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