Clinical Insights in Hereditary Antithrombin Deficiency in Pregnancy and the Role of Thrombate III® (Antithrombin III [Human])

In Our Discussion Today...

• Discuss the prevalence, clinical relevance, and risks associated with venous thromboembolism (VTE) and hereditary antithrombin (AT) deficiency in pregnancy
• Review the role of endogenous AT in coagulation and heparin therapy
• Discuss the data supporting the use of Thrombate III® (antithrombin III [human]) in patients with hereditary AT deficiency in high-risk situations, such as childbirth
• Review safety profile, dosing, and administration of Thrombate III
• Address commonly asked questions

Thrombate III is a registered trademark of Grifols Inc.; 2012.
Is Stephanie Your Next Patient?

- **Stephanie’s history**
  - 28-year-old female
  - Two first-trimester spontaneous abortions in past year
  - Diagnosed with hereditary AT deficiency
  - Family history
    - Father: peripheral artery disease and fatal massive PE at age 55
    - Sister: nonfatal DVT after long flight; 3 miscarriages with no full-term pregnancies preceding DVT episode

- **Current status**
  - Uncomplicated pregnancy; took enoxaparin 40 mg BID and wore compression stockings
  - Admitted for induction of labor at 39 weeks’ gestation
  - AT level at admission: 57%

*BID, twice daily; DVT, deep vein thrombosis; PE, pulmonary embolism.*

Hypothetical case profile is not intended to convey clinical diagnostic or therapeutic recommendations.

What Is Hereditary AT Deficiency? Who Should Be Tested and When Should Those Patients Be Tested?
Overview of Hereditary AT Deficiency

- Rare but serious autosomal dominant disorder\(^1\)
- >150 known AT mutations; various phenotypes\(^1\)
- Defined as 40%-60% reduction in AT activity\(^2\)
  - Activated procoagulant proteins circulate longer\(^3\)
  - Increased risk of venous thromboembolism (VTE) and pulmonary embolism (PE)\(^2,4\)
- No specific ethnic group or gender is affected more than others\(^3,4\)

1. MacLean PS, Tall RC. Drugs. 2007;67:1429-1440.

Prevalence

- Overall prevalence: 1 in every 500 to 5000 individuals\(^1-3\)
  - Approximately 60,000 to 600,000 people in the US are affected\(^4\)
- >250,000 patients are hospitalized for VTE each year in the US\(^5\)
  - Up to 7500 (3%) may have hereditary AT deficiency\(^6\)
- Up to 70% of pregnant women with hereditary AT deficiency who do not receive prophylactic therapy may experience thromboembolic complications\(^7\)

Hereditary AT Deficiency: Defect May Be Quantitative or Qualitative

• Type I
  - Quantitative defect
  - Approximately 50% reduction in AT activity and antigen levels
  - More common among symptomatic patients

• Type II
  - Qualitative defect
  - More common among the general population
  - Reduction in AT activity but antigen levels may be normal
    - Subtype IIa: defect in the reactive site; high risk of thrombosis
    - Subtype IIb: defect in the heparin-binding site; low risk of thrombosis
    - Subtype IIc: defects in both sites; high risk of thrombosis


When Is the Risk Highest in Hereditary AT Deficiency?

• Pregnancy
  - VTE risk:
    - Increases 7- to 10-fold during pregnancy
    - Is greatest after delivery
  - Pregnancy-related VTE incidence: up to 70% in women with hereditary AT deficiency

• Surgery
  - Orthopedic, oncologic, general, neurosurgery, and gynecologic surgeries
  - Thrombotic complications in 17%-22% of surgical patients who did not receive AT concentrate

• Thromboembolism
  - VTE: up to 85% of patients by age 50
  - Recurrent thromboses: approximately 60% of patients

Patient and Family History May Raise Suspicion of Hereditary Thrombophilia

- **Patient History**
  - Unexplained VTE at a younger age (<50 years)
  - Recurrent spontaneous VTE or unusually extensive spontaneous VTE
  - Unexplained arterial thromboembolism in a younger patient
  - Unexplained VTE at an unusual site
  - Recurrence of VTE while adequately anticoagulated

- **Family History**
  - Family history of spontaneous VTE
  - Asymptomatic individual with family history of known thrombophilia

- **History of Pregnancy Loss**
  - ≥3 unexplained pregnancy losses before 10 weeks’ gestation or ≥1 loss after week 10

Functional and Antigenic Assays Are Used in Making the Diagnosis

- **Functional AT assays**
  - Based on factor inhibition
  - Initial testing
  - High specificity and sensitivity
  - Positive predictive value of 96%

- **Antigenic AT assays**
  - May differentiate type I from type II
  - High specificity; limited sensitivity

*Functional assays measuring thrombin or factor Xa inhibition are the most commonly used assays*
Diagnostic Algorithm for Hereditary AT Deficiency

Results of functional AT assay: LOW

Repeat functional AT assay + Consider antigenic assay

• Functional assay result: LOW
• Antigenic assay result: LOW

Possible type I hereditary AT deficiency

• Functional assay result: LOW
• Antigenic assay result: NORMAL

Possible type II hereditary AT deficiency

Kotke-Marchant K, Duncan A. Arch Pathol Lab Med. 2002;126:1326-1336.

When Are Pregnant Patients at Greatest Risk of VTE?
Hereditary AT deficiency increases thrombotic risk 20-fold.

Thrombotic risk may be lower depending on type of defect.

Thrombate III® (antithrombin III [human]) is not indicated for the treatment of thrombophilias other than hereditary antithrombin deficiency.


Pregnant women are 4 times more likely to suffer from VTE.

Each component of Virchow’s triad is present in the pregnant woman.

Hypercoagulability

Venous stasis

Vascular damage

“During pregnancy and the postpartum period, women are 4 times more likely to suffer from VTE than when they are not pregnant” because of Virchow’s triad.


Changes That Occur During Pregnancy

- Venous distention begins in 1st trimester
- Venous flow to lower extremities is reduced by half by 3rd trimester
- Increase in clotting factors I, II, VII, IX, X, XII and fibrinogen
- Decrease in factors XI and XIII


Risk of VTE Increases 25-Fold Immediately After Delivery

Incidence of VTE increases 25-fold in the first week after delivery

- Census estimates of the female population of Olmsted County were used to estimate person-years at risk.
- First trimester data not captured.
- Trim, trimester; PP, postpartum.
What Is the Role of Antithrombin in Achieving Anticoagulation?

AT Provides 80% of the Natural Anticoagulant Effect Against Thrombin

- 58 kDa glycoprotein produced in the liver
- Half-life ~ 2-3 days
- Binds irreversibly to thrombin and factor Xa, preventing the conversion of fibrinogen into fibrin
- AT is necessary for the anticoagulation effects of heparin

Antithrombin Inactivates Several Clotting Factors

Intrinsic Pathway
- FXII
- FXI
- FXa
- ATIII

Common Pathway
- FX
- FVIIIa
- FIlla
- AT

Tissue Factor Pathway
- TF
- FVIIa
- FXa
- AT

TF
- FIIa (thrombin)
- FII
- FXa
-FIXa
- FXIIa
- FIX
- FXII

HMWK, high-molecular-weight kininogen; PK, prekallikrein; TF, tissue factor.


Antithrombin Inactivates Several Clotting Factors

AT Irreversibly Binds to and Inhibits Factor Xa and Thrombin

AT provides 80% of the natural anticoagulant effect against thrombin


What Is the Role of AT Replacement in Patients With Hereditary AT Deficiency During Pregnancy, Labor, and Childbirth?
How Do We Approach the Management of Stephanie’s Case?

• Patient assessment
  – Last dose of enoxaparin administered 24 hours before arrival at hospital
  – Normal blood pressure, pulse, temperature
  – Normal fetal status per fetal monitoring
  – Ultrasound and examination to assess for signs of DVT were unremarkable
  – Patient height: 5’4”
  – Patient weight: 154 lbs (70 kg)
  – AT activity level of 57%

• Call to action: Schedule intermittent measurements of patient’s AT activity level in anticipation of delivery

Hypothetical case profile is not intended to convey clinical diagnostic or therapeutic recommendations.

Goal of Guidelines: Minimize Bleeds and Return AT Levels to Normal

According to Consensus Report and Recommendations for Prevention and Treatment of Venous Thromboembolism and Adverse Pregnancy Outcomes:

• AT deficient patients are “hypercoagulable” during the ante-, intra-, and postpartum periods
• Patients who develop or are at increased risk to develop acute thrombosis should receive
  – AT concentrate
  – Adjusted-dose anticoagulation
• AT levels should be returned to normal and maintained at the normal level for 2-8 days in obstetric patients receiving AT concentrate

Thromboprophylaxis in Pregnancy

According to the ACOG Practice Bulletin:

- Recommended thromboprophylaxis for pregnancies complicated by inherited thrombophilias:¹,²

<table>
<thead>
<tr>
<th></th>
<th>High Risk* (no previous VTE)</th>
<th>High Risk* (single previous VTE, not on long-term anticoagulation therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum Management</td>
<td>Prophylactic LMWH or UFH</td>
<td>Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH regimen</td>
</tr>
<tr>
<td>Postpartum Management</td>
<td>Anticoagulation therapy</td>
<td>Anticoagulation therapy, intermediate- or adjusted-dose LMWH/UFH x 6 weeks†</td>
</tr>
</tbody>
</table>

- Women with AT deficiency may be candidates for AT concentrates in the peripartum period¹,²

* Including AT deficiency.
† Therapy level should be at least as high as antepartum treatment.


AT Replacement Can Be Used During the Critical Window

- The time period before initiating regional anesthesia is a critical window during which hereditary AT deficiency patients are at high risk for VTE¹,²
- AT replacement can be used during this critical window³

AT Concentrate: Proven Safety and Effectiveness

• The effect of heparin and AT concentrate* during pregnancy was evaluated in 8 women with hereditary AT deficiency during 9 pregnancies
• AT concentrate was administered during delivery or abortion and the AT level was maintained at ≥80%
• The anticoagulant effect of heparin was enhanced with the increase in AT activity level
• No bleeding complications, allergic reactions, thrombocytopenia, or liver insufficiencies occurred
• No thrombotic events occurred during the time period in which AT concentrate was administered

* The AT concentrate used in this study was not Thrombate III® (antithrombin III [human]).

AT Concentrate in the Peripartum Period Helps Prevent VTE Without Complications

• Retrospective study of 18 pregnancies among 9 patients with hereditary AT deficiency. Treatment defined as LMWH during pregnancy and AT concentrate* during the peripartum period

<table>
<thead>
<tr>
<th>Event</th>
<th>Diagnosed and Treated (n/N)</th>
<th>Not Diagnosed and Not Treated† (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td>0/11 (0%)</td>
<td>3/7 (43%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Potential Complication</th>
<th>Incidence of Complication With AT Concentrate Treatment</th>
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</thead>
<tbody>
<tr>
<td>Complications following neuraxial anesthesia‡</td>
<td>0%</td>
</tr>
<tr>
<td>Heavy bleeding</td>
<td>0%</td>
</tr>
</tbody>
</table>

n = number of pregnancies with the listed event; N = total number of pregnancies in the analysis group.

* The AT concentrate used in this study was not Thrombate III® (antithrombin III [human]).
† Thromboprophylaxis was given in all pregnancies in which hereditary AT deficiency was diagnosed at the time.
‡ All patients received neuraxial anesthesia.
A Treatment Plan for Stephanie

- **Treatment goals**
  - Overall treatment goal: deliver full-term infant while preventing VTE due to hereditary AT deficiency
  - Increase AT activity level via administration of Thrombate III®
    - Increase level from 57% of normal to between 80% and 120% during delivery and postpartum

- **Birth plan**
  - Induce labor
  - Deliver vaginally with epidural anesthesia
  - Administer Thrombate III before initiating regional anesthesia and postpartum for up to 1 week

Hypothetical case profile is not intended to convey clinical diagnostic or therapeutic recommendations.

FDA-approved for patients with hereditary AT deficiency in connection with surgery or obstetrical procedures or when they suffer from thromboembolism

Please see Important Safety Information about Thrombate III® on slides 45 and 46 and refer to complete Prescribing Information for complete prescribing details.
**Thrombate III®: Mimics the Mechanism of Action of Endogenous AT**

- Thrombate III is a preparation of antithrombin concentrate purified from human plasma
- Replaces antithrombin that is normally present in the body
- Restores body’s natural ability to inhibit clot formation
- Half-life (3.8 days) similar to endogenous antithrombin

**Thrombate III®: Pivotal Efficacy**

**Objective**

- Patients with hereditary AT deficiency were treated with Thrombate III if they
  - Required prophylaxis for a condition associated with increased risk of thromboembolism (surgery or pregnancy)
  - Required short-term treatment for thrombosis or pulmonary embolism

**Treatment with Thrombate III**

- Dosed to maintain plasma AT levels in the range of 75%-120%* of normal
- Continued until clinical condition resolved, patient was treated with oral anticoagulants, no further benefit was expected, or patient experienced side effects that led to withdrawal

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1. Data on file, Grifols.

* This is per the study protocol.
No Cases of Thrombotic Complications During Surgical and Obstetrical Procedures\(^1,2\)

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>No. of cases</th>
<th>Therapeutic outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childbirth</td>
<td>5(^*)</td>
<td>No thrombosis or pulmonary embolism</td>
</tr>
<tr>
<td>Surgery</td>
<td>11(^*)</td>
<td>No thrombosis or pulmonary embolism</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>8(^†)</td>
<td>No further thromboembolic episodes(^‡)</td>
</tr>
</tbody>
</table>

\(^*\) Data included 13 patients treated on 16 separate occasions (1 patient was treated for both surgery and childbirth). Average baseline antithrombin level was 53% (range, 22%-71%). Heparin was administered in 3 of the 11 surgical procedures and all 5 deliveries. 

\(^†\) All patients received heparin.

\(^‡\) One patient died of nontreatment-related causes.


One Dosing Formula for Thrombate III\(^®\)

- Dosing recommendations
  - As a general recommendation, increase AT activity to 120% of normal levels
  - Plasma levels between 80% and 120% may be maintained with maintenance doses of 60% of the initial loading dose, given every 24 hours for 2-8 days
  - Adjustments in the maintenance dose and/or interval between doses should be made based on the actual plasma AT levels achieved

Calculation of initial loading dose of AT

\[
\text{Units required (IU)} = \frac{\text{[desired – baseline AT level\(^*\)] x weight (kg)}}{1.4}
\]

\(^*\) Expressed as percent of normal level based on functional AT assay.

The anticoagulant effect of heparin is enhanced by concurrent treatment with Thrombate III in patients with hereditary antithrombin deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with Thrombate III.

Thrombate III\(^®\) (antithrombin III [human]) [prescribing information]. Research Triangle Park, NC: Grifols; 2009.
**Easy Dosing Calculations: Use the App for Thrombate III®**

- Digital dosing calculator
  - Allows you to quickly calculate the loading and maintenance doses
  - Available for the iPhone®, iPad®, and DROID® mobile digital devices
  - Easy and free: go to app store and search for “Thrombate”

![Digital dosing calculator image]

**Thrombate III® Provides Concentrated Antithrombin Replacement for Patients With Hereditary AT Deficiency**

<table>
<thead>
<tr>
<th></th>
<th>Thrombate III®</th>
<th>FFP ², ³</th>
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<tbody>
<tr>
<td>How supplied</td>
<td>500-IU vials</td>
<td>250-mL bags</td>
</tr>
<tr>
<td>AT concentration</td>
<td>50 IU/mL</td>
<td>~1 IU/mL</td>
</tr>
<tr>
<td>Volume in a 3500-IU loading dose*</td>
<td>70 mL (bolus infusion)</td>
<td>3500 mL (14 bags)</td>
</tr>
<tr>
<td>Other considerations</td>
<td>• Convenient to store, reconstitute, and administer</td>
<td>• Requires thawing time and coordination with blood bank</td>
</tr>
</tbody>
</table>

FPF, fresh frozen plasma.

* Head-to-head clinical trials comparing Thrombate III and FFP in patients with hereditary AT deficiency have not been conducted.

† Loading dose example based on a 70-kg patient with 50% AT activity.

‡ Based on calculation of 7 vials and 10 mL of diluent per vial.

Easy Administration and Convenient Storage

• Bolus intravenous infusion
• Infusion rate is adapted to patient response
  – Total infusion time of 10-20 minutes is generally well tolerated
• Administer within 3 hours following reconstitution
• Room temperature storage (not to exceed 25°C [77°F])
• Convenient vial size to minimize waste
  – Approximately 500 IU reconstituted to 10 mL


Approach to Dosing for Stephanie

• Initial Thrombate III® dose of 3150 IU administered without complication
  Units required (IU) = $\frac{[120 – 57] \times 70 \text{ (kg)}}{1.4}$
• Low-volume bolus: 63 mL
• Epidural catheter placed when Stephanie’s cervix was dilated to 4 cm; placement uneventful
• AT activity assay 5 hours after epidural placement was 105%
• No complications of delivery; healthy infant delivered

Hypothetical case profile is not intended to convey clinical diagnostic or therapeutic recommendations.
Postpartum Approach for Stephanie

- Individualized maintenance dose of Thrombate III®
  - 60% of total loading dose administered every 24 hours
  - Goal: maintain AT activity levels in the normal range (80% to 120%) until discharge
  - Adjustments in maintenance dose and/or interval between doses should be based on actual plasma AT levels achieved

Hypothetical case profile is not intended to convey clinical diagnostic or therapeutic recommendations.

Safety Profile for Thrombate III®

Commitment to Safety
- No known contraindications
- Pregnancy category B
- Pasteurized to inactivate viruses, with no confirmed cases of virus transmission
  - Thrombate III is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob agent that can cause disease

Tolerability
- In clinical studies with Thrombate III, the most common side effects were dizziness (2%), chest tightness (0.9%), nausea (0.9%), and foul taste in the mouth (0.9%)

Experience
- Used for the treatment of hereditary antithrombin deficiency for >20 years

The anticoagulant effect of heparin is enhanced by concurrent treatment with Thrombate III in patients with hereditary antithrombin III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with Thrombate III.

Thrombate III®: Proven Effective in Pregnant Women With Hereditary AT Deficiency

- Risk of VTE is highest in the first week after delivery
- Up to 70% of pregnant women with hereditary AT deficiency who do not receive prophylactic therapy may experience thromboembolic complications
- Patient and family history may indicate a need for AT deficiency testing
- In clinical studies of Thrombate III, no cases of thrombotic complications during surgical and obstetrical procedures were reported
- Thrombate III® replaces antithrombin that is normally present in the body

Thrombate III is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jacob disease (CJD) agent that can cause disease. There is also the possibility that unknown infectious agents may be present in such products.


Case Study: Denise

Thrombate III® in the Peripartum Period
Denise: 25-Year-Old Patient in the 36th Week of Pregnancy

- **History**
  - After an episode of mesenteric vein thrombosis at age 17 years, Denise was diagnosed with hereditary AT deficiency and placed on lifelong anticoagulation with warfarin.
  - Denise has a history of one missed abortion.

- **Current Status**
  - Denise is being admitted for induction of labor due to oligohydramnios.
  - Warfarin was changed to enoxaparin at a dose of 60 mg BID when she was found to be pregnant.
  - Her AT level on warfarin was 47%.

**Denise’s Postpartum Course**

- Weight was 152 pounds on admission; antithrombin level was 45%. She received antithrombin concentrate targeting 100% as the desired level on Day 0, Day 2, and Day 4 of hospitalization.
- Delivery was late on Day 1, with last enoxaparin dose prior to that on the day of admission. The newborn had an uneventful recovery.
- Enoxaparin 30 mg BID was started immediately after delivery (Day 2) and continued until discharge.
- Warfarin was also started on Day 2, and she was discharged home on a dose of 5 mg/day, with instructions to watch for bleeding and have regular PT/INR checks. No complications were noted.

INR, international normalized ratio; PT, prothrombin time.

Data on file, Grifols.
Important Safety Information

• Thrombate III is indicated for the treatment of patients with hereditary antithrombin deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism.

• In clinical studies with Thrombate III, the most common side effects were dizziness, chest tightness, nausea, and foul taste in the mouth.

• The anticoagulant effect of heparin is enhanced by concurrent treatment with Thrombate III in patients with hereditary antithrombin III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with Thrombate III.

Please see accompanying Thrombate III full Prescribing Information for complete prescribing details.

Important Safety Information

• Thrombate III is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent that can cause disease. There is also the possibility that unknown infectious agents may be present in such products.

• Individuals who receive infusions of blood or blood plasma may develop signs and/or symptoms of some viral infections, particularly hepatitis C.

Please see accompanying Thrombate III full Prescribing Information for complete prescribing details.