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Management of antithrombin III deficiency in pregnancy: a representative case and a literature review

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Abstract

The work is aimed at discussing pregnancy management for the most thrombogenic genetic thrombophilia – antithrombin III (AT-III) deficiency. A detailed analysis of the literature and clinical case of pregnancy management in a patient with AT-III deficiency, pulmonary embolism and habitual history of miscarriage has been performed and presented. Patients with AT-III deficiency are at high risk for developing thrombotic and obstetric complications even despite using therapeutic doses of anticoagulants. Indications for use and modes of administration of AT-III concentrate have not been currently defined clearly. Monitoring therapy with low molecular weight heparin is largely complicated because a test for determining anti-Xa activity is AT-III-dependent. In addition to standard methods for controlling antithrombotic therapy, we used tests characterizing the dynamic blood clot parameters: thromboelastography and thrombin generation test. The peak risk resulting in both thrombotic and hemorrhagic complications in such patients occurs during period of labor and the postpartum period, when a change in the regimen of anticoagulant therapy is required with its temporary withdrawal and additional administration of AT-III concentrate.

Keywords: antithrombin III deficiency, pregnancy, low molecular weight heparin, antithrombin III concentrate, rivaroxaban

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Ведение беременности при дефиците антитромбина III: обзор литературы и описание клинического случая

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Резюме

Работа посвящена проблеме ведения беременности при наиболее тромбогенной генетической тромбофилии – дефиците антитромбина III (AT-III). Проведен детальный анализ литературы и представлен разбор собственного клинического случая

ведения беременности у пациентки с дефицитом АТ-III, тромбоэмболией легочной артерии и привычным невынашиванием беременности в анамнезе. Пациентки с дефицитом АТ-III относятся к группе высокого риска по развитию тромботических и акушерских осложнений, даже несмотря на терапевтические дозы антикоагулянтов. Показания к применению и режимы введения концентрата АТ-III в настоящее время четко не определены. Контроль терапии низкомолекулярным гепарином в значительной степени затруднен, так как тест на определение анти-Ха активности является АТ-III-зависимым. Помимо стандартных методов контроля антитромботической терапии, мы использовали тесты, характеризующие динамические параметры сгустка: тромбоэластограмму, тест генерации тромбина. Наибольший риск с точки зрения как тромботических, так и геморрагических осложнений у таких больных представляет период родов и послеродовой период, когда требуется изменение режима антикоагулянтной терапии с временной ее отменой и дополнительное введение концентрата АТ-III.

Ключевые слова: дефицит антитромбина III, беременность, низкомолекулярный гепарин, концентрат антитромбина III, ривароксабан

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Highlights

What is already known about this subject?

- ▶ Patients with antithrombin III (AT-III) deficiency are at high risk for developing thrombotic and obstetric complications even despite using therapeutic doses of anticoagulants during pregnancy.
- ▶ Indications for use and modes of administration of AT-III concentrate in pregnancy have not been currently defined clearly.
- ▶ Monitoring therapy with low molecular weight heparin (LMWH) in pregnant patients with AT-III deficiency is largely complicated.

What are the new findings?

- ▶ We share with our strategy of successful pregnancy management in patient with AT-III deficiency, pulmonary embolism and recurrent miscarriage.
- ▶ Along with standard approaches for controlling antithrombotic therapy, we also used tests characterizing the dynamic blood clot parameters.
- ▶ Detailed analysis of therapeutic strategies in patients with AT-III deficiency was presented including guidelines on using LMWH, AT-III concentrate and oral anticoagulants during pregnancy and postpartum.

How might it impact on clinical practice in the foreseeable future?

- ▶ We believe that our research would allow for refining approaches to pregnancy management, choice and control of anticoagulation therapy during pregnancy and postpartum in patients with the most thrombogenic thrombophilia – AT-III deficiency.

Основные моменты

Что уже известно об этой теме?

- ▶ Пациентки с дефицитом антитромбина III (АТ-III) относятся к группе высокого риска по развитию тромботических и акушерских осложнений, даже несмотря на терапевтические дозы антикоагулянтов.
- ▶ Показания к применению и режимы введения концентрата АТ-III в настоящее время четко не определены.
- ▶ Контроль терапии низкомолекулярным гепарином (НМГ) во время беременности у пациенток с дефицитом АТ-III в значительной степени затруднен.

Что нового дает статья?

- ▶ Мы делимся нашей тактикой успешного ведения беременности у пациентки с дефицитом АТ-III, тромбоэмболией легочной артерии и привычным невынашиванием беременности.
- ▶ Помимо стандартных методов контроля антитромботической терапии мы использовали тесты, характеризующие динамические параметры сгустка.
- ▶ Представлен подробный анализ терапевтических стратегий у пациенток с дефицитом АТ-III, включая рекомендации по применению НМГ, концентрата АТ-III и пероральных антикоагулянтов во время беременности.

Как это может повлиять на клиническую практику в обозримом будущем?

- ▶ Мы надеемся, что наша работа позволит усовершенствовать подходы к ведению беременности, к подбору и контролю антикоагулянтной терапии во время беременности и послеродовом периоде у пациенток с самой тяжелой формой тромбофилии – дефицитом АТ-III.

Introduction / Введение

Antithrombin III (AT-III) deficiency is a rare but one of the most thrombogenic thrombophilias. Its prevalence varies from 1:500 to 1:5000, and among patients with thrombosis, it is found in 1 % of cases. Patients with AT-III deficiency encounter 20–30 times higher risk of

thrombosis compared to the general population [1]. The lifelong risk of venous thromboembolic complications with AT-III deficiency reaches 50–90 % even in the absence of provoking factors. The most common contributing factors of venous thromboembolism (VTE) include pregnancy, hormonal contraceptives and surgery [2]. 3–7 % of asymptomatic patients with AT-III deficiency develop first

thrombosis during pregnancy, whereas recurrence rate of thromboembolic complications during pregnancy reaches 40 % [3].

Antithrombin III is a 58 kDa glycoprotein that inhibits all serine proteases of coagulation system – thrombin, factor (F) Xa, FIXa, to a lesser extent FXIa, XIIa, as well as kallikrein and plasmin. AT-III exerts irreversible effects, providing an 80 % inhibitory effect on thrombin. The action of AT-III is potentiated by heparin and heparan sulfate – endothelial proteoglycans. Heparin increases the activity of AT-III by 1000-fold due to conformational changes.

The diagnostic criterion of AT-III deficiency is based on activity less than 60 % (normal is 80–120 %). Hereditary and acquired AT-III deficiencies differ. More than 250 mutations of the AT-III gene have been described [4]. The type of inheritance is autosomal dominant. In addition, various causes of acquired AT-III deficiency such as rheumatoid factor, paraproteins, DIC-syndrome, massive thrombosis, surgery, sepsis, systemic inflammatory response syndrome, inflammatory bowel diseases, heparin therapy, liver failure, nephrotic syndrome, combined oral contraceptives use, estrogen therapy, pregnancy, neonatal period (recovery of AT-III activity occurs within 72 hours after childbirth) and factors affecting the sensitivity of laboratory tests such as hemolysis, hyperlipidemia, elevated hematocrit (> 55 %) have been identified [5, 6].

The risk of VTE during pregnancy with AT-III deficiency is not fully understood. Even recent studies have many limitations and provide variable data on the risk of VTE, ranging from 3 to 17.7 %, during pregnancy and the postpartum period [7, 8]. Patients with AT-III deficiency have an increased risk of VTE including fatal VTE, fetal losses and severe placental complications, including fetal growth restriction, placenta abruption, preeclampsia, which occurs even despite using anticoagulants at therapeutic doses during pregnancy [9, 10]. At the same time therapeutic doses of anticoagulants allow us to believe in favorable pregnancy outcomes. In particular, it was shown that the risk of VTE during pregnancy after therapeutic anticoagulation in patients with AT-III deficiency was the same as outside pregnancy (1.7 % per year) [2]. Another study (18 patients with AT-III deficiency) showed 27 % fetal growth restriction syndrome and 0 % stillbirths while using anticoagulant therapy versus 50 % and 33 % respectively in the absence of prophylaxis [9].

Antithrombin III deficiency, being the most thrombogenic thrombophilia, requires intensive anticoagulant use at therapeutic doses during pregnancy. The drug of choice is a low molecular weight heparin (LMWH). The dose can only be reduced below the calculated per kg body weight with abnormally high anti-Xa activity, with chronic renal failure or with emerging bleeding [5].

According to currently available data AT-III concentrate is effective for the treatment of acute VTE and prevention of VTE recurrence during pregnancy and the postpartum period [11, 12]. The guidelines of the international

communities on dosage, control and time frame for using AT-III concentrate in pregnancy and postpartum period have not been well clarified [13–16]. AT-III concentrate is the drug of choice in conditions of discontinued LMWH administration (e. g., in case of bleeding, labor, invasive procedures) [17]. AT-III concentrate should be used starting 12–24 hours before the expected childbirth and rarely lasts for more than few days after delivery (therapy is cancelled after resumption of proper anticoagulant therapy). AT-III concentrate is indicated for the treatment of VTE developed during pregnancy despite anticoagulation therapy [18]. The majority of studies used AT-III concentrate starting from the time of verified thrombosis and up to several weeks postpartum (usually 6–9 days postpartum) [11]. AT-III concentrate therapy may not be justified as a primary prevention of VTE during pregnancy in asymptomatic patients with AT-III deficiency due to its high cost and the risks exceeding the benefits [5]. Possible indications for initiating prophylactic therapy with AT-III concentrate during pregnancy include a personal history of VTE, recurrent miscarriage, high risk of VTE recurrence (history of atypical thrombosis, history of pregnancy related VTE, recurrent VTE despite anticoagulants) [19, 20] (**Table 1**).

Calculation of the loading dose of AT-III: 1 IU is equivalent to AT-III activity in 1 ml of normal human plasma; 1 IU per kg of body weight increases AT-III activity by 2 %; required dose (IU) = body weight (kg) × (target level – initial AT-III activity level, %) × 0.5 (usually 30–50 IU/kg). Generally, the maintenance dose is 60 % of the loading dose and is administered every 2–3 days (on average 24–65 IU/kg). The average half-life of AT-III comprises 3 days, so that concomitant heparin treatment is shortened to 1.5 days.

According to the latest recommendation of the Royal College of Obstetrics and Gynecology [21] pregnancy management in patients with medical history of AT-III and VTE deficiency implies the use of high doses of LMWH throughout pregnancy as well as at least for 6 weeks in the postpartum period or prior to switching to oral anticoagulants (50–75 % of the treatment dose/doses) by controlling anti-Xa activity (targeted to 0.5–1.0 IU/ml 4 hours after LMWH injection). The AT-III concentrate should be also used in cases of ineffectiveness of LMWH and before the delivery.

Case report / Клинический случай

Patient Sh., 35 years old, height – 172 cm, weight – 54 kg, body mass index – 18.3 kg/m², admitted to the Department of Obstetrics and Gynecology of Sechenov University in October 2018, at 5–6 weeks of gestational age. She suffered from pulmonary embolism (PE) 1 month after the removal of breast fibroadenoma, mastoplasmy and abdominoplasty (June 2017). The patient received enoxaparin 0.4 ml per day for 10 days in the postoperative period. After PE AT-III deficiency

Table 1. Expert consensus on using antithrombin III (AT-III) concentrate during pregnancy [5].**Таблица 1.** Соглашение экспертов по применению концентрата антитромбина III (АТ-III) во время беременности [5].

Clinical case in a patient with AT-III deficiency Клинический случай пациентки с дефицитом АТ-III	Anticoagulant therapy Антикоагулянтная терапия	Antithrombin III concentrate Концентрат антитромбина III
VTE in medical history, long-term anticoagulant therapy ВТЭ в анамнезе, пациентка получает длительную антикоагулянтную терапию	Therapeutic doses of LMWH during pregnancy and the postpartum period Терапевтические дозы НМГ в течение беременности и послеродовом периоде	LMWH withdrawal (labor, hemorrhages, surgery) При отмене НМГ (роды, кровотечения, операции)
VTE in medical history, the patient received no long-term anticoagulant therapy (AT-III < 60 %) ВТЭ в анамнезе, пациентка не получает длительную антикоагулянтную терапию (АТ-III < 60 %)	Therapeutic doses of LMWH during pregnancy and the postpartum period Терапевтические дозы НМГ в течение беременности и послеродовом периоде	LMWH withdrawal (labor, hemorrhages, surgery) При отмене НМГ (роды, кровотечения, операции)
No VTE in medical history, AT-III < 60 %, family history of VTE ВТЭ не было, АТ-III < 60 %, ВТЭ в семейном анамнезе	No clear recommendations. From prophylactic to full therapeutic doses of LMWH. LMWH applied for at least 6 weeks postpartum Нет четких рекомендаций. От профилактических до полных терапевтических доз НМГ. НМГ минимум 6 нед после родов	No clear recommendations. Application is possible depending on the clinical situation Нет четких рекомендаций. Применение возможно в зависимости от клинической ситуации
No VTE in familial or personal history, AT-III < 60 % ВТЭ не было ни в семейном, ни в личном анамнезе, АТ-III < 60 %	No clear recommendations. From prophylactic to full therapeutic doses of LMWH. LMWH applied for at least 6 weeks postpartum Нет четких рекомендаций. От наблюдения до профилактической терапии, в том числе минимум 6 нед в послеродовом периоде	Use of AT-III concentrate with AT-III activity > 40 % is unlikely to be required Применение концентрата АТ-III при активности АТ-III > 40 % вряд ли понадобится

Note: VTE – venous thromboembolism; LMWH – low molecular weight heparin.

Примечание: ВТЭ – венозная тромбоземболия; НМГ – низкомолекулярный гепарин.

diagnosing was first detected (43 %), tests for IgG and IgM anticardiolipins, IgG and IgM antibodies to β_2 -glycoprotein 1, FV Leiden and prothrombin G201010A polymorphisms were negative. Pulmonary multispiral computed tomography dated of November 2017 showed full recanalization. Three months after PE (03.11.2017) markers of antiphospholipid syndrome were negative (IgG and IgM anticardiolipins, IgG and IgM antibodies to β_2 -glycoprotein 1, lupus anticoagulant), antinuclear factor was not detected, protein S activity was 41 % (normal more than 56 %), protein C – 100 %, homocysteine – 10.9 μ mol/L. After PE diagnosis patient received LMWH, followed by switching to rivaroxaban 20 mg per day which she personally stopped taking 3 months later. According to echocardiography performed 3 months later patent foramen ovale had no signs of pulmonary hypertension.

Familial history: father had PE at the age of 32 and 48 years old, aunt from the father side had fatal PE at age of 60 years. Patient's brother has laboratory-confirmed asymptomatic AT-III deficiency.

Obstetric history: uncomplicated delivery was in 2002 at the age of 20 years; healthy full-term boy was born weighing 4030 g. The patient reported that cardiotocography showed signs of fetal hypoxia, weight gain was 35 kg, blood pressure reached 190/100 mm Hg starting from 36 weeks, but despite this she refused to go

into premature delivery (medical records are not available). From 2003 to 2005, the patient had 5 miscarriages occurring at gestational age of 5–6 weeks. Cytogenetic studies were not performed. The patient received no anticoagulant therapy during any of the pregnancies.

For the patient, it was personal experience of the seventh pregnancy. On admission, (5–6 weeks) D-dimer was 687 ng/ml, AT-III – 51.3 % (**Fig. 1**). LMWH at therapeutic dose of 1 mg/kg two times a day (BID) was applied (enoxaparin 60 mg = 0.6, anti-Xa IU = 0.6 ml in the morning and 0.4 ml in the evening with 12-hour interval), starting from week 14 the dose was increased up to 0.6 ml BID, from the week 25 – up to 0.8 ml BID (weight 71.5 kg), from the week 32 (body weight 79 kg) the dose of enoxaparin was 1.0 in the morning and 0.8 ml in the evening. The maximum dose of enoxaparin was 1.0 ml BID within weeks 33–34. Despite stable levels of AT-III activity (53 %) and anti-Xa activity close to target levels (0.89 U/ml), it was decided to increase the dose in connection with the data of the thrombin generation test which showed a hypercoagulation state (**Fig. 2**). Patient blood pressure during pregnancy did not exceed 125–140/90 mm Hg, total body weight gain was 28 kg, complete blood count, blood biochemistry and urinalysis were within normal ranges. At 20 weeks of gestation, protein S level was 39.6 %, thus showing no significant

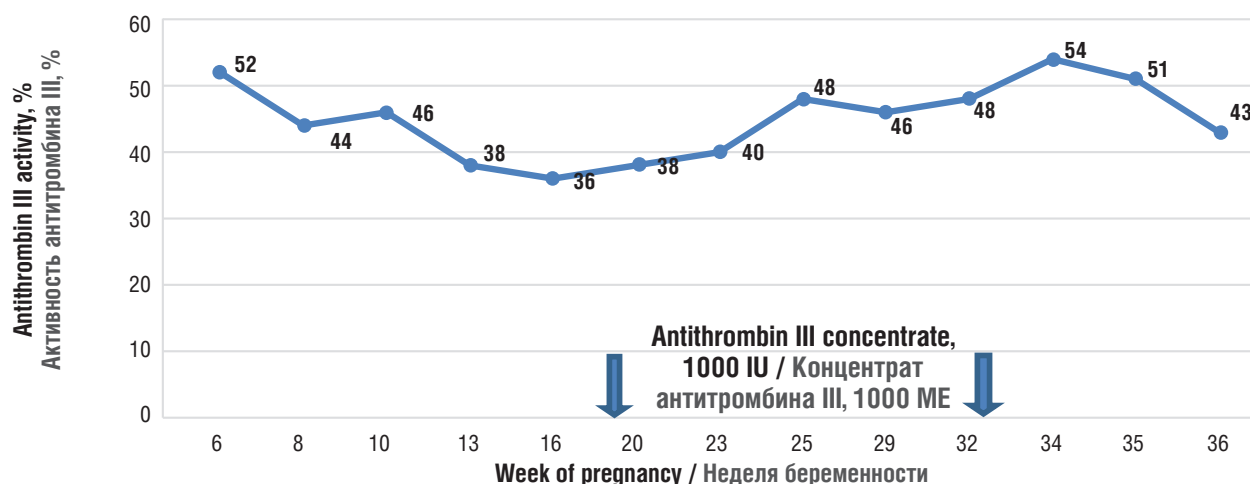


Figure 1. Dynamics of antithrombin III activity during pregnancy related to doses of low molecular weight heparin used and anti-Xa activity.

Рисунок 1. Динамика активности антитромбина III в течение беременности в зависимости от использованных доз низкомолекулярного гепарина и анти-Xa активности.

decrease in protein S activity during pregnancy compared with previously recorded (41 % in 2017).

In the current clinical case, AT-III concentrate was not systematically used during pregnancy. AT-III concentrate at dose of 1000 IU was on the week 20, before the air flight, and at week 32–33 (at week 32 AT-III was 30 %, anti-Xa activity was 0.52 IU/ml by applying enoxaparin at dose of 1.0 ml in the morning and 0.8 ml in the evening).

AT-III concentrate at dose of 1000 IU was also administered on the week 36 due to a significant decline of AT-III activity down to 22 % (anti-Xa activity 0.36 IU/ml at dose of enoxaparin of 1.0 ml and 0.8 ml every 12 hours).

The patient was delivered by cesarean section under spinal anesthesia at 37–38 weeks (08.05.2019). Indications for cesarean section included breech presentation, gestational hypertension, compromised umbilical artery flow (first registered upon admission at the hospital at 37 weeks). A full-term boy was born weighing 3970 g, height 55 cm, with an Apgar score of 7/8. The blood loss was 600 ml. On a day of surgery enoxaparin 0.8 ml was administered, whereas starting from the next day the dose of enoxaparin was 0.6 ml BID. A total of 6 doses of 1000 IU AT-III were administered before and after the cesarean section (**Table 2**).

The patient was discharged on the 7th day after cesarean section, from the 5th day after the surgery the patient was switched to rivaroxaban 15 mg BID, so that 3 weeks later dose of rivaroxaban was increased to 20 mg per day. Lactation was suppressed in accordance with the recommendations of the mammologist, taking into account previously performed mastoplasty. The patient was monitored for AT-III level comprising 59 % only once 6 weeks postpartum. According to the patient decision her son was not tested for an AT-III deficiency.

Unexpectedly, the patient was repeatedly admitted to our clinic with new pregnancy on July 2020. The

patient cancelled taking rivaroxaban 20 mg one month after the cesarean section without any consultation with hematologist and started to apply enoxaparin 0.4 ml BID from the 7th gestational week (patient body weight was 62 kg). On admission, patient AT-III activity was 45.6 %, D-dimer level – 390 ng/ml (normal up to 440 ng/ml), homocysteine content – 15.6 μ mol/L. The enoxaparin dose was gradually escalated up to 0.6 ml BID starting from the 8th gestational week and further up to 0.8 ml BID from the 20th pregnancy week (patient body weight at 36 weeks was 84 kg). AT-III concentrate 1000 IU was administered on the 29th week (AT-III was 13 % and 46 % 24 hours before and after treatment), 1500 IU and 1000 IU in two consecutive days on the 31st pregnancy week (AT-III was 22 % and 59% 24 hours before and after treatment), 1000 IU on the 33th week (24 hours before the onset AT-III was 10 %, anti-Xa was 0.3 IU/ml and 24 hours after treatment AT-III level was 33 %, anti-Xa was 0.3 IU/ml while receiving enoxaparin 0.8 ml BID) and 1000 IU in two consecutive days on the 36th pregnancy week (AT-III was 29 % while receiving enoxaparin 0.6 ml BID) (**Fig. 3**). Altered uterine blood flow was detected on the 29th gestational week (AT-III was 13 %), that restored after the AT-III concentrate infusion. Due to the elevated preeclampsia risks according to the first prenatal screening (astria) (1:30 for the early preeclampsia and 1:10 for the late preeclampsia) and to the personal history of preeclampsia we decided to additionally apply acetylsalicylic acid 75 mg a day (started from 17th week). We recorded no bleeding episodes while applying concomitant therapy with LMWH and acetylsalicylic acid.

The patient was delivered by cesarean section at 36⁺² weeks (03.02.2021) (tubal ligation was also performed upon patient's request). The indication for cesarean section was based on moderate preeclampsia (blood pressure – 168/95 mm Hg, daily proteinuria – 0.55 g).

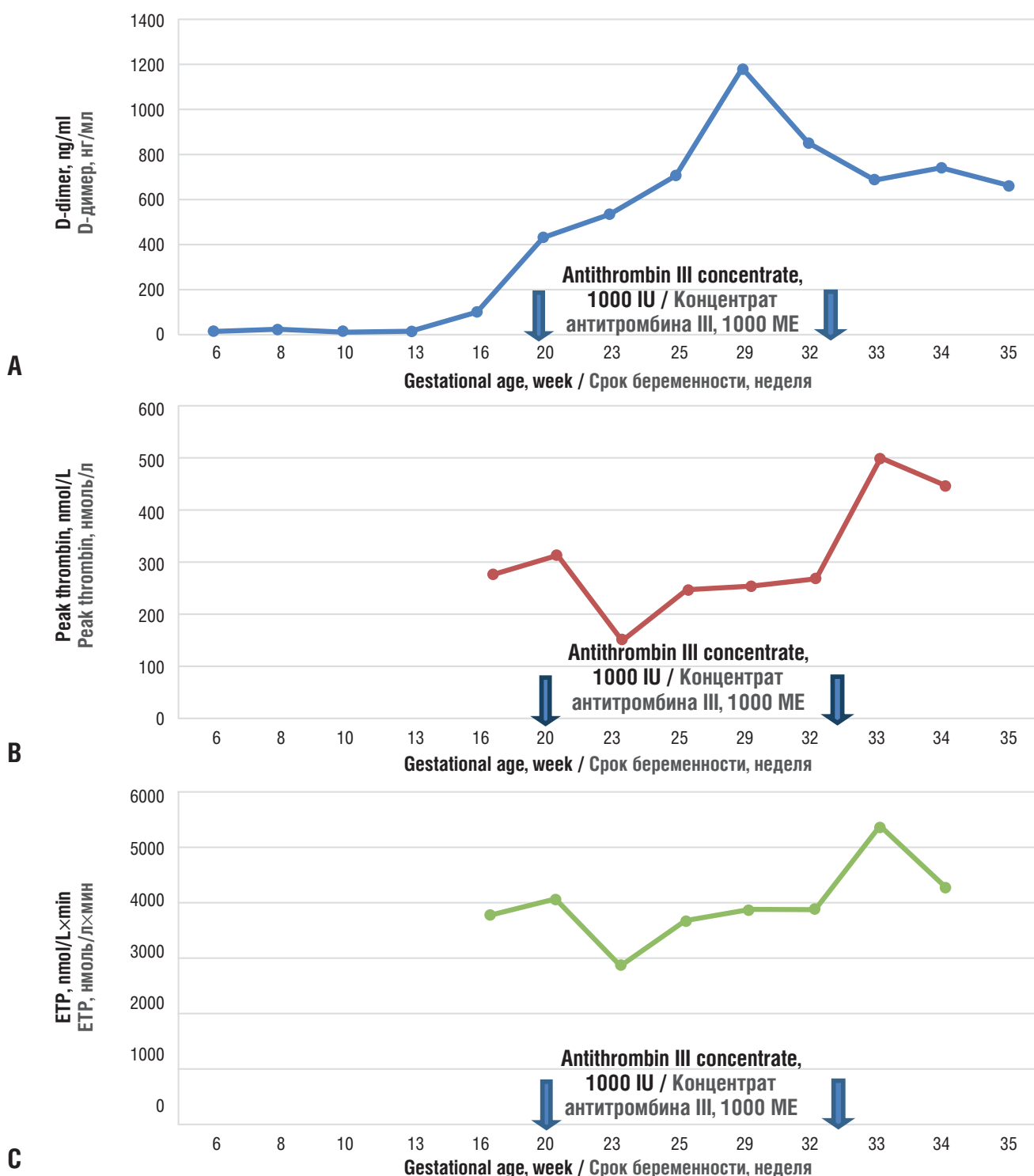


Figure 2. Dynamics of the D-dimer level (A) and data of the thrombin generation test – peak thrombin (B) and ETP (C) related to doses of low molecular weight heparin used and anti-Xa activity.

Note: D-dimer – according the local laboratory normal ranges were up to 250 ng/ml for nonpregnant state, up to 300 ng/ml in the I trimester, up to 500 ng/ml in the II trimester and up to 1000 ng/ml in the III trimester.

Peak thrombin – thrombin peak in the thrombin generation test, normal range 75–150 nmol/L.

ETP – endogenous thrombin potential index (area under the concentration-time curve in the thrombin generation assay), normal range is 1000–2100 nmol/L×min.

Рисунок 2. Динамика уровня Д-димера (А) и показателей теста генерации тромбина – peak thrombin (В) и ETP (С) в зависимости от использованных доз низкомолекулярного гепарина и анти-Ха активности.

Примечание: Д-димер – согласно местной лаборатории нормальные диапазоны составляли до 250 нг/мл для небеременного состояния, до 300 нг/мл в I триместре, до 500 нг/мл во II триместре и до 1000 нг/мл в III триместре.

Peak thrombin – пик тромбина в тесте образования тромбина, нормальный диапазон – 75–150 нмоль/л.

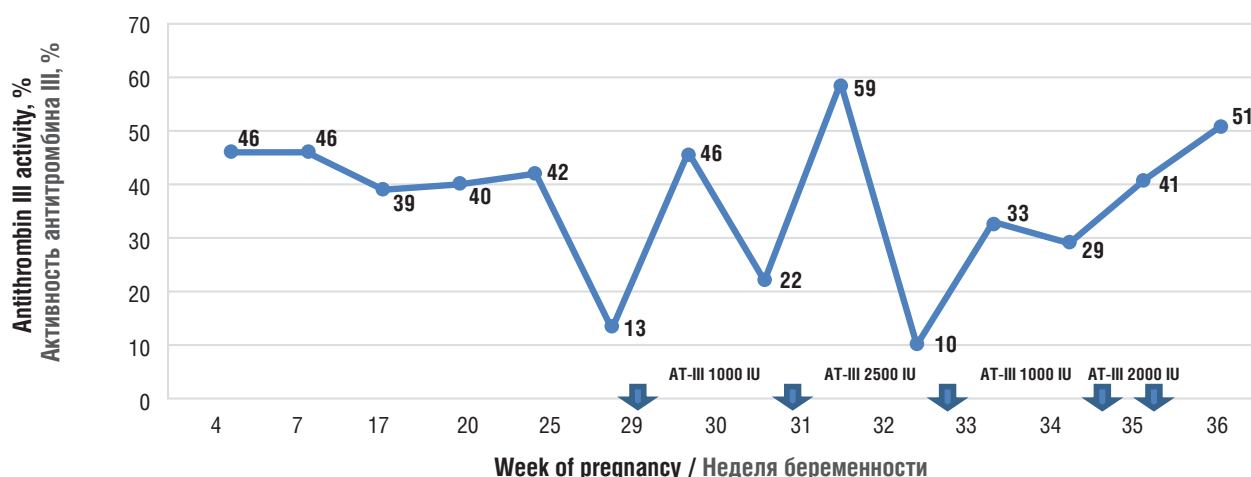
ETP – индекс эндогенного тромбинового потенциала (площадь под кривой концентрация-время в анализе образования тромбина), нормальный диапазон – 1000–2100 нмоль/л×мин.

Table 2. Management of the pre- and postoperative period in the patient with antithrombin III (AT-III) deficiency.**Таблица 2.** Ведение пред- и послеоперационного периода у пациентки с дефицитом антифотромбина III (AT-III).

Day before and after cesarean section День до и после кесарева сечения	-2	-1	The day of surgery День операции	+1	+2	+3	+4	+5
AT-III concentrate, IU Концентрат AT-III, ME		1000	1000	2000	1000		1000	
AT-III activity, % Активность AT-III, %		26		38			47	66
Anticoagulation therapy Антикоагулянтная терапия	LMWH 0.8 ml BID	LMWH 0.8 ml in the morning	LMWH 0.8 ml in the evening	LMWH 0.6 ml BID	LMWH 0.6 ml BID	LMWH 0.6 ml BID	LMWH 0.6 ml BID	Rivaroxaban 15 mg BID
	НМГ 0,8 мл 2 раза в день	НМГ 0,8 мл утром	НМГ 0,8 мл вечером	НМГ 0,6 мл 2 раза в день	НМГ 0,6 мл 2 раза в день	НМГ 0,6 мл 2 раза в день	НМГ 0,6 мл 2 раза в день	Риварокса- бан 15 мг 2 раза в день

Note: LMWH – low molecular weight heparin; BID – two times a day.

Примечание: НМГ – низкомолекулярный гепарин; BID – два раза в день.

**Figure 3.** Dynamics of antithrombin III activity and the regimen of antithrombin III concentrate infusion during pregnancy (2020).

Note: AT-III – antithrombin III concentrate; IU – international units.

Рисунок 3. Динамика активности антифотромбина III и схема введения концентрата антифотромбина III во время беременности (2020 г.).

Примечание: AT-III – концентрат антифотромбина III; IU – международные единицы.

A preterm girl was born weighing 2710 g, height 48 cm, with an Apgar score of 7/8. The blood loss was 600 ml. AT-III concentrate 1000 IU was administered 24 hours before surgery and on the day of surgery. The final dose of enoxaparin 0.8 ml was done 01.02.2021 in the evening. LMWH (nadroparin calcium 5700 anti-Xa IU 0.6 ml BID) was restarted 22 hours after the surgery and replaced by rivaroxaban 15 mg BID 3 days later; 3 weeks after that the patient was switched to rivaroxaban 20 mg once a day. Lactation was suppressed. Our patient personally decided to stop receiving rivaroxaban 20 mg 8 weeks after the cesarean section. AT-III was 41 % and 51%, respectively before surgery (01.02.2021) and 3rd day afterwards. The patient was not further tested for AT-III level till present

day (July 2021). The AT-III level measured to the patient paired daughter on week 2 after the birth was 110 %, and the patient refused to retest her infant daughter for AT-III activity. During the 5 months after delivery, the patient had no thrombotic and hemorrhagic complications, with no clinical signs observed in any of her children.

What laboratory markers were chosen to assess anticoagulant therapy correction? Despite weight-adjusted doses of LMWH (1 mg/kg BID) target anti-Xa activities were not achieved and varied from 0.3 to 0.6. However, no marked D-dimer elevation or hypercoagulation state, based on the thrombin generation test (peak thrombin, ETP) were noted. We elevated the enoxaparin dose from 0.6 to 0.8 ml BID after detecting a shift toward the

hypercoagulation by using the thromboelastography. At gestational age of 35–36 weeks, the hypocoagulation was detected by thromboelastography, hence justifying application of the final dose of enoxaparin more than 22 hours before the cesarean section (the patient was on the therapeutic dose 0.8 ml BID).

Discussion / Обсуждение

Here, we described the clinical case of two pregnancies with successful outcome in the patient with history of AT-III deficiency, PE, repeated fetal loss and preeclampsia.

The correlation between hereditary thrombophilia and placenta-mediated obstetric complications, as well as the effectiveness of anticoagulant therapy for the secondary prevention of pregnancy complications still being debated. The clinical case described here allowed to result in two live birth babies in two consecutive pregnancies after using therapeutic doses of LMWH during pregnancy. By gestational age of 35–36 weeks mild signs of preeclampsia and placental insufficiency were developed, however, they were less severe compared to the first pregnancy. Despite young age and the absence of symptoms of thrombophilia in the first pregnancy, the patient had severe preeclampsia, and the next 5 pregnancies resulted in spontaneous abortions. In this case, the first debut of severe thrombophilia was manifested as obstetric complications, but not thrombosis, whereas the patient developed first thrombosis outside of the pregnancy at later age after a minor surgery, traditionally associated with a lower risk of thromboembolic complications.

In accordance with international guidelines, screening for thrombophilia is not mandatory before pregnancy planning, including patients with obstetric complications. Screening for thrombophilia may be necessary in case of personal history of VTE and thrombophilia confirmed in close relatives, because such data can change pregnancy management. The patient described in our study allow to conclude that the burdened familial history of venous thromboembolic complications and the history of placental obstetric complications should account for conducting further examination for thrombophilia, which is especially important while planning surgical interventions and pregnancy.

Despite using therapeutic doses of LMWH, proper levels of anti-Xa activity were not achieved according to the majority of measurements due to the specifics of the laboratory method applied to assess anti-Xa activity. While using this laboratory technique, exogenous factor Xa is added to the patient's plasma at the peak of the LMWH action (4 hours after the injection), however the recorded anti-Xa activity depends on the presence of endogenous AT-III. At the same time, anti-Xa activity is recommended as a method for monitoring the adequacy of anticoagulant therapy in patients with AT-III deficiency [19–21]. In the described clinical case, we used the thromboelastography

and the thrombin generation test as indirect methods for assessing the anticoagulant effect of LMWH. The LMWH dose adjustment was carried out taking into account hypercoagulation revealed by thrombin generation test. The safety and effectiveness of such approach requires further studies.

The optimal target and the safe level of AT-III during pregnancy remain unknown. Currently, no unequivocal guidelines on the prophylactic regimen for AT-III concentrate during pregnancy in asymptomatic patients have been proposed. In the current clinical case, AT-III concentrate therapy was not applied regularly throughout pregnancy, but rather was reserved for situations associated with an increased risk of thrombosis (air travel, cesarean section and postpartum period). In addition, the patient received AT-III concentrate when a pronounced decrease in AT-III activity was detected (below 30 %). The safety of such strategy by using therapeutic doses of LMWH without simultaneous regular administration of AT-III concentrate remains unknown. Despite the favorable pregnancy outcome, the patient belonged to a group of extremely high risk for VTE recurrence. The venous duplex lower limb ultrasound performed in 2019 at gestational age of 32 and 34 weeks indicated the presence of spontaneous contrast in the superficial and deep femoral veins, common femoral veins and external iliac veins, which may indirectly suggest a low threshold for thrombosis. Adequate therapy with AT-III concentrate during delivery period requiring anticoagulant withdrawal is of critical importance. According to international protocols for the management of pregnant women receiving antithrombotic therapy, the final prophylactic dose of LMWH 24 hours before cesarean section is recommended, anticoagulants can be resumed not earlier than 4–6 hours after vaginal birth and not earlier than 6–12 hours after a cesarean section, the therapeutic dose of LMWH can be resumed not earlier than 8–12 hours postpartum [22, 23].

The data on the efficiency and safety of new oral anticoagulants in patients with genetic thrombophilia is currently sparse but suggest about good perspectives for this group of drugs [24, 25]. In our case, the patient was switched from LMWH to rivaroxaban on the fifth day after delivery. The safety of such approach in patients with deficiency of AT-III remains unknown.

Conclusion / Заключение

Antithrombin III deficiency represents the most severe form of hereditary thrombophilia, with markedly increased risk of thromboembolic and placental obstetric complications during pregnancy. Pregnancy management, anticoagulant therapy regimens, methods of the laboratory control and recommendations for the use of AT-III concentrate in such patients still remain debated and require to be further investigated.

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