

**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA  
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**Ph D  
Thesis**

**Assessment of the Thromboembolic Risk and Anesthetic  
Particularities in Pregnant Women with  
Hereditary Thrombophilia**

**ABSTRACT**

*Thesis Coordinator:*  
**Professor Liliana Novac**

*PhD Candidate:*  
**Dr. Gavrilă Alice Olguta**

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## *Table of contents*

<b>Introduction</b>	<b>1</b>
<b>I. The Current State of Knowledge</b>	<b>2</b>
Chapter 1. Physiological Changes in the Coagulation System during Pregnancy	2
Chapter 2. Hereditary Thrombophilia and Its Impact on Pregnancy	2
Chapter 3. Paraclinical Investigations in Pregnant Women with Hereditary Thrombophilia	3
Chapter 4. Management of Pregnant Women with Thrombophilia	3
Chapter 5. Types of Anesthesia in Thrombophilia	4
<b>II. PERSONAL CONTRIBUTIONS</b>	<b>4</b>
Purpose and Significance of the Study	4
Results and Discussions	5
Study on the Type of Hereditary Thrombophilia	6
Study on the Thromboembolic Risk	8
Study on the Assessment of Coagulation Status Correlated with Anesthetic Management	9
Duration of the Therapeutic Window	13
<b>FINAL CONCLUSIONS</b>	<b>16</b>
<b>SELECTIVE BIBLIOGRAPHY</b>	<b>19</b>

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## ***Introduction***

Anesthesia in a pregnant woman with thrombophilia involves special attention on the part of the anesthesiologist, especially because of the coagulation status of the pregnant woman who has received anticoagulant treatment during the pregnancy. The anesthesiologist is faced with a case of either immediate emergency or not, and has to manage the case and make the right decision. Medical history and pre-anesthetic examination will lead to the right decision about the type of anesthesia that the anesthesiologist will choose. Generally, there is a 4 to 10 times higher thrombotic risk during pregnancy and during the postpartum period.

A very important aspect of the research into thrombophilia is the correct assessment of the haemostatic function. Over 15% of the European population presents one of the forms of hereditary thrombophilia that can predispose, during pregnancy, to thrombotic events, recurrent miscarriage, premature births, intrauterine growth restriction, and severe preeclampsia.

The role of stasis and venous injury in the pathology of thrombosis has been studied for over 100 years; this has led to the development of a treatment for these thromboembolic

disorders. If we consider all thrombophilic disorders together, over 50% of women with pregnancy associated to venous thromboembolism will have an identified thrombophilia test.

Thromboembolic complications are some of the main causes of maternal death. Antithrombotic therapy is used during pregnancy to treat and prevent venous thromboembolism.

### ***The Current State of Knowledge***

**Chapter I. Physiological Changes in the Coagulation System during Pregnancy.** This chapter presents the physiological changes in the coagulation system during pregnancy, and the main factors of hematological changes in normal pregnancies.

**Chapter II. Hereditary Thrombophilia and Its Impact on Pregnancy.** This chapter presents recent data on hereditary thrombophilia and its impact on pregnancy, the physiopathology of hereditary thrombophilia, the gene mutations associated with hereditary thrombophilia, thrombophilia and pregnancy complications. The effect of thrombophilia is thrombosis, which develops rapidly and is accompanied by numerous effects both on the mother and on the fetus.

**Chapter III. Paraclinical Investigations in Pregnant Women with Hereditary Thrombophilia.** Taking into consideration the high risk of maternal thrombosis and/or pregnancy complications resulting from the association with thrombophilia, especially after the first term of the pregnancy, each pregnant woman and each woman who plans a pregnancy should do a screening for thrombophilia, if they present risk factors.

**Chapter IV. Management of Pregnant Women with Thrombophilia.** This chapter presents the importance of antithrombotic therapy in pregnant women with thrombophilia, the assessment and management of the high-risk pregnancy in women with thrombophilia, data about the prophylaxis of venous thromboembolism and pregnancy complications. An important subchapter refers to the use of anticoagulants in women with thrombophilia.

**Chapter IV. Types of Anesthesia in Thrombophilia.** Nowadays, since genetic testing for hereditary thrombophilia is ever more common, anesthesiologists are faced with more and more genetic data introduced in preoperative lab analyses. A lot of times, this raises a question: what effect should these genetic thrombophilic defects have on perioperative management?

### ***Personal Contributions***

**Purpose of the Study.** Since there are non specific recommendations for anesthetic practice in female patients who have received anticoagulant treatment in prophylactic doses, and starting

from the necessity to identify a possible solution to complications caused by the complex aspect of this matter, I have decided to research this pathology, thrombophilia associated to pregnancy, from the point of view of the risks it involves, especially the thromboembolic risk, in correlation with the involvement of the anesthetic method used for these patients. The purpose was to precisely indicate the physiopathological implications and the practical significance of monitoring cases of thrombophilia associated to pregnancy, in order to establish an anesthetic plan according to the evolution of the pregnancy, the specific complications associated to thrombophilia; all these factors are also taken into consideration when establishing the type of anesthesia or analgesia used at birth.

I have chosen this subject because rachianesthesia in pregnant women receiving anticoagulant drugs is controversial, due to the high risk of spinal epidural hematoma.

The problem raised is the time interval recommended between the administration of anticoagulants, the spinal canal block and the removal of the catheter in peridural anesthesia, all this in order to increase patients' safety and reduce the risk of hematoma.

For this purpose, I have investigated a series of parameters that could be used to determine the optimal moment in which to apply regional anesthesia in a pregnant woman with hereditary thrombophilia.

### ***Results and Discussion***

The prospective study included a group of 98 patients, pregnant women with thrombophilia, which were observed in the period January 2006 – December 2011. The study took place in the Obstetrics and Gynecology Clinic and in the Intensive Care Unit of the Filantropia Municipal University Hospital in Craiova; the 98 patients, pregnant women with thrombophilia, included in the study represent just 0.89% of all deliveries in the same period.

From a total of 268 patients with thrombophilia, 136 patients, diagnosed with hereditary thrombophilia and undergoing prophylactic anticoagulant therapy, were selected. The group of patients that were studied included 3<sup>rd</sup> trimester pregnant women, with a gestational age between 32 and 40 weeks. The 98 pregnant women included in the study represent the pregnant women with hereditary thrombophilia under anticoagulant therapy, who received, during delivery, regional or general anesthesia, in the case of C-sections, or peridural anesthesia, in the case of vaginal deliveries.

### *Study on the Type of Hereditary Thrombophilia*

Of all thrombophilic gene mutations present in the cases observed, the most frequent was the MTHFR gene mutation, in 79.59 % of the cases; the factor V Leiden mutation was found in 19.38 % of the cases; the S protein deficit was discovered in 12.24 % of the pregnant women, while the G20210A prothrombin gene mutation was found in 14.28 % of the cases. I have also encountered mutations of the PAI-1 gene (675 4G/5G polymorphism) in 7.14 % of the cases observed. A compound heterozygosity of FVL and PT G20210A was also encountered in 7.14 % of the cases. In 46 cases (46.93%) there was only one type of thrombophilic defect involved; these cases included MTHFR gene mutation – 17 cases, FVL – 8 cases, PT G20210A – 8 cases, PAI-1 gene mutation – 3 cases, and the S protein deficit – 5 cases.

It is important to emphasize that the presence of single allele polymorphism, by itself, is not enough to cause thrombosis. All studies concur with the multifactor etiology of the disease, therefore the risk of thromboembolic disease increases proportionally with the number of risk factors.

Although the risk score for thromboembolism was elevated in the cases included in the study, I have not identified thromboembolism associated with this mutation in any of the cases.

### *Study on the Thromboembolic Risk*

Several factors are known for increasing the obstetric risk of VTE, including personal or family history of VTE, thrombophilia, age of the mother > 35 years, BMI > 28-30, immobilization, surgical procedures, smoking, nulliparity, etc.

In this study, I have used mainly the weighted risk score, to which I have added the corroboration with major and minor risk factors. In order to facilitate the assessment of VTE risk during pregnancy and the puerperal period, the grading system was created by adding the different significance of risk factors for obstetric VTE.

The cases with maximal risk score were 20; 7 cases (7.14%) had a VTE risk that was considered very high, the same as the other 13 cases (13.26%), which had a risk score  $\geq 4$ .

In the very high risk group, I have encountered only 1 case with recurrent thrombotic phenomena, the 2 cases (2.04%) with single gene mutations being represented by FVL and G20210A homozygosity.

### *Study on the Assessment of Coagulation Status Correlated with Anesthetic Management*

The assessment of the coagulation status in pregnant women is very important, and even more so in pregnant women with associated thrombophilia, because pregnancy itself is an added VTE risk factor and the combination between delivery and bed rest is reason enough to ensure VTE prophylaxis.

Regional anesthesia in the spinal canal is relatively contraindicated in patients who have received anticoagulant treatment. Spinal hematoma after regional anesthesia in the spinal canal is rarely encountered in modern anesthetic practice. In the group included in the study, I have not encountered any case that developed spinal hematoma after rachidean or epidural anesthesia.

The values found for each parameter of the coagulation status were correlated with the type of anesthesia performed and the type of delivery, in order to establish which of these markers have statistical significance; the purpose was to obtain highly significant statistical data for future use as screening markers for the monitoring of anticoagulant therapy and anesthesia type.

### *Duration of the Therapeutic Window*

Anesthesia in obstetrics is considered one of the higher risk areas in anesthetic practice. Modifications in maternal physiology during pregnancy, as well as the fact that we are dealing with two patients, mother and fetus, represent unique challenges for anesthesiologists in obstetrics. Both regional and general anesthesia can cause a series of potential complications which, although rare, can be serious, life-threatening or permanently disabling. The last hour when the anticoagulant drug was administered must be known.

The duration of the therapeutic window for the group included in the study was differentiated on the basis of the type of anesthesia used. Thus, in cases in which I performed general anesthesia with OTI, the average interval between the last administration of anticoagulants and the induction of anesthesia was 9 hours. In the case of spinal anesthesia, the average interval was 11 hours, while in the case of natural delivery with peridural anesthesia, the average duration of the therapeutic window was 13 hours and 30 minutes.

The unpredictable timetable of the delivery can alter anesthetic management and decision making in the cases of pregnant women who have received anticoagulants. Thus, I have

established a series of anesthetic intervention protocols for analgesia during labor and the choice of anesthesia during C-sections for all women who have received anticoagulant treatment.

### ***Conclusions***

- Establishing an anesthetic plan is extremely important, because the use of anticoagulant drugs in pregnant patients involves important challenges for obstetric anesthesiologists.
- Although the risk score for thromboembolism was high in the case of prothrombin gene mutation found in 14.28% of the patients, I have not encountered any case with thromboembolism associated with this mutation. The homozygous forms presented a very elevated risk of venous thromboembolism, equal to 4 or higher than 4, according to the risk score calculated.
- I consider that the presence of single allele polymorphism, by itself, is not enough to cause thrombosis, because thrombosis has a multifactor etiology, therefore the risk of thromboembolic disease increases proportionally with the number of risk factors, and these have to be correctly identified.
- Studying the involvement of age in the hereditary thrombosis cases observed, I have noticed that a significant percentage, 23.47%, was represented by the ages between 35 and 39; these patients had a risk score  $\geq 4$  or an elevated risk score, which raised a series of anesthetic problems because of maternal and fetal complications and of anesthetic risk.
- By comparing the average APTT values of patients who had given birth by c-section and those who had natural deliveries, I have noticed that, both before and after giving birth, there was a statistically significant difference ( $p = 0.028 > 0.5$ , and  $p = 0.024 > 0.5$ ).
- If before surgery there was no statistically significant difference ( $p$  ANOVA = 0.158) in the average INR values of the 3 categories of patients (grouped on the basis of the type of anesthesia), after the induction of anesthesia I have noticed statistically significant differences ( $p$  ANOVA = 0.020  $p < 0.05$ ).
- After performing general anesthesia, homocysteine values rose, while in the case of peridural anesthesia or rachianesthesia they dropped, and the average values for the 3 groups of patients (type of anesthesia) became significantly different ( $p$  ANOVA  $< 0.0001$ ).
- As far as the type of anesthesia necessary in c-sections is concerned, I have noticed that the anesthetic technique influences the evolution of the procoagulant status. I have

noticed that locoregional anesthesia (rachianesthesia or peridural anesthesia) has the least influence on the coagulation status.

- I have noticed that, although the anesthetic maneuver was performed in a 6-12 hours therapeutic window from the last administration of low molecular weight heparin, in most cases, there were no incidents or complications specific for the anesthetic maneuver, which leads to the idea that dynamic monitoring of the pregnant woman's coagulation status in the last 4 weeks of pregnancy can be beneficial the intra- and postoperative status.

## CURRICULUM VITAE

**Name:** Alice-Olguta Gavrilă

**Address:** Craiova, 61 Anul 1848 Street

Date and place of birth: June 8<sup>th</sup>, 1971; Craiova, Dolj County, Romania

**Telephone:** 0251/449075 0721-284480

**e-mail:** [alice\\_gavrilă@yahoo.com](mailto:alice_gavrilă@yahoo.com)

**Marital status:** married, 1 child

**Education:** 1985 – 1989: “Fratii Buzesti” National High school, mathematics & physics stream;

1989 – 1995: University of Medicine and Pharmacy of Craiova, Faculty of General Medicine;

1995: Bachelor's Degree Examination – Bachelor of Medicine

1997 – 2002: Anesthesia and Intensive Care residency, Faculty of Medicine of Craiova;

Main specialization: Anesthesia and Intensive Care

2006 – 2008: MBA program: ”Healthcare Management”

### **Contests and examinations:**

1995: National examination for vacant general physician positions, Bucharest, November session;

1997: National residency contest, Bucharest, January session – Anesthesia and Intensive Care;

2002: Specialty certificate examination in Anesthesia and Intensive Care, OMSF n. 256/2002 March session, mark 9.30;



2002: Examination for positions as Anesthesia and Intensive Care specialist, organized by the Ministry for Health and Family, April 15<sup>th</sup> 2002, Bucharest

2006: Entrance examination for the PhD program in Obstetrics – Gynecology “Assessment of Thromboembolic Risk and Anesthetic Particularities in Pregnant Women with Hereditary Thrombophilia”

2008: Consultant certificate examination in Anesthesia and Intensive Care, OMSF n. 1200/2008 June session

2008: MBA dissertation: ” Healthcare Management”

**Professional experience:**

1996 – 1997: General Physician – DMC Voineasa, Olt County

1997 – 2002: Anesthesia and Intensive Care resident – County Emergency University Hospital in Craiova

2002 – 2008: Anesthesia and Intensive Care specialist – Intensive Care Unit, Filantropia Municipal University Hospital in Craiova

2008 – up to the present: Anesthesia and Intensive Care consultant – Intensive Care Unit, Filantropia Municipal University Hospital in Craiova