Normal pregnancy is associated with major physiological alterations in the coagulation and fibrinolytic systems that aim to maintain placental function and prevent excessive bleeding at delivery.\(^1\) These alterations mostly promote a procoagulant state and thus unfortunately enhance the risk of thromboembolism. There is an estimated 4.5-fold increase in thrombotic risk throughout gestation and the postpartum period.\(^2,3\) and 22-fold risk in the 6 weeks period following delivery.\(^4\) Pulmonary embolism remains the leading cause of direct maternal deaths in developed countries and accounts for approximately 20% of pregnancy-related deaths.\(^5\)

On the contrary, inherited bleeding disorders can lead to life-threatening hemorrhage during pregnancy and in the postpartum period.\(^5,7\) Postpartum hemorrhage (PPH) is associated with substantial maternal morbidity and continues to also be a leading cause of maternal mortality worldwide with a prevalence rate of approximately 6%,\(^8\) with severe obstetric hemorrhage now identified in 1.1% women.\(^9\)

The correct diagnosis and management of hemostasis-related disorders of pregnancy require appropriate laboratory testing. This is challenged by two major issues: first is that most normal values shift during pregnancy and puerperium\(^10,11\); a problem that is complicated by the lack of available sensitive tests and also the poor applicability and interpretation—at times—of some of these hemostatic tests. The second issue is that conventional routine assays of hemostasis, which most laboratories and thus clinicians rely on, are insufficient to represent the in vivo conditions, making it difficult to assess some complex pregnancy hemostatic complications.\(^12,13\)

This issue of *Seminars in Thrombosis & Hemostasis* is therefore devoted to thrombosis and hemostasis issues related to women and, in particular, to pregnancy. Due to the wide spectrum of potential disorders, we have focused on some selected seasoned—currently hot—topics. A review of the diagnostic challenges and current treatment of each of these disorders will be provided, together with the recently available recommendations and guidelines for better management.

To begin with, and in the first article of this issue, Fazoil et al\(^14\) provide a comprehensive state-of-the-art review of the molecular changes in the hemostatic system in normal pregnancy and also in association with pregnancy complications. A rich discussion of the various classic and global assays, which supports diagnosis of pregnancy-related hemostatic complications, is also provided. The authors also describe the potential future applications and suitability of these assays to match evolving needs.

von Willebrand disease (VWD) is estimated to affect 0.01 to 1.3% of the general population, making it the most common inherited mild bleeding disorder. Women with VWD require specific considerations during pregnancy and puerperium. In the second article, Reynen and James\(^15\) provide a review of evidence and the expert opinion of the management of VWD with pregnancy, in light of the lack of high-quality evidence supporting monitoring and treatment of this disorder. The reported high risk of PPH when von Willebrand factor ristocetin cofactor or factor VII levels fall below 0.50 IU/mL and even when aiming for levels > 0.50 to 1 IU/mL suggests that a higher level than recommended by current guidelines may be considered.\(^16\) This article also discusses issues associated with pregnancy in women with VWD, including analgesia during delivery, risk of PPH, and recommended treatment options for various types of VWD.
James et al.\textsuperscript{17} then review in detail patient blood management—an evidence-based, comprehensive, multidisciplinary approach to optimizing the care of patients who might need transfusion in the management of PPH. The authors discuss blood product administration strategies, including the role of the blood bank, the role of massive transfusion protocols, the role of laboratory monitoring, and the role of anesthesia management with the optimal management approach of coagulopathy at the time of PPH.

There is little information in the literature with respect to pregnancy in association with rare bleeding disorders (RBDs) and the management these pregnancies can be challenging.\textsuperscript{18} RBDs can have a wide spectrum of bleeding phenotypes and can be associated with various obstetric complications such as miscarriage, placental abruption and fetal loss, antepartum hemorrhage, and PPH. Despite sharing common features, each of these disorders has unique/variable characteristics and the optimal management usually requires a multidisciplinary approach and individualized plan.\textsuperscript{19}

In this issue of Seminars in Thrombosis & Hemostasis, Davies and Kadir\textsuperscript{20} review the bleeding risk associated with factor XI (FXI) deficiency and discuss management of pregnancy in affected women. The authors recommend a multidisciplinary approach and an individual care plan to prevent bleeding complications. They provide data to support assessment of PPH risk using bleeding history and plasma FXI level, together with the consideration of global tests of hemostasis as an aid to guide provision of appropriate hemostatic prophylaxis for delivery.

Bleeding and thrombotic disorders in the neonate are rare but can have life-long complications. Based on a recent Italian registry, the incidence of neonatal thrombosis is 3.4 to 6.5/10,000 live births.\textsuperscript{21} and among the inherited bleeding disorders, hemophilia appears to be the most common bleeding disorder.\textsuperscript{22} Randomized clinical trials of neonates are lacking and recommendations are often based on small studies, expert opinion, or published guidelines.\textsuperscript{23}

The next article by Hanmod et al.\textsuperscript{24} thus reviews the issues and challenges related to neonatal hemostatic disorders. They describe the evolution and physiology of neonatal hemostasis as well as the characteristic features of coagulation and the fibrinolytic system, including the laboratory testing of hemostasis in neonates and then comprehensively discuss the thrombotic and hemorrhagic disorders commonly observed in this age group while also providing the optimal management.

In neonates, more than 90% of thrombi are catheter related.\textsuperscript{25,26} The next article by van Ommen and Soj\textsuperscript{27} is complementary to the preceding one as it deals with neonatal central venous catheter thrombosis. The authors detail the incidence, risk factors, and diagnostic issues. Since optimal management of this condition is currently unknown, the authors present their proposed approach for appropriate management, which takes into consideration the assessment of the risk–benefit ratio of all available therapeutic options before initiating treatment.

Moving on from bleeding to thrombosis, the subsequent set of articles cover thrombotic disorders rather than bleeding. We begin with the article by Chunilal and Bennett,\textsuperscript{28} which discusses the pregnancy-associated venous thromboembolism (PAVTE). This condition continues to be a major cause of maternal morbidity and mortality.\textsuperscript{29} Pulmonary embolism accounts for 20 to 30% of all PAVTE and is associated with a case fatality rate of 2.4%.\textsuperscript{30} The pathophysiology, comprehensive laboratory testing, and treatment options including various anticoagulant therapies during pregnancy and in the postpartum period are described in detail.

Following a general overview of the management of thrombotic disorders in pregnancy, Scully\textsuperscript{31} discusses thrombotic microangiopathies in the next article, including thrombotic thrombocytopenic purpura and atypical hemolytic uremic syndrome; two clinical conditions with microvascular thrombosis and variable clinical features. The article provides an update on the diagnosis and management of the conditions and details therapeutic options to improve fetal and maternal outcomes.

The next article by Schreiber and Hunt\textsuperscript{32} focuses on pregnancy and antiphospholipid syndrome (APS), due to the presence of antiphospholipid antibodies (aPL). The description of aPL in the revised classification criteria includes lupus anticoagulant, anticardiolipin, and anti-β2 glycoprotein-I antibodies, which may occur in the absence of systemic lupus erythematosus.\textsuperscript{33} The article details the description of each of these antibodies and the pathogenesis of thrombosis and relation to placental insufficiency, pre-eclampsia, and fetal loss. The updated standard of care of both thrombotic and obstetric APS is also presented with a recommendation for randomized controlled trials to generate robust evidence for the use of newer therapeutic options.

The next article in this issue of Seminars in Thrombosis & Hemostasis deals with the use of direct oral anticoagulants (DOACs) in pregnancy. Cohen et al.\textsuperscript{34} describe how DOACs are an effective, safe, and convenient therapeutic alternative to warfarin and other vitamin K antagonists and are now established for a wide range of indications. They explain that the use of this group of drugs requires special consideration in relation to fertility, pregnancy, and lactation in women of reproductive age, and with respect to the bleeding risk and complications.

The final article by D’Souza et al.\textsuperscript{35} is on optimal anticoagulation for pregnant women with mechanical heart valves. The lack of high-quality data from prospective studies makes the choice of the optimal method of anticoagulation challenging. A discussion of the particular risks and benefits with each of three available therapeutic strategies is given in light of competing maternal and fetal adverse-event profiles. The authors conclude that a multidisciplinary team, including hematologists, cardiologists, obstetric physicians, and high-risk obstetricians with expertise in the management of pregnant women with cardiac disease, is required to optimize outcomes.

We sincerely thank all the contributors to this special issue of Seminars in Thrombosis & Hemostasis for their excellent contributions and collaboration during the production of this issue and on behalf of all the contributors, I sincerely wish that you, the reader, enjoy this selection of topics around thrombotic and hemorrhagic issues related to pregnancy. With this, we hope you stay up to date with the state-of-the-art.
diagnosis and management of these issues and you become familiar with current expert opinions and best practices to improve maternal and fetal outcomes, for the betterment of your clinical and research work.

References