

## Preface

**Maternal and Neonatal Hemostasis**Gili Kenet, MD<sup>1,2</sup> Benjamin Brenner, MD<sup>3,4</sup><sup>1</sup>National Hemophilia Center, Amalia Biron Research Institute of Thrombosis and Hemostasis, Sheba Medical Center, Tel-HaShomer, Israel<sup>2</sup>Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel<sup>3</sup>Department of Hematology, Rambam Health Care Campus, Haifa, Israel<sup>4</sup>The Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

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Hemostasis is a dynamic process that begins at early stages of fetal development. The hemostatic system comprises procoagulant, natural anticoagulant, and fibrinolytic proteins that interact with each other, as well as with the endothelial wall and blood cells in a complex, yet balanced manner, aiming to avoid either bleeding or thrombosis. Pregnancy is a unique physiological state in which natural biologic alterations predispose both mothers and their offspring to higher risk of hypercoagulability and bleeding. This special issue of *Seminars in Thrombosis and Hemostasis* is dedicated to maternal and neonatal hemostasis.

In the article entitled “Hemostasis in the pregnant women, the placenta, the fetus and the newborn infant,” Warren et al<sup>1</sup> address increased maternal thrombotic risk, caused, in part, by elevation of von Willebrand factor (VWF), factor VIII (FVIII) and fibrinogen, activated protein C resistance, reduction of free protein S, and decreased fibrinolysis. The placental vascular surface is of trophoblastic origin, and yet exhibits high expression of tissue factor. The fetal hemostatic system has a decreased capacity to generate or regulate thrombin. The authors suggest that dysfunction of the maternal/placental/fetal unit gives rise to gestational complications, including preeclampsia, fetal growth restriction, placental abruption, and premature delivery.

Thrombotic events may occur even prior to pregnancy, during ovulation or following assisted reproductive techniques (ARTs). As the number of women utilizing ART to conceive is steadily increasing, while solid data regarding the optimal management are scarce, Grandone et al<sup>2</sup> discuss the ART of thromboprophylaxis in this setting. The authors focus on general risk factors for venous thromboembolism in these women (age, body mass index, thrombophilia, and immobilization) as well as ART-specific conditions (polycys-

tic ovary syndrome, ovarian hyperstimulation syndrome) and attempt to provide suggestions and some guidance to be applied in clinical practice.

Women with hereditary or acquired thrombophilia are at a particularly high risk of thrombosis and pregnancy-related complications. Gris et al<sup>3</sup> describe how antiphospholipid antibodies (APLAs) may affect maternal and neonatal outcomes. APLAs have long been known to be associated with the occurrence of certain pregnancy-related complications and therefore antithrombotic-based prophylaxis has become the standard of care, improving maternal morbidity and prognosis. Late pregnancy placental diseases still occur. Some APLA-positive mothers are predisposed to develop neuropsychiatric disorders or even cancer, and a concern is raised regarding the neurodevelopment of children born following such pregnancies. Hence, the systemic impact of APLA should be further investigated, as suggested by authors.

Certain comorbidities may increase the risk of thrombosis in pregnant women. Among these, hematological malignancies, hemolytic anemia, and human immunodeficiency virus (HIV) deserve special attention. Both cancer and thrombosis induce a procoagulant environment that may lead to maternal and fetal complications. As the incidence of hematological malignancies diagnosed during pregnancy is rising, the management of thrombosis during pregnancy poses specific challenges. Krayem et al<sup>4</sup> present a case-based review regarding the complex issue of thrombotic risk assessment and management in pregnant women with myeloproliferative neoplasms, lymphoma, and leukemia. Schapkaitz et al<sup>5</sup> address HIV infection, promoting inflammation and endothelial dysfunction, as well as the prothrombotic risks associated with antiretroviral therapy during gestation. Among the research priorities mentioned by authors is generation of

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HIV-specific thromboprophylaxis recommendations that should be agreed upon by a multidisciplinary team managing these women.

Papadakis and Brenner<sup>6</sup> highlight the latest advances in diagnosis and management of women with hemolytic anemia during pregnancy, as hemolytic anemias frequently occur at the reproductive age. While a link between hemolysis and hypercoagulability has previously been suggested, the extent of thrombotic risk in pregnant women with hemolytic anemia remains debatable. This review is of importance due to the paucity of data regarding its topic.

The article by Malinowski and Abdul-Kadir<sup>7</sup> addresses the issues of bleeding during pregnancy and around delivery in women with inherited rare bleeding disorders (RBDs). Obstetric challenges may sometimes unmask the presence of a previously unknown bleeding disorder, and certainly among women with a known inherited RBD, gestation, labor, and puerperium may be adversely influenced. The article delineates the clinical approach to the management of pregnancy and delivery in the presence of RBD and emphasizes the importance of a multidisciplinary team in this setting.

The role of the fibrinolytic system in maternal peripartum depression is described by Hoirisch-Clapauch.<sup>8</sup> Both tissue plasminogen activator and plasmin are involved in brain remodeling underlying resilience, depression remission, and reward processing rather than dissolution of fibrin clots. The article depicts the fibrinolytic status in the healthy brain, in stress, and depression and discusses a potential association between hypo-fibrinolysis and peripartum depression. Additionally, it reviews the evidence and suggestions for antiplatelet medications as well as diverse interventions aimed at restoring fibrinolytic activity to reduce maternal depression.

Following delivery, birth asphyxia may lead to impaired organ function, which can be associated with coagulopathy. Tsaousi et al<sup>9</sup> present a systematic literature review, analyzing hemostatic tests used to evaluate coagulation disorders in neonates who suffered perinatal hypoxia or asphyxia. The authors conclude that hypoxic neonates seem to have a hypocoagulable profile compared with healthy ones, and results of viscoelastic clotting tests could more accurately reflect the risk for bleeding or thrombosis.

Fetal bleeding complications are dealt with in two reviews of this special issue. First, Barg and Bonstein<sup>10</sup> discuss fetal and neonatal alloimmune thrombocytopenia, a common cause of neonatal thrombocytopenia that may lead to severe intracranial hemorrhage (ICH). They explore advances in diagnosis, including noninvasive prenatal testing using fetal cell-free DNA, and provide insights into novel therapeutic options. Pregnancy risk stratification is suggested for future management, considering the biological characteristics of

maternal alloantibodies and their potential association with fetal bleeding.

The review by Andersson and Kenet<sup>11</sup> focus upon ICH, one of the most devastating complications associated with neonatal bleeding. The authors address the high bleeding risk that stems from developmental hemostasis and the multifaceted maternal and fetal risk factors as well as from the mode of delivery. Special attention is given to neonates with congenital hemophilia or RBDs and an updated approach for treatment or attempted prevention is discussed.

Overall, this special issue presents an update on developments related to pathogenesis, risk assessment, diagnosis, and treatment of mothers prone to thrombosis or bleeding during pregnancy and the peripartum period and discusses approaches to the assessment and management of neonates with asphyxia or severe bleeding complications. We hope the articles included in this special issue will contribute to better understanding of the field and promote future research and guidance.

#### Conflict of Interest

None declared.

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