Hemostasis and Thrombosis in Obstetrics & Gynecology

Michael J. Paidas, MD
Yale University School of Medicine, New Haven, CT, USA

Nazli Hossain, MBBS, FCPS
Dow University of Health Sciences, Karachi, Pakistan

Tahir S. Shamsi, MBBS, FRCPath, FCPP
National Institute of Blood Disease and Bone Marrow Transplantation
Karachi, Pakistan and University of Health Sciences, Lahore, Pakistan

Marc A. Rodger, MD, MSc
Ottowa Hospital General, ON, Canada

Jens Langhoff-Roos, MD, DMSc
Roskilde Hospital, Roskilde and Rigshospitalet, Copenhagen, Denmark

Charles J. Lockwood, MD, MHCM
Yale University School of Medicine, New Haven, CT, USA
Hemostasis and Thrombosis in Obstetrics & Gynecology
Hemostasis and Thrombosis in Obstetrics & Gynecology

Michael J. Paidas, MD
Yale University School of Medicine, New Haven, CT, USA

Nazli Hossain, MBBS, FCPS
Dow University of Health Sciences, Karachi, Pakistan

Tahir S. Shamsi, MBBS, FRCPath, FCPP
National Institute of Blood Disease and Bone Marrow Transplantation
Karachi, Pakistan and University of Health Sciences, Lahore, Pakistan

Marc A. Rodger, MD, MSc
Ottowa Hospital General, ON, Canada

Jens Langhoff-Roos, MD, DMSc
Roskilde Hospital, Roskilde and Rigshospitalet, Copenhagen, Denmark

Charles J. Lockwood, MD, MHCM
Yale University School of Medicine, New Haven, CT, USA
Contents

List of Contributors, vi
Preface, vii
Acknowledgments and Dedication, vii

1 Hematologic Changes in Pregnancy, 1
   Michael J. Paidas & Nazli Hossain

2 Red Cell Disorders, 12
   Tahir S. Shamsi

3 Hemolytic Disease of the Newborn, 28
   Tahir S. Shamsi, Nazli Hossain & Michael J. Paidas

4 Maternal and Fetal Thrombocytopenia, 41
   Michael J. Paidas & Nazli Hossain

5 Inherited and Acquired Thrombophilia in Obstetrics, 67
   Michael J. Paidas, Christina S. Han, Nazli Hossain, and Charles J. Lockwood

6 Anticoagulant Therapy During Pregnancy and Gynecology, 111
   Marc A. Rodger & Genevieve Le Templier

7 Inherited Bleeding Disorders in Obstetrics, 153
   Nazli Hossain & Michael J. Paidas

8 Inherited Bleeding Disorders in Gynecology, 161
   Nazli Hossain & Michael J. Paidas

9 Postpartum Hemorrhage, 167
   Nazli Hossain, Jens Langhoff-Roos & Michael J. Paidas

10 Disseminated Intravascular Coagulation, 182
    Nazli Hossain & Michael J. Paidas

11 Transfusion of Blood and Blood Products in Obstetrics, 195
    Tahir S. Shamsi & Nazli Hossain

Index, 216
List of Contributors

**Christina S. Han, MD**  
Clinical instructor, Division of Maternal Fetal Medicine, Department of Obstetrics, Gynecology & Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA

**Nazli Hossain, MBBS, FCPS**  
Associate Professor, Department of Obstetrics and Gynecology, Dow University of Health Sciences, Karachi, Pakistan

**Jens Langhoff-Roos, MD, DMSc**  
Department of Obstetrics and Gynaecology, Roskilde Hospital, Roskilde, and Department of Obstetrics, Rigshospitalet, Copenhagen, Denmark

**Charles J. Lockwood, MD, MHCM**  
Anita O'Keefe Young Professor and Chair, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA

**Michael J. Paidas, MD**  
Associate Professor  
Co-Director, Yale Women and Children’s Center for Blood Disorders  
Co-Director, National Hemophilia Foundation- Baxter Clinical Fellowship Program at Yale  
Division of Maternal Fetal Medicine  
Department of Obstetrics, Gynecology and Reproductive Sciences  
Yale University School of Medicine, New Haven, CT, USA

**Marc A. Rodger, MD, MSc (Epidemiology)**  
Professor of Medicine  
University of Ottawa Research Chair in Thrombosis and Thrombophilia  
Ottowa Hospital General, ON, Canada

**Tahir S. Shamsi, MBBS, FRCPath, FCPP**  
Professor of Haematology, Consultant Haematologist and Transplant Physician, National Institute of Blood Disease and Bone Marrow Transplantation, Karachi, Pakistan and University of Health Sciences, Lahore, Pakistan

**Genevieve Le Templier, MD, FRCP**  
Ottawa Hospital, Ottawa Health Research Institute, University of Ottawa, Ottawa, ON, Canada
Preface

Interest in reproductive hemostasis continues to develop among care providers, basic science and translational researchers across a variety of disciplines. This phenomenon, it seems, is not a regional, country or even a continent-specific evolution, but rather a global response. Several factors have probably contributed to this niche area which is garnering widespread appeal. International meetings of our respective primary specialties encourage dialogue with members of other disciplines to tackle common scientific and clinical dilemmas in women’s health. At many higher academic institutions, investments in infrastructure to foster a more ‘thematic’ and integrated approach are being promoted. It is obvious to everyone that communication among colleagues separated by great physical distances is not as difficult as in the past. Several programs are in place that support interaction between the developing and the developed countries. Finally, drugs or biologics, which represent present and future interventions, are definitely global endeavors.

Our goal for this textbook is to provide a contemporary, international, multidisciplinary approach to common obstetric, gynecologic and hematologic issues, and present the data in a comprehensive, but simplified manner. This textbook is written for trainees including residents and fellows, seasoned care providers, obstetrician/gynecologists, hematologists, primary care providers, consultants, and students. We have made deliberate attempts to address concerns in the developing and the developed countries. The chapters are divided according to relevant clinical conditions. We have intended that this textbook be a useful ‘pocket’ reference for residents, fellows and care providers who might not have immediate internet access to search a particular question, but need an answer quickly. This book will provide firm guidelines for obstetricians in the management of pregnant women in labor and delivery suites.

We have enjoyed writing this book and hope that it stimulates further collaborative research and discourse directed toward a better understanding of hemostasis and thrombosis issues in the reproduction sciences.

Michael J. Paidas MD
Nazli Hossain MBBS FCPS
Acknowledgments and Dedication

There are a few individuals who deserve special mention because they have influenced my career path that intersects obstetrics, gynecology, the reproductive sciences, and hematology. I credit Michael J. Haut, MD, who cultivated my interest in maternal and fetal hematologic disorders during residency at Pennsylvania Hospital. Together, we studied aspects of both maternal and fetal platelet disorders, and he encouraged me to pursue evaluation of in utero fetal platelet function. I have always admired Fernand Daffos, MD, as a pioneer in many aspects of fetal medicine and appreciated his encouragement early in my career. Richard L. Berkowitz, MD, taught me many things, but two lessons in particular have resonated with me throughout my entire career. Dr. Berkowitz stressed that we, as physicians, must dedicate ourselves to providing our patients, who entrust their lives in our hands, with the best care possible. They deserve nothing less than 100% of our best efforts. Secondly, he provided me with much insight and guidance with his contributions to defining management of antenatal alloimmune thrombocytopenia. Perhaps more than any other individual, I learned from Mary D’Alton, MD, to insist upon carrying out good clinical trials in obstetrics to drive practice management guidelines. For several years, Yale S. Arkel, MD, and Wayne Ku, PhD, galvanized our clinical research efforts focused on the protein C system and hemostatic derangements associated with pregnancy complications. Both of them taught me so much about hemostasis and laboratory medicine. Finally, I owe much to my mentor, collaborator, and colleague, Charles J. Lockwood, MD, MHCM, who I first met over 25 years ago, for nurturing my career over such a long period.

Over the years, my patients have served as a daily source of inspiration. Their courage and determination have been infectious and I wish to thank them collectively for allowing me to share some aspect of their lives. I wish to thank my parents, Angela and Nicholas Paidas, who have sacrificed so much of their life for their children. Finally, I wish to thank my family, Anne Marie, Nicholas, and Lauren because without their patience, love, and support, I would not have been able to devote time and energy to this endeavor and my profession in general.
Acknowledgments and Dedication

This book is dedicated to Diana S. Beardsley, MD, PhD, Director of the Yale Hemophilia Treatment Center. For 24 years, from 1986–2010, Dr. Beardsley was the face of Pediatric Hemostasis at Yale. She was a superb physician, brilliant scientist, and tireless advocate and mentor for her fellows, who she mentored during the past three decades. Diana was beloved by her patients, colleagues, and students. This textbook is a tribute to her legacy.

Diana S. Beardsley, MD, PhD, December 8, 1947 to March 30, 2010

Michael J. Paidas, MD.

We would like to acknowledge our parents and our families who have helped us in taking this path; we dedicate this book to mothers who suffered because of ignorance of their disease and taught us how to manage blood disorders in women.

Nazli Hossain
Tahir S. Shamsi
Marc A. Rodger
Jens Langhoff-Roos

For Nancy, Sarah, John and Billy

Charles J. Lockwood
CHAPTER 1
Hematologic Changes in Pregnancy
Michael J. Paidas & Nazli Hossain

Introduction

Normal pregnancy is characterized by profound changes in nearly every organ system to accommodate the demands of the fetoplacental unit. Maternal hematological adaptations to the pregnant state are reviewed in this chapter. The most significant hematological changes are physiologic anemia, neutrophilia, mild thrombocytopenia, increased procoagulant factors, and diminished fibrinolysis.

This chapter will review the pregnancy-associated changes in plasma volume, red blood cells, white blood cells, platelets, and coagulation factors.

Plasma Volume

Plasma volume increases by 10–15% at 6–12 weeks of gestation [1–3], expands rapidly until 30–34 weeks, after which there is only a modest rise. The total gain of plasma volume at term averages 1100–1600 mL and results in a plasma volume of 4700–5200 mL, 30–50% above that found in nonpregnant women [1, 4]. Plasma volume decreases immediately postpartum, then increases again 2–5 days after delivery, possibly because of a simultaneous rise in aldosterone secretion. Plasma volume then decreases; it is still elevated by 10–15% above nonpregnant levels at 3 weeks postpartum, but is usually at normal nonpregnant levels at 6 weeks postpartum.

During pregnancy, plasma renin activity is typically increased and atrial natriuretic peptide levels are slightly reduced, suggesting that the increase in plasma volume represents underfilling due to systemic vasodilatation and the ensuing rise in vascular capacitance, rather than true blood
volume expansion, which would produce the opposite hormonal profile (low plasma renin activity, elevated atrial natriuretic peptide) [5, 6]. Furthermore, the degree of sodium retention is physiologically regulated, as increasing sodium intake does not produce further volume expansion [7].

**Red Blood Cells**

Red blood cell mass begins to increase at 8–10 weeks of gestation and steadily rises by 20–30% (250–450 mL) above nonpregnant levels by the end of pregnancy in women receiving iron supplementation [4, 8–11]. Among women not on iron supplements, the red cell mass may only increase by 15–20% [12]. Erythrocyte life span is slightly decreased during normal pregnancy [13].

Erythropoietin levels increase by 50% in normal pregnancies and vary according to the presence of pregnancy complications [14]. The increased plasma erythropoietin induces the rise in red cell mass, which partially supports the higher metabolic requirement for oxygen during pregnancy [15]. Mean corpuscular volume decreases during pregnancy and averages 80–84 fL in the third trimester [16].

**Anemia**

A greater expansion of plasma volume relative to the increase in hemoglobin mass and erythrocyte volume is responsible for the modest fall in hemoglobin levels (i.e., physiological or dilutional anemia of pregnancy) observed in healthy pregnant women. The greatest disproportion between the rates at which plasma and erythrocytes are added to the maternal circulation occurs during the late second to early third trimester. (Lowest hematocrit is typically measured at 28–36 weeks [16].) Nearer to term, hemoglobin concentration increases due to cessation of plasma expansion and continuing increase in hemoglobin mass. Conversely, the absence of physiologic anemia appears to be a risk factor for stillbirth [17].

Determining a good definition of anemia in pregnant women is not straightforward, given the pregnancy-associated changes in plasma volume and red cell mass, normal differences in hemoglobin concentrations between women and men, ethnic variation between white and black women, and the frequent use of iron supplementation in pregnancy. The Centers for Disease Control and Prevention has defined anemia as hemoglobin levels of less than 11 g/dL (hematocrit less than 33%) in the first and third trimesters and less than 10.5 g/dL (hematocrit less than 32%) in the second trimester [18]. Since hemoglobin and hematocrit
levels are lower in African-American adults, the Institute of Medicine re-ommends lowering of the hemoglobin cutoff level by 0.8 g/dL in this pop-i-lation [19].

Women with hemoglobin values below these levels can be considered anemic and should undergo a standard evaluation [20]. Sixteen to twenty-nine percent of pregnant women become anemic in the third trimester [21].

Severe anemia with maternal hemoglobin below 6 g/dL has been asso-ciated with reduced amniotic fluid volume, fetal cerebral vasodilation, and nonreassuring fetal heart rate patterns [22]. Increased risks of prematu-rity, spontaneous abortion, low birth weight, growth restriction, and fetal death have also been reported [23]. The administration of lactoferrin to treat iron deficiency anemia in pregnancy requires further investigation. Lactoferrin chelates two ferric ions, decreases interleukin-6, thereby de-ceasing hepcidin and increasing ferroportin expression.

Iron Requirements
In a typical singleton gestation, maternal iron requirements average close to 1000 mg over the course of pregnancy: approximately 300 mg for the fetus and placenta and approximately 500 mg, if available, for the expa-n-sion of the maternal hemoglobin mass. Two hundred milligrams is shed through the gut, urine, and skin. Since most women do not have ade-quate iron stores to handle the demands of pregnancy, iron is commonly prescribed as part of a prenatal multivitamin or as a separate supplement. In general, women taking iron supplements have a mean hemoglobin concentra-tion that is 1 g/dL greater than that of women not taking supple-ments. Normal iron indices for pregnancy are listed in Table 1.1.

Folate Requirements
The increase in red cell mass also necessitates an increased folic acid re-quirement. In nonpregnant women, the daily folic acid requirement is 50–100 mg/d. However, because folate deficiency is associated with neural tube defects (and possibly other birth defects) as well as macrocytic ane-mia, all women of reproductive age are advised to consume 0.4 mg of folic acid daily [24].

<table>
<thead>
<tr>
<th>Table 1.1 Normal iron indices during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma iron</td>
</tr>
<tr>
<td>Plasma total iron-binding capacity</td>
</tr>
<tr>
<td>Transferrin saturation</td>
</tr>
<tr>
<td>Serum ferritin</td>
</tr>
</tbody>
</table>
Hemostasis and Thrombosis in Obstetrics & Gynecology

Platelet Count

Although platelet counts remain in the normal nonpregnant range in most women during uncomplicated pregnancies [25], mean platelet counts of pregnant women may be slightly lower than in healthy nonpregnant women [26]. Serial platelet counts during uncomplicated pregnancies may [27] or may not [28] decrease, but the mean values in these groups do not necessarily reflect both increases and decreases in individual women [29]. The lower limit of normal platelet counts in pregnancy has been reported to be 106,000–120,000 platelets/μL.

Thrombocytopenia

The most significant obstetrical consideration concerning platelet physiology in pregnancy is thrombocytopenia, which may be related to complications of pregnancy (e.g., severe preeclampsia, HELLP syndrome), medical disorders (e.g., idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome), or gestational. Gestational or incidental thrombocytopenia is characterized by mild asymptomatic thrombocytopenia occurring in the third trimester in a patient without any history of thrombocytopenia (other than in a prior pregnancy). It is not associated with maternal, fetal, or neonatal sequelae and spontaneously resolves postpartum [30–32]. Platelet counts are typically greater than 70,000/μL.

White Blood Cells

Pregnancy is associated with leukocytosis, primarily related to increased circulation of neutrophils. The neutrophil count begins to increase in the second month of pregnancy and plateaus in the second or third trimester, at which time the total white blood cell counts ranges from 9000 to 15,000 cells/μL [33]. Data from two series reported mean white blood cell counts of 10,000–16,000 cells/μL in laboring patients, with an upper level as high as 29,000 cells/μL [34,35]; the mean count increased linearly with the duration of elapsed labor [35]. The white blood cell count falls to the normal nonpregnant range by the sixth day postpartum. Dohle bodies (blue staining cytoplasmic inclusions in granulocytes) are a normal finding in pregnant women.

In healthy women with normal pregnancies, there is no change in the absolute lymphocyte count and no significant changes in the relative numbers of T and B lymphocytes [36]. The monocyte count is generally stable; the basophil count may slightly decrease and the eosinophil count may slightly increase. Normal pregnant women can have a small number of myelocytes or metamyelocytes in the peripheral circulation.
Chapter 1 Hematologic Changes in Pregnancy

Coagulation

Normal pregnancy is a prothrombotic state [37–46]. The circulating levels of several coagulation factors change during pregnancy (Table 1.2):

- Protein S activity and free protein S antigen decrease due to estrogen-induced increases in the complement 4b binding protein and possibly due to other mechanisms related to the hormonal changes of pregnancy.
- Resistance to activated protein C increases in the second and third trimesters.
- Fibrinogen, factors II, VII, VIII, and X increase by 20–200% [47]; von Willebrand factor also increases.
- Activity of the fibrinolytic inhibitors, thrombin activatable fibrinolytic inhibitor (TAFI), PAI-1, and PAI-2 increases [48].
- Factors V and IX remain unchanged and factor XI levels decrease by 30% [47].

The net effect of these changes is to increase the tendency toward thrombus formation, extension, and stability. Normalization of coagulation parameters varies depending on the factor, but all should return to baseline by 8 weeks postpartum.

Table 1.2 Hemostatic changes in pregnancy.

<table>
<thead>
<tr>
<th>Variables (mean ± SD)</th>
<th>First tri*</th>
<th>Second tri*</th>
<th>Third tri*</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet (× 10^9 L^-1)</td>
<td>275 ± 64</td>
<td>256 ± 49</td>
<td>244 ± 52</td>
<td>150–400</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>3.7 ± 0.6</td>
<td>4.4 ± 1.2</td>
<td>5.4 ± 0.8</td>
<td>2.1–4.2</td>
</tr>
<tr>
<td>Prothrombin complex (%)</td>
<td>120 ± 27</td>
<td>140 ± 27</td>
<td>130 ± 27</td>
<td>70–30</td>
</tr>
<tr>
<td>Antithrombin (U/mL)</td>
<td>1.02 ± 0.10</td>
<td>1.07 ± 0.14</td>
<td>1.07 ± 0.11</td>
<td>0.85–1.25</td>
</tr>
<tr>
<td>Protein C (U/mL)</td>
<td>0.92 ± 0.13</td>
<td>1.06 ± 0.17</td>
<td>0.94 ± 0.2</td>
<td>0.68–1.25</td>
</tr>
<tr>
<td>Protein S, total (U/mL)</td>
<td>0.83 ± 0.11</td>
<td>0.73 ± 0.11</td>
<td>0.77 ± 0.10</td>
<td>0.70–1.70</td>
</tr>
<tr>
<td>Protein S, free (U/mL)</td>
<td>0.26 ± 0.07</td>
<td>0.17 ± 0.04</td>
<td>0.14 ± 0.04</td>
<td>0.20–0.50</td>
</tr>
<tr>
<td>Soluble fibrin (nmol/L)</td>
<td>9.2 ± 8.6</td>
<td>11.8 ± 7.7</td>
<td>13.4 ± 5.2</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Thrombin–antithrombin (µg/L)</td>
<td>3.1 ± 1.4</td>
<td>5.9 ± 2.6</td>
<td>7.1 ± 2.4</td>
<td>&lt;2.7</td>
</tr>
<tr>
<td>D-dimers (µg/L)</td>
<td>91 ± 24</td>
<td>128 ± 49</td>
<td>198 ± 59</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1 (AU/mL)</td>
<td>7.4 ± 4.9</td>
<td>14.9 ± 5.2</td>
<td>37.8 ± 19.4</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-2 (µg/L)</td>
<td>31 ± 14</td>
<td>84 ± 16</td>
<td>160 ± 31</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Cardiolipin antibodies positive</td>
<td>2/25</td>
<td>2/25</td>
<td>3/23</td>
<td>0</td>
</tr>
<tr>
<td>Protein Z (µg mL^-1)</td>
<td>2.01 ± 0.76</td>
<td>1.47 ± 0.45</td>
<td>1.55 ± 0.48</td>
<td></td>
</tr>
<tr>
<td>Protein S (%)</td>
<td>34.4 ± 11.8</td>
<td>27.5 ± 8.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*First tri, 12–15 weeks; second tri, week 24; third tri, week 35.
†First tri, 0–14 weeks; second tri, 14–27 weeks; third tri, 27 weeks or more.

Adapted from Bremme [46], table 3, p. 157 and Paidas et al. [51], with permission.
6 Hemostasis and Thrombosis in Obstetrics & Gynecology

Protein S
Protein S (PS) is a vitamin K-dependent glycoprotein with several anticoagulant functions [49]. In the presence of PS, activated protein C inactivates factor Va and factor VIIIa, resulting in reduced thrombin generation. PS also serves as a cofactor for protein C enhancement of fibrinolysis. PS has a direct anticoagulant effect independent of its co-factor function with activated protein C. It prevents the binding of surface phospholipids with factors such as Va, Xa, and VIIIa, thereby decreasing the activation of the factors.

Pregnancy is associated with decreased levels of PS activity and free PS antigen [44, 50]. The significance and degree of decrease in PS levels commonly seen in pregnancy has not been vigorously evaluated. To address this question, we compared second and third trimester PS levels in 51 healthy women with a normal pregnancy outcome with 51 healthy women with a poor pregnancy outcome [51]. Protein S levels were significantly lower in the second and third trimesters among patients with adverse pregnancy outcome compared to patients with normal pregnancy outcome (second trimester 34.4 ± 11.8% versus 38.9 ± 10.3%, respectively; and third trimester 27.5 ± 8.4 versus 31.2 ± 7.4%, respectively).

Resistance to Activated Protein C
During pregnancy, normal women acquire some degree of resistance to activated protein C (APC), when measured by the first generation global assays and tests that measure endogenous thrombin potential [45, 52, 53].

Factor X
Factor X, its activation to FXa and participation in the activation of prothrombin, is a central element in the generation of thrombin [54]. It is possible that derangements in the control of factor Xa contributes to adverse prothrombotic sequelae in pregnancy.

Protein Z
Protein Z (PZ) is a 62 kDa vitamin K-dependent plasma protein that serves as a co-factor for a PZ-dependent protease inhibitor (ZPI) of Factor Xa [55, 56]. It is a component in the regulation of factor Xa activity in addition to tissue factor pathway inhibitor [57–59]. PZ deficiency increases the prothrombotic phenotype in factor V Leiden patients and has been associated with various adverse clinical sequelae [60–63].

There is a reported increased prevalence of PZ deficiency in patients with unexplained early fetal loss (10–19 weeks of gestation) and other adverse pregnancy outcomes [51, 64–67]. As an example:

- One study reported the odds ratio for fetal loss associated with PZ deficiency was 6.7 (95% CI 3.1–14.8) and noted that the patients with late fetal loss and recurrent miscarriages had lower PZ levels [65].
Another study found that women with a variety of adverse pregnancy outcomes (e.g., intrauterine growth restriction, preeclampsia, preterm delivery, and antepartum bleeding) had significantly lower PZ levels in each trimester than women with normal pregnancy outcomes [51]. Protein Z levels at the twentieth percentile (1.30 mcg/mL) were associated with an increased risk of adverse pregnancy outcome (OR 4.25, 95% CI 1.5–11.8, sensitivity 93%, specificity 32%).

An inverse correlation was found between anti-protein Z IgM antibody levels and protein Z concentrations ($p = -0.43$) in patients with recurrent embryonic loss and PZ deficiency [66]. However, the relationship between PZ antibodies and PZ levels is not straightforward. Anti-protein Z IgG antibody and anti-protein Z IgM antibody levels were not correlated with protein Z levels in the entire cohort of patients with normal and abnormal outcomes. The immunological response to coagulation factors in pregnancy requires further inquiry. A recent meta-analysis of 28 case-control studies (33 patient cohorts), including 4,218 patients with thrombotic diseases and 4,778 controls, were analyzed [68]. Low protein Z levels were associated with an increased risk of thrombosis (odds ratio [OR] 2.90, 95% confidence interval [CI] 2.05–4.12; $p < 0.00001$). A significant association was found between low protein Z levels and arterial vascular diseases (OR 2.67, 95% CI 1.60–4.48; $p = 0.0002$), pregnancy complications (OR 4.17, 95% CI 2.31–7.52; $p > 0.00001$), and venous thromboembolic diseases (OR 2.18, 95% CI 1.19–4.00; $p = 0.01$). Thus, protein Z deficiency appears to play a role in thrombotic diseases, including arterial thrombosis, pregnancy complications and venous thromboembolism.

Activation Markers
Activation markers are often increased in pregnancy. Normal pregnancy is associated with both increased thrombin activity, increased soluble fibrin levels (9.2–13.4 nmol/L) and increased thrombin–antithrombin complexes (3.1–7.1 mcg/L), and fibrinolysis, as evidenced by increased levels of fibrin D-dimer (91–198 mcg/L) [69].

Summary and Key Points
The major hematological changes during pregnancy are physiologic anemia, neutrophilia, mild thrombocytopenia, increased procoagulant factors, and diminished fibrinolysis.

Plasma volume increases by 10–15% at 6–12 weeks of gestation, and then expands rapidly until 30–34 weeks, after which there is only a modest rise.
8  Hemostasis and Thrombosis in Obstetrics & Gynecology

- Red blood cell mass begins to increase at 8–10 weeks of gestation and steadily rises by 20–30% (250–450 mL) above nonpregnant levels by the end of pregnancy.
- A greater expansion of plasma volume relative to the increase in hemoglobin mass and erythrocyte volume is responsible for the modest fall in hemoglobin levels (i.e., physiological or dilutional anemia of pregnancy) observed in healthy pregnant women.
- The Centers for Disease Control in the United States and Prevention has defined anemia as hemoglobin levels of less than 11 g/dL in the first and third trimesters and less than 10.5 g/dL in the second trimester.
- Mean platelet counts of pregnant women may be slightly lower than in healthy nonpregnant women.
- The neutrophil count begins to increase in the second month of pregnancy and plateaus in the second or third trimester, at which time the total white blood cell counts ranges from 9000 to 15,000 cells/μL.
- There is no change in the absolute lymphocyte count.
- The circulating levels of several coagulation factors change during pregnancy and contribute to the prothrombotic and antifibrinolytic changes associated with pregnancy.

References

Chapter 1 Hematologic Changes in Pregnancy


Chapter 1 Hematologic Changes in Pregnancy


CHAPTER 2
Red Cell Disorders

Tahir S. Shamsi

Introduction

Anemia during pregnancy is a well-known risk factor for mother and fetus [1]. Fetal consequences include risk of intrauterine growth restriction, prematurity, intrauterine death, preterm rupture of membranes and infection [2]. Maternal consequences of anemia include cardiovascular symptoms, reduced physical and mental performance, reduced immune function, tiredness, reduced peripartum blood reserves and finally increased risk of postpartum hemorrhage and need for blood transfusion in the postpartum period [2–4]. Severe anemia is associated with increased low birth weight babies, induction rates, operative deliveries, preterm deliveries and prolonged labor [5–8].

Anemia

Sixty million pregnant women worldwide are anemic; four million live in industrialized countries [1]. Worldwide, the prevalence lies between 25 and 50%, reflecting race, socio-economic factors, nutritional habits, medical care, and the frequency of malaria and other parasitic illnesses. In developing countries, it ranges between 35 and 75%. It is lower in developed countries, with estimates of 18–20%. The prevalence of iron deficiency without anemia (which is termed latent iron deficiency) is much higher. It is most prevalent in pregnant women, infants, and children and is more common in lower socio-economic groups and in uneducated [3, 9]. Anemia is caused by inadequate diet (mostly insufficient iron but also dietary deficiencies of folate and vitamin B12); impaired absorption; or blood loss resulting from hemorrhage or helminths or, in women, from menstruation, childbirth, or repeated pregnancies. Non-nutritional anemia may be caused by thalassemia and other disorders such as malaria and sickle
cell disease (SCD). Rarely, hematological malignancies and aplastic anemia present during pregnancy.

**Pathophysiology During Pregnancy**

Fifty percent of iron deficiency anemia (IDA) occurs after the twenty-fifth gestational week; it is low during the first trimester and increases during the second trimester. Pregnancy and lactation stress iron balance. Beginning in the sixth week of pregnancy, maternal plasma volume expands by approximately 50% during the first and second trimester; whereas the corresponding increases in red cell mass are only 20–30%. A dilutional anemia results, so that the lower limit of normal hemoglobin (Hb) concentration is approximately 10.5 g/dL between 16 and 40 weeks of pregnancy. The increase in red cell mass is due to transfer of iron to the fetus, which takes place largely in the third trimester, and blood loss during labor, together they impose a requirement of about 800–1000 mg of iron, so that iron deficiency frequently arises in mothers with normal or reduced iron stores if not treated with supplemental iron. It is typically present before or aggravated by pregnancy. Under normal conditions, up to 10–15% of nutritional iron is absorbed in the intestine. The main factors influencing intestinal absorption during pregnancy are the iron demands of the maternal red cell pool, the fetus and the placenta. Up to 30% of transferrin-bound iron is released to placental transferrin receptors. There is a positive feedback mechanism between the placental iron needs and intestinal iron absorption reaching a maximum rate of 5 mg iron per day. In contrast, iron need during pregnancy is estimated to be 6–7 mg per day (median need 4.6 mg/d) or 800–1200 mg for the entire pregnancy. As a result, up to 10 years of normal dietary intake is required to replace the loss of iron incurred with each pregnancy. A store of more than 500 mg, present in only 20% of menstruating women, is required to avoid iron deficiency during pregnancy. Thus, the iron deficit grows despite increasing iron absorption. If iron stores are low before pregnancy, negative iron balance will surely end in iron deficiency and ultimately IDA.

Anemia is an end result of iron deficiency. The latent and pre-latent stages of iron deficiency, which produces ineffective erythropoiesis and defective heme synthesis, are often not detected. Iron absorption is related to the maternal ferritin concentration, but the influence of maternal iron stores is limited. Decrease in ferritin concentration of 10 mg/L increases iron absorption by 1.5%. Women with iron deficiency during the third trimester are able to increase the percentage of iron absorbed above 20–25%. Red blood cell incorporation of iron varies between 76 and 92%, depending on whether or not iron supplements are given. Recent studies