INTRODUCTION

Interpretation of laboratory investigations relies on reference intervals. Physiological changes in pregnancy may result in significant changes in normal values for many hematology assays, and as such results may be misinterpreted as abnormal or mask a pathological state. There is significant variability between laboratories depending on the method of testing, the assay used and population factors. Wherever possible clinicians should use a reference interval specific to the laboratory that has performed the test.

RED CELL COUNT

Healthy pregnancy is associated with a fall in hemoglobin (Hb) and hematocrit due to the increase in plasma volume being greater than the increase in red cell mass, and occurring at an earlier gestation (Table 1). Plasma volume starts to increase from the 6th gestational week, being approximately 10% above pre-pregnancy levels in early second trimester, then rising rapidly reaching levels greater than 50% above pre-pregnancy levels by 26 weeks' gestation, then plateauing for the remainder of pregnancy. Plasma volume starts to fall from the 6th postpartum day, reaching non-pregnant levels at 6 weeks postpartum. Red blood cell mass does not increase until approximately 20 weeks' gestation, and increases approximately 30% above the non-pregnant state. Red cell mass also returns to normal levels by 6 weeks postpartum.

Table 1  Sample reference intervals for hematological assays in healthy pregnancy.

<table>
<thead>
<tr>
<th>Assay</th>
<th>Baseline</th>
<th>First trimester</th>
<th>Second trimester</th>
<th>Third trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (Hb) (g/dL)²</td>
<td>12–16</td>
<td>11.5–14</td>
<td>10–15</td>
<td>9.5–15</td>
</tr>
<tr>
<td>Hematocrit²</td>
<td>35–44</td>
<td>31–41</td>
<td>30–39</td>
<td>28–40</td>
</tr>
<tr>
<td>White blood cells (WBC) (×10⁹/L)²</td>
<td>4–10</td>
<td>6–16</td>
<td>6–16</td>
<td>6–16</td>
</tr>
<tr>
<td>Assay</td>
<td>Baseline</td>
<td>1st trimester</td>
<td>2nd trimester</td>
<td>3rd trimester</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>--------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Erythropoietin (EPO) (U/L)²</td>
<td>4–27</td>
<td>12–25</td>
<td>8–67</td>
<td>14–222</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (APTT) (s)³</td>
<td>30–40</td>
<td>26–42</td>
<td>24–36</td>
<td>26–35</td>
</tr>
<tr>
<td>Thrombin time (s)³</td>
<td>12–14</td>
<td>11.7–17</td>
<td>10–16</td>
<td>11.1–15.5</td>
</tr>
<tr>
<td>Prothrombin time (PT) (s)³</td>
<td>11–15</td>
<td>9.7–12.5</td>
<td>8.5–13.2</td>
<td>8.6–12.4</td>
</tr>
<tr>
<td>Antithrombin (AT) III (%)³</td>
<td>80–120</td>
<td>72–120</td>
<td>68–125</td>
<td>56–119</td>
</tr>
<tr>
<td>Fibrinogen (g/L)³</td>
<td>1.5–4.0</td>
<td>2.38–4.44</td>
<td>2.4–5.97</td>
<td>2.8–5.9</td>
</tr>
<tr>
<td>Protein C (%)³</td>
<td>70–140</td>
<td>80–120</td>
<td>83–138</td>
<td>67–135</td>
</tr>
<tr>
<td>Protein S (free) (%)³</td>
<td>70–140</td>
<td>21–133</td>
<td>19–113</td>
<td>20–165</td>
</tr>
<tr>
<td>D-Dimer (µg/mL)³</td>
<td>&lt;0.5</td>
<td>0.01–0.31</td>
<td>0.05–0.73</td>
<td>0.14–2.82</td>
</tr>
<tr>
<td>von Willebrand factor (VWF) : Ag (U/dL)⁴</td>
<td>60–95</td>
<td>90–150</td>
<td>100–175</td>
<td>135–245</td>
</tr>
<tr>
<td>Factor VIII : C (U/dL)⁴</td>
<td>90–140</td>
<td>110–160</td>
<td>125–200</td>
<td>160–230</td>
</tr>
<tr>
<td>ADAMST513 (% activity)</td>
<td>122 ± 34</td>
<td>–</td>
<td>–</td>
<td>118 ± 29</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (ESR) (mm/h)⁵</td>
<td>0–20</td>
<td>4–57 (18.5)</td>
<td>7–47 (19)</td>
<td>13–70 (32)</td>
</tr>
<tr>
<td>Ferritin (ng/ml)⁶</td>
<td>10–150</td>
<td>14–133 (32)</td>
<td>7–130 (18)</td>
<td>5–110 (21)</td>
</tr>
<tr>
<td>Transferrin sat (%)⁶</td>
<td>12–45</td>
<td>12–54</td>
<td>10–56</td>
<td>5–65</td>
</tr>
<tr>
<td>Total iron-binding capacity (TIBC) (mmol/L)⁶</td>
<td>41–77</td>
<td>40–84</td>
<td>52–100</td>
<td>54–120</td>
</tr>
<tr>
<td>Soluble transferrin receptor⁶</td>
<td>1.9–4.4</td>
<td>0.4–2.0</td>
<td>1.2–3.0</td>
<td>2.3–5.2</td>
</tr>
<tr>
<td>Total vitamin B12 (pmol/L)⁷</td>
<td>130–650</td>
<td>60–320 (230)</td>
<td>50–360 (170)</td>
<td>60–390 (170)</td>
</tr>
<tr>
<td>Active vitamin B12 (pmol/L)⁷</td>
<td>35–260</td>
<td>35–260 (79)</td>
<td>35–190 (76)</td>
<td>30–260 (79)</td>
</tr>
<tr>
<td>Serum folate (nmol/L)⁸</td>
<td>10–45</td>
<td>7–30 (14)</td>
<td>6–20 (10)</td>
<td>5–20 (10)</td>
</tr>
<tr>
<td>Red blood cell folate (mmol/L)⁸</td>
<td>0.5–1.4</td>
<td>0.5–1.4 (0.84)</td>
<td>0.45–1.3 (0.75)</td>
<td>0.4–1.2 (0.65)</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH) (U/L)²</td>
<td>115–211</td>
<td>78–433</td>
<td>80–447</td>
<td>82–524</td>
</tr>
<tr>
<td>Haptoglobin (g/L)⁹</td>
<td>0.3–2.0</td>
<td>0.44–0.49 (0.47)</td>
<td>0.24–0.32 (0.28)</td>
<td>0.27–0.36 (0.32)</td>
</tr>
<tr>
<td>Total bilirubin (mmol/L)²</td>
<td>5–22</td>
<td>2–7</td>
<td>2–14</td>
<td>2–19</td>
</tr>
<tr>
<td>Unconj. bilirubin (mmol/L)²</td>
<td>3–15</td>
<td>2–7</td>
<td>2–7</td>
<td>2–8</td>
</tr>
</tbody>
</table>

NB. These reference intervals are included solely to illustrate trends in changes during pregnancy. They are not to be used as reference intervals to guide patient diagnosis and management. Clinicians must use reference intervals as per the laboratory where testing was performed.

Anemia in pregnancy is defined by the World Health Organization (WHO) as a Hb less than 110 g/dL in the first and third trimesters, and less than 105 g/dL in the second trimester.

Anemia affects an estimated 30% of women of child-bearing age, and more than 40% of pregnant women worldwide.
The highest prevalence of anemia in pregnant women is in South-East Asia (48.7%) and Africa (46.3%).

Mean corpuscular volume (MCV) rises by an average of 4 fL during pregnancy in healthy women having an adequate iron intake. In women not supplemented with iron, mean corpuscular Hb (MCH) falls from late in the second trimester, with a further significant decrease postpartum, and mean corpuscular Hb concentration (MCHC) falls gradually until the end of third trimester. In women adequately supplemented with iron, MCH and MCHC are unchanged during pregnancy.

The most common cause of microcytosis (MRC) in pregnancy is iron deficiency, followed by thalassemia trait. Generally, the reduction in MCV with iron deficiency is in proportion to the reduction in Hb, whereas in thalassemia trait the reduction in MCV is proportionally greater than the reduction in Hb. Screening for hemoglobinopathy with Hb electrophoresis is recommended in all women of African, Mediterranean, Middle Eastern, South-East Asian or West Indian descent. Hb electrophoresis is also recommended in all other women with low MCH or MCV on screening complete blood count. A Swiss study suggested targeted screening for non-sickling hemoglobinopathies in nonanemic pregnant women with MCV <80 fL, MCH <27.5 pg, or MRC >3%, and in anemic women with MCV <76 fL, MCH <24 pg, or MRC >10%.

Maternal anemia in pregnancy is associated with increased rates of preterm birth, low birth weight, placental abruption, pre-eclampsia and postpartum hemorrhage. Severe anemia is associated with increased risk of maternal death (aOR 2.36). Additional maternal effects with anemia in pregnancy include increased susceptibility to infection, increased likelihood of blood transfusion, and greater risk of postpartum depression. Adverse fetal outcomes of maternal anemia include delayed growth and development, impaired psychomotor and mental development, increased risk of cognitive and behavior abnormalities, and increased perinatal and neonatal mortality. Iron deficiency anemia in late pregnancy is associated with abnormal neonatal auditory maturation. Serum immunoreactive erythropoietin (EPO) levels remain unchanged with pre-conception values in first trimester, absolute values progressively rising approximately 2–4-fold during second and third trimesters. However, EPO levels are below predicted value for hematocrit in first and second trimesters, generally being in agreement with hematocrit values in third trimester and peripartum.

Anemia is a common finding in women with human immunodeficiency virus (HIV) infection particularly those with advanced disease or using antiretroviral agents such as zidovudine. Most individuals with HIV have an inadequate rise in serum EPO for a given degree of anemia.

Erythrocyte deformability is decreased in the first trimester compared with non-pregnant controls, and declines further in the second and third trimester. In addition erythrocyte deformability is significantly lower with pre-eclampsia than in healthy third trimester pregnancies.

Malaria is an important cause of severe anemia. Diagnosis of malaria is based upon finding parasites on thick and thin blood smears, as well as malaria rapid diagnostic tests. In areas where malaria is endemic and pregnant women may have a high background level of immunity, infection is generally not associated with fever but may be associated with severe anemia. Peripheral smears are frequently negative despite placental infection. The sensitivity of highly sensitive rapid diagnostic testing, conventional rapid diagnostic tests and light microscopy to detect malaria in peripheral blood samples in pregnant women in a low-transmission setting were 86%, 83% and 77%, respectively.

**WHITE BLOOD CELL COUNT**

White blood cell (WBC) count increases significantly in healthy pregnancy due to neutrophil leucocytosis. Typical reference intervals during pregnancy are 6–16 × 10⁹/L. WBC count rises markedly during normal delivery with mean WBC counts of 10–16 × 10⁹/L, and an upper level of 29 × 10⁹/L. The administration of betamethasone to assist fetal lung maturity results in a mean increase in neutrophil count of 35%, and fall in lymphocyte count by 45%, the total WBC rising to a mean of 13.5 × 10⁹/L, with maximum values for WBC usually being less than 20 × 10⁹/L. Typically, neutrophil leucocytosis peaks 24 h after corticosteroid administration though elevation lasts at least 5 days. Immature white cell forms such as myelocytes and metamyelocytes may be found in the peripheral blood film of healthy...
Lymphocyte count decreases in the first and second trimester, subsequently rising in the third trimester. Levels of monocytes increase in the first trimester, then fall as pregnancy advances. Eosinophil and basophil counts remain unchanged during pregnancy.

Pregnancy related changes in WBC persist for 6–8 weeks after delivery. Leucocytosis is not a discriminating feature in pregnant women with hepatic injury being common to acute fatty liver of pregnancy (AFLP), severe pre-eclampsia (PET)/hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, sepsis and thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome (TTP-HUS).

**PLATELET COUNT**

Studies examining changes in platelet counts during normal pregnancy have yielded inconsistent results. Seven longitudinal studies reported a decrease in platelet counts during pregnancy, while four reported no change. Thrombocytopenia defined as a platelet count less than 150 × 10⁹/L complicates approximately 8–10% of pregnancies. In uncomplicated pregnancy and delivery 1% of women had a platelet count of less than 100 × 10⁹/L. A 1-year prospective study of pregnant Indian women with platelet counts less than 100 × 10⁹/L found 12% of cases occurred before 20 weeks' gestation, 24% were diagnosed between 20 and 29 weeks' gestation, and 64% occurred between 30 weeks' gestation and term. Gestational thrombocytopenia is the cause in approximately 75% of cases, PET/HELLP 21% and immune thrombocytopenia (ITP) 4%. Less common causes include systemic lupus erythematosus, antiphospholipid syndrome, TTP-HUS, acute fatty liver of pregnancy (AFLP), disseminated intravascular coagulation (DIC), HIV infection, hypersplenism and medications. In the absence of a previously abnormal result it may be difficult to differentiate ITP from gestational thrombocytopenia. Characteristics of gestational thrombocytopenia include relatively mild thrombocytopenia (>70 000 × 10⁹/L), no history of thrombocytopenia pre-conception or early in pregnancy, return of the platelet count to the normal range within 12 weeks postpartum, and the absence of a history of bleeding.

There is no consensus regarding the platelet count above which it is safe to perform neuraxial anesthesia. The British Committee for Standards in Hematology guidelines recommend a platelet count greater than 80 × 10⁹/L for neuraxial blockade in women with ITP.

Thromboelastography (TEG) simultaneously measures coagulation and fibrinolysis, and may be a better test than platelet function analysis in the pregnant woman with thrombocytopenia. During pregnancy TEG demonstrates increased coagulability and decreased fibrinolysis compared with at 8 weeks postpartum. Hemostasis occurred 20–35% faster, and minor increases in clot strength were demonstrated. One case series suggested neuraxial blockade could be performed in pregnant women with a platelet count greater than 56 × 10⁹/L and normal thromboelastography. TTP-HUS and HELLP syndrome share common features of thrombocytopenia, hemolysis, abnormal liver function and may be complicated by acute kidney injury and seizures. It is critical to differentiate TTP-HUS from HELLP, as TTP-HUS typically follows a course of multi-organ failure leading to death without plasma exchange (Table 2). Hemolysis in TTP-HUS is usually severe with fragmented red blood cells/schistocytes on blood film, markedly elevated lactate dehydrogenase (LDH), elevated indirect bilirubin, low haptoglobin and hemoglobinuria. Liver function tests are usually only mildly elevated in TTP-HUS compared with more marked elevation in HELLP. An LDH : aspartate aminotransferase (AST) ratio greater than 22.12 was found to be diagnostic of TTP-HUS rather than HELLP syndrome in one study. ADAMS-TS 13 activity is usually <10% with TTP-HUS, while the mean ADAMS-TS 13 activity was 31% in HELLP. In healthy pregnancy ADAMTS13 activity decreased progressively from 12 to 16 weeks' gestation reaching a mean level of 52% (range 22–89) at the end of early puerperium.

<p>| Table 2 | Differentiating hemolysis, elevated liver enzymes and low platelet count (HELLP) from thrombotic thrombocytopenic purpura (TTP). | Obstetrics - V8 - Maternal medical health and disorders in pregnancy - Chapter | Page 4 of 13 |</p>
<table>
<thead>
<tr>
<th>Feature</th>
<th>HELLP</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Variable</td>
<td>Mean platelet count $25 \times 10^9/L$</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Variable</td>
<td>Severe</td>
</tr>
<tr>
<td>Fever</td>
<td>Absent</td>
<td>25%</td>
</tr>
<tr>
<td>Jaundice</td>
<td>5–10%</td>
<td>Rare</td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>Rare eclampsia</td>
<td>75%</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>7–36%</td>
<td>80–90%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Common</td>
<td>Variable</td>
</tr>
<tr>
<td>Antithrombin III levels</td>
<td>60–80%</td>
<td>85–120% (normal)</td>
</tr>
<tr>
<td>LDH : AST ratio</td>
<td>&lt;22</td>
<td>&gt;22</td>
</tr>
<tr>
<td>ADAMTS13 activity</td>
<td>Mean 31%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation (DIC)</td>
<td>5–13%</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

**BONE MARROW ASPIRATION**

Compared with non-pregnant women, bone marrow examination of healthy pregnant women revealed increased cellularity in the latter half of pregnancy and the first 8 days postpartum, an increase of normoblastic erythropoiesis with increased numbers of nucleated red blood cells, increased granulopoiesis, and a slight increase in plasma cells and phagocytic reticulum cells.\(^{50}\)

**COAGULATION PROFILE**

Activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time all decrease by 10%–20% from pre-conception to the third trimester of healthy pregnancy.\(^{51,52,53,54,55}\) Authors have quoted reference intervals of 8.5–11.05, 8.5–12.4 and 9.5–12.6 s for PT in third trimester. Prolonged PT is a near universal feature of AFLP.\(^{56}\)

Studies examining possible physiologic changes in antithrombin III (ATIII) during uncomplicated pregnancy have revealed inconsistent results. Several studies described no change in ATIII throughout pregnancy compared with values prior to conception.\(^{52,57,58,59,60}\) Other authors reported a fall in ATIII from midtrimester, third trimester values being 13%–20% lower than non-pregnant values.\(^{51,52,53,54,55}\) Reductions in ATIII during pregnancy were greater in twin than in singleton pregnancies.\(^{62}\) Immediately after delivery, ATIII levels decrease reaching a nadir (mean ATIII 76%) at 12-h postpartum, before returning to baseline 72-h postpartum.\(^{61}\) ATIII activity is lower in pre-eclampsia than in uncomplicated pregnancy, with mean levels ranging between 60% and 85% in five studies.\(^{63,64,65,66,67,68}\) Similarly mean levels of ATIII ranged between 62% and 80% in HELLP syndrome.\(^{64,66,67,69}\) Low ATIII in HELLP syndrome is thought to occur primarily as a result of increased consumption rather than increased urine losses.\(^{72}\) ATIII level has been considered to be helpful in the differentiation of AFLP from HELLP. A review of 61 cases in the literature of women diagnosed with AFLP found a mean ATIII level of 16.1% (range 0–69%).\(^{56}\) ATIII may be low in AFLP due to reduced hepatic synthesis, altered transcapillary flux ratio, consumptive coagulopathy and urine loss with proteinuria.\(^{71,72}\)

In healthy pregnancy there is a significant fall in total and free protein S levels from first to second trimester.\(^{73}\) A large
variability in protein C changes has been described, with some studies finding an increase in protein C, and other studies no change compared with non-pregnant adults. Activated protein C resistance remained constant throughout pregnancy. Evaluation of pregnant women with thromboembolic events for protein S deficiency should be deferred until 3 months postpartum.

The prevalence of anticardiolipin antibodies, anti-β2 glycoprotein 1 and lupus anticoagulant in healthy pregnancy has been described as 1.6–11%, 2–3.9% and 7–8%, respectively. Fibrinogen levels rise significantly during pregnancy, and the use of non-pregnant reference intervals may underestimate the prevalence of disseminated intravascular coagulation (DIC). A fibrinogen level less than 3 g/L together with platelet count less than 50 and prolonged PT and APTT is consistent with DIC in pregnancy. A pregnancy modified score taking into account the physiological changes in PT, fibrinogen and platelets reported a sensitivity of 88% and specificity of 96% for the diagnosis of DIC (Table 3). DIC complicates 0.03% of pregnancies. Causes include placental abruption (37%), postpartum hemorrhage (29%), PET/HELLP (14%), AFLP (8%), sepsis (6%) and amniotic fluid embolism (6%). Coagulopathy/DIC is far less prevalent with HELLP syndrome than in AFLP. Six studies described DIC complicating 5.6–13% of cases of HELLP syndrome. A 20-year review found that DIC complicated only 0.2% of cases of severe PET. Case series of AFLP reported DIC in 16–77% of patients.

D-dimer levels rise steadily during pregnancy. Studies have reported D-dimer levels above the non-pregnancy threshold in 15–50% of women in the first trimester, 67–78% in second trimester and 96–100% in third trimester. D-dimer levels are markedly elevated during labor, decreasing rapidly during the first 3 days post-delivery, though normalization may not occur until 4 weeks postpartum. Pregnancy-specific D-dimer thresholds have been suggested; however, validated cut-offs for the exclusion of thromboembolic disease are lacking. The role of clinical probability assessment in the diagnostic management of pregnant patients is uncertain. Guidelines by professional societies provide contradictory recommendations. Until further validation studies have been performed, algorithms based on measurement of D-dimer should not be used for exclusion of pulmonary embolus in pregnancy or postpartum.

Table 3  Modified disseminated intravascular coagulation (DIC) score for pregnancy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Modified score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count (×10⁹/L)</td>
<td>&lt;50 = 1</td>
</tr>
<tr>
<td></td>
<td>50–100 = 2</td>
</tr>
<tr>
<td></td>
<td>100–185 = 2</td>
</tr>
<tr>
<td></td>
<td>&gt;185 = 0</td>
</tr>
<tr>
<td>Prothrombin time (patient/normal value)</td>
<td>0.5–1 = 5</td>
</tr>
<tr>
<td></td>
<td>1.0–1.5 = 12</td>
</tr>
<tr>
<td></td>
<td>&gt;1.5 = 25</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>≤3.0 = 25</td>
</tr>
<tr>
<td></td>
<td>3.0–4.0 = 6</td>
</tr>
<tr>
<td></td>
<td>4.0–4.5 = 1</td>
</tr>
<tr>
<td></td>
<td>&gt;4.5 = 0</td>
</tr>
<tr>
<td>Total score</td>
<td>&gt;26 = high probability DIC</td>
</tr>
</tbody>
</table>

Levels of von Willebrand factor (VWF) increase approximately 2-fold from pre-conception to third trimester peaking...
Shortly before birth in both healthy women and individuals with von Willebrand's disease (VWD). Postpartum VWF activities and factor VIII activity (FVIII : C) remain at higher levels for 2 days before beginning to decline on the third day after delivery. In 32 women with VWD type 1, VWF : Ag and factor VIII activity (FVIII : C) normalized during pregnancy, von Willebrand ristocetin co-factor (VWF : RCo) remaining below the normal non-pregnant range in only three patients. In four of nine pregnancies in women with VWD type 2 all coagulation factors normalized in third trimester. The qualitative abnormalities in women with VWD type 2 will persist however, and thrombocytopenia may worsen. For regional anesthesia, delivery, and at least the first 5 days postpartum, levels of VWF and FVIII : C should be maintained at greater than 50 IU/ml. Low FVIII : C appears to be the most important determinant of peripartum bleeding. Levels of VWF may fall rapidly postpartum, and excessive bleeding may occur as late as 21 days postpartum.

**ACUTE PHASE REACTANTS**

Most studies reported that C-reactive protein (CRP) levels remain unchanged during healthy pregnancy, though levels rise up to fourfold in the first 2 days postpartum. Erythrocyte sedimentation rate (ESR) rises significantly during pregnancy, levels being dependent on gestational age and hemoglobin concentration. In a study of 1019 women, the 95% reference range in non-anemic women rose from 4–57 mm/h in first trimester to 13–70 mm/h in third trimester. The corresponding values in anemic women were 8–83 mm/h in second trimester and 12–91 mm/h in third trimester. CRP is therefore preferable to ESR as a guide to inflammation or infection in pregnancy.

**IRON STUDIES**

Serum ferritin is usually adequate for the diagnosis of iron deficiency, with the exception of where there is active inflammation, as ferritin acts as an acute phase reactant. Diagnostic thresholds for iron deficiency in pregnancy vary significantly. While WHO defines iron deficiency anemia based on a serum ferritin <15 ng/mL, pregnant women with serum ferritin levels <30 ng/mL are considered to be at risk for iron deficiency anemia in the United Kingdom, and in Denmark it is suggested that women with serum ferritin <70 g/mL be treated with iron supplements. Serum ferritin drops progressively from first trimester and reaches a nadir by third trimester of approximately 50% of pre-conception values, independent of iron balance.

Studies correlating the presence or absence of stainable marrow iron with serum ferritin indicated that a level of <30 ng/mL has a 92% sensitivity and 98% specificity for diagnosing iron deficiency, whereas a serum ferritin less than 10 ng/mL has only a 25% sensitivity in detecting iron deficiency. In the setting of acute inflammation measurement of transferrin saturation (TS) may be useful. TS less than 16% is considered a marker of functional iron deficiency.

The use of microcytosis in screening will underestimate the prevalence of iron deficiency anemia, as a fall in Hb commonly antedates the fall in mean corpuscular volume. Microcytosis was present in only 27.5–65% of patients with iron deficiency. Soluble transferrin receptor levels increase in iron deficiency, and are unaffected by inflammation. A meta-analysis of 10 studies found that soluble transferrin receptor levels had a sensitivity of 86% and a specificity of 75% in detecting iron deficiency. The assay is not standardized and not widely available. Hepcidin regulates systemic iron bioavailability, determining how well oral iron is absorbed. Levels of hepcidin fall during pregnancy, women with undetectable levels transferring more maternally ingested iron to their fetus than women with detectable hepcidin. The utility of hepcidin levels as a biomarker of iron deficiency is being evaluated, one recent study suggesting that serum hepcidin is superior to Hb, serum iron, serum ferritin, TS, and transferrin iron binding capacity as an indicator of IDA in pregnant women. Hepcidin may be particularly useful in the setting of detecting iron deficiency in the setting of infectious or inflammatory disease.

Based upon measures of erythrocyte and reticulocyte indices including reticulocyte Hb content and percentages of hypochromic erythrocytes and microcytic erythrocytes, Demmers et al. concluded that in contrast to iron-deficient
nonpregnant women, low ferritin concentrations in pregnant women are not associated with functional iron deficiency. Iron metabolism might be differentially regulated for optimal fetal growth and development despite low maternal iron stores. Serum iron levels remain relatively stable in pregnancy. Serum transferrin increases by approximately 10%. Transferrin saturation falls slightly. Transferrin iron-binding capacity increases progressively from first trimester.

**VITAMIN B12**

Serum total vitamin B12 falls significantly in pregnancy due to reduction in holohaptocorrin. Holotranscobalamin (active B12), the fraction of B12 that is available to cross the placenta, does not change and should be used in the diagnosis of B12 deficiency in pregnancy. Methylmalonic acid is the most specific functional indicator of B12 status, as homocysteine is also determined by folate status and other B vitamins. Vitamin B12 levels vary significantly between different ethnicities, thus reference intervals during pregnancy need to be population and laboratory specific. Women of South Asian ethnicity living in Vancouver demonstrated substantially lower vitamin B12 levels and higher rates of vitamin B12 deficiency and inadequacy in first trimester than women of European ancestry. The reported prevalence of B12 deficiency in early pregnancy is up to 70% in India, compared with 5–17% in North America.

**FOLATE**

In women not receiving supplementation, plasma and red blood cell folate levels progressively fell from 16–18 weeks' gestation until 8 weeks postpartum, accompanied by a reciprocal rise in plasma homocysteine.

**MARKERS OF HEMOLYSIS**

Some authors have reported that LDH may rise from those in the first trimester, values in healthy women in the third trimester being up to double the values pre-pregnancy. Other authors report no change in LDH. LDH isoenzyme studies in nine women with HELLP syndrome found LDH isoenzyme 5 (liver, skeletal muscle) was the predominant type, with a relative decrease in LDH isoenzymes 1 and 2 (erythrocytes, heart muscle). Total LDH is therefore not a reliable marker for intravascular hemolysis in HELLP syndrome. Haptoglobin levels fall by approximately 25% from first trimester values, reaching a nadir at 24–27 weeks' gestation, before rising again towards the end of healthy pregnancy. One study found low haptoglobin levels in 39% of 220 healthy pregnant women, with a direct relationship between low haptoglobin levels and hemoglobin concentration. The authors concluded that the cause of low haptoglobin values was probably hemodilution and increased blood estrogen concentrations during pregnancy. A case report also described undetectable haptoglobin levels at 31 weeks gestation without other evidence of hemolysis, serum haptoglobin returning to normal values within 3 days of delivery. There is no change in reticulocyte subpopulations and maturity between non-pregnant women and those in the first trimester. From the second trimester there is a change in reticulocyte maturity, with significantly increased numbers of immature reticulocytes, and a decrease of mature reticulocytes. Reticulocyte maturity index decreases abruptly 1–4 weeks postpartum dropping to the level of non-pregnant women 5 weeks postpartum. Smokers have lower absolute reticulocyte counts in the third trimester than non-smokers. There may be significant ethnic difference in reticulocyte counts in healthy pregnancy, non-anemic Greek and Italian women demonstrating significantly higher reticulocyte counts than Anglo-Saxon women. Generally if the reticulocyte count is greater than 3% in the setting of anemia, the mechanism is hemolysis or blood loss, whereas a reticulocyte count less than 3% suggests a hypoproliferative marrow. A mild reduction in the upper end of the reference interval for total and unconjugated bilirubin is seen throughout pregnancy.
PRACTICE RECOMMENDATIONS

- Physiological changes in pregnancy may result in significant changes in normal values for many hematology assays
- There is significant variability between laboratories depending on the method of testing, the assay used and population factors
- Wherever possible clinicians should use a reference interval specific to the laboratory that has performed the test.

CONFLICTS OF INTEREST

The authors of this chapter declare that they have no interests that conflict with the contents of the chapter.
REFERENCES

Weiner CP and Bonsib SM. Relationship between renal histology and plasma antithrombin III activity in women with early onset hypertension.

Vigil-De Gracia P. Acute fatty liver and HELLP syndrome: two distinct pregnancy disorders.


Petrosyan I, Blaison G, Andres E, Jolobe OMP. Caveats in the work-up of iron deciency anaemia. 10.3390/nu6083062.


