Physiological Changes in Hematological Parameters During Pregnancy

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Abstract Pregnancy is a state characterized by many physiological hematological changes, which may appear to be pathological in the non-pregnant state. The review highlights most of these changes along with the scientific basis for the same, as per the current knowledge, with a special reference to the red blood and white blood cells, platelets and hemostatic profile.

Keywords Pregnancy · Physiological · Hematological changes

Physiological changes in pregnancy and puerperium are principally influenced by changes in the hormonal milieu. Many hematological changes also, occurring during these periods are physiological and are of inconsequential concern to the hematologist.

Red Blood Cells

During pregnancy, the total blood volume increases by about 1.5 liters, mainly to supply the demands of the new vascular bed and to compensate for blood loss occurring at delivery [1]. Of this, around one liter of blood is contained

within the uterus and maternal blood spaces of the placenta. Increase in blood volume is, therefore, more marked in multiple pregnancies and in iron deficient states. Expansion of plasma volume occurs by 10–15 % at 6–12 weeks of gestation [2, 3]. During pregnancy, plasma renin activity tends to increase and atrial natriuretic peptide levels tend to reduce, though slightly. This suggests that, in pregnant state, the elevation in plasma volume is in response to an underfilled vascular system resulting from systemic vasodilatation and increase in vascular capacitance, rather than actual blood volume expansion, which would produce the opposite hormonal profile instead (i.e., low plasma renin and elevated atrial natriuretic peptide levels) [4, 5].

Red cell mass (driven by an increase in maternal erythropoietin production) also increases, but relatively less, compared with the increase in plasma volume, the net result being a dip in hemoglobin concentration. Thus, there is dilutional anemia. The drop in hemoglobin is typically by 1–2 g/dL by the late second trimester and stabilizes thereafter in the third trimester, when there is a reduction in maternal plasma volume (owing to an increase in levels of atrial natriuretic peptide). Women who take iron supplements have less pronounced changes in hemoglobin, as they increase their red cell mass in a more proportionate manner than those not on hematinic supplements.

The red blood cell indices change little in pregnancy. However, there is a small increase in mean corpuscular volume (MCV), of an average of 4 fl in an iron-replete woman, which reaches a maximum at 30–35 weeks gestation and does not suggest any deficiency of vitamins B12 and folate. Increased production of RBCs to meet the demands of pregnancy, reasonably explains why there is an increased MCV (due to a higher proportion of young RBCs which are larger in size). However, MCV does not change

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significantly during pregnancy and a hemoglobin concentration <9.5 g/dL in association with a mean corpuscular volume <84 fl probably indicates co-existent iron deficiency or some other pathology [6].

Post pregnancy, plasma volume decreases as a result of diuresis, and the blood volume returns to non-pregnant values. Hemoglobin and hematocrit increase consequently. Plasma volume increases again two to five days later, possibly because of a rise in aldosterone secretion. Later, it again decreases. Significant elevation has been documented between measurements of hemoglobin taken at 6–8 weeks postpartum and those taken at 4–6 months postpartum, indicating that it takes at least 4–6 months post pregnancy, to restore the physiological dip in hemoglobin to the non-pregnant values [7].

White Blood Cells

White blood cell count is increased in pregnancy with the lower limit of the reference range being typically 6,000/cumm. Leucocytosis, occurring during pregnancy is due to the physiologic stress induced by the pregnant state [8]. Neutrophils are the major type of leucocytes on differential counts [9, 10]. This is likely due to impaired neutrophilic apoptosis in pregnancy [9]. The neutrophil cytoplasm shows toxic granulation. Neutrophil chemotaxis and phagocytic activity are depressed, especially due to inhibitory factors present in the serum of a pregnant female [11]. There is also evidence of increased oxidative metabolism in neutrophils during pregnancy. Immature forms as myelocytes and metamyelocytes may be found in the peripheral blood film of healthy women during pregnancy and do not have any pathological significance [12]. They simply indicate adequate bone marrow response to an increased drive for erythropoiesis occurring during pregnancy.

Lymphocyte count decreases during pregnancy through the first and second trimesters and increases during the third trimester. There is an absolute monocytosis during pregnancy, especially in the first trimester, but decreases as gestation advances. Monocytes help in preventing fetal allograft rejection by infiltrating the decidual tissue (7th–20th week of gestation) possibly, through PGE2 mediated immunosuppression [13]. The monocyte to lymphocyte ratio is markedly increased in pregnancy. Eosinophil and basophil counts, however, do not change significantly during pregnancy [14].

The stress of delivery may itself lead to brisk leucocytosis. Few hours after delivery, healthy women have been documented as having a WBC count varying from 9,000 to 25,000/cumm. By 4 weeks post-delivery, typical WBC ranges are similar to those in healthy non-pregnant women.

Platelets

Large cross-sectional studies done in pregnancy of healthy women (specifically excluding any with hypertension) have shown that the platelet count does decrease during pregnancy, particularly in the third trimester. This is termed as “gestational thrombocytopenia.” It is partly due to hemodilution and partly due to increased platelet activation and accelerated clearance [15]. Gestational thrombocytopenia does not have complications related to thrombocytopenia and babies do not have severe thrombocytopenia (platelet count $\leq 20,000$ /cumm). It has hence been recommended that the lower limit of platelet count in late pregnancy should be considered as 1.15 lac/cumm [1]. The platelet volume distribution width increases significantly and continuously as gestation advances, for reasons cited before. Thus, with advancing gestation, the mean platelet volume becomes an insensitive measure of the platelet size.

Post delivery platelet count increases in reaction to and as a compensation for increased platelet consumption during the process of delivery.

Hemostatic Profile

Pregnancy is associated with significant changes in the hemostatic profile. Fibrinogen and clotting factors VII, VIII, X, XII, vWF and ristocetin co-factor activity increase remarkably as gestation progresses. Increased levels of coagulation factors are due to increased protein synthesis mediated by the rising estrogen levels. In *in vitro* experiments, pregnant plasma has been demonstrated to be capable of increased thrombin generation [16]. Thus, pregnancy is a prothrombotic state. In pregnancy, aPTT is usually shortened, by up to 4 s in the third trimester, largely due to the hormonally influenced increase in factor VIII. However, no marked changes in PT or TT occur [1].

There are changes in the levels and activity of the natural anticoagulants also. Levels and activity of Protein C do not change and remain within the same range as for non-pregnant women of similar age. Levels of total and free (i.e., biologically available) Protein S, decrease progressively with the advancement of gestation. Antithrombin levels and activity are usually stable throughout the pregnancy, fall during labor and rise again soon after delivery. Acquired activated Protein C (APC) resistance has been found to occur in pregnancy, even when Factor V Leiden and antiphospholipid antibodies are not present. [18]. This has been attributed to the high factor VIII and factor V activity and low free Protein S levels. Hence, APC sensitivity ratio does not serve as a screening test for Factor V Leiden during pregnancy.

Coagulation factors remain elevated for up to 8–12 weeks post partum and assays for them may be falsely negative during this period.

Markers of hemostatic activity which are clinically relevant are thrombin–antithrombin complexes (TAT) and prothrombin fragments (F 1 + 2), which reflect in vivo thrombin formation, as also, tests which demonstrate plasmin degradation of fibrin polymer to yield fragments, namely D-dimer and fibrin degradation products (FDP) assay. TAT levels increase with gestation; in early pregnancy the upper limit of normal is similar to the adult range of 2.63 g/L, whereas by term, the upper limit of normal is 18.03 g/L. D-dimer levels are markedly increased in pregnancy, with typical reference range being tenfold higher in late pregnancy than in early pregnancy or in the nonpregnant state [1]. The increase in D-dimers reflects the overall increase in total amount of fibrin during pregnancy consequent to increased thrombin generation, increased fibrinolysis or a combination of both [17]. This also explains why the D-dimer assay is not reliable for predicting the possibility of venous thrombo-embolism in pregnant patients [13].

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