Hematological Profile of Normal Pregnant Women

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Abstract

With the advent of many interventions to improve maternal and child health, pregnant women have become the focus of many health programs. However, few data exist regarding this important population. Although pregnancy-induced changes occur in hematological values, very few laboratories provide specific reference ranges for pregnant women. Most laboratory information systems report reference values based on samples obtained from non-pregnant women which may not be useful for clinical decisions during pregnancy. Thus, there is an increased risk of overlooking important physiologic alterations resulting from pathological conditions and of misinterpreting normal changes as pathological events. It is therefore important to understand pregnancy-induced hematological changes for correct clinical evaluation of pregnant women. In this review, we discuss complete blood count and the associated pregnancy-induced hematological changes. We also highlight the dynamic changes of these parameters per trimester and show how they differ between populations.

Keywords: Pregnancy; Complete blood count; Hematological changes; Trimester

Introduction

Pregnancy, also known as gestation or gravidity, is a state in which an embryo(s) implants unto maternal uterus and subsequently develops unto a fetus(es) [1]. Pregnancy starts at conception, when an ovum is fertilized by a spermatozoan to form a zygote, and ends in childbirth, abortion or miscarriage [2,3]. It lasts 40 weeks from last menstruation or 38 weeks from conception date. Normal pregnancy term is 38 to 42 weeks [4-6].

With the advent of many interventions to improve maternal and child health, pregnant women have become the focus of many health programs [7-10]. However, few data exist regarding this important population. Although pregnancy-induced changes occur in hematological values, very few laboratories provide specific reference ranges for pregnant women [11,12]. Most laboratory information systems report reference values based on samples obtained from non-pregnant women [13-16]. Thus, there is an increased risk of overlooking important physiologic alterations resulting from pathological conditions and of misinterpreting normal changes as pathological events [17-19]. It is therefore important to understand pregnancy-induced hematological changes for correct clinical evaluation of pregnant women [20-22].

In this review, we discuss complete blood count and the associated pregnancy-induced hematological changes. We also highlight the dynamic changes of these parameters per trimester and show how they differ between populations (Table 1).

Complete blood count

The complete blood count (CBC) is a blood panel that gives cell type in patient’s blood [22,23]. These cell types are red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (thrombocytes) [24]. A normal adult has about 5 L of blood (2 L of blood cells and 3 L plasma). All blood cells are synthesized in the bone marrow’s hematopoietic stem cells [25].

Red blood cell indices

Red blood cell indices include Red Blood Cell (RBC) count, Hematocrit (Hct), Hemoglobin (Hb or Hgb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC) [5,26]. RBCs, Hgb and Hct can be measured directly in the lab, the rest are calculated based on previous values [27]. MCV, MCH and MCHC give evidence to support pathologies in RBCs [18,28]. The red corpuscular indices give an overview of anemias and polycythemias while in parallel differentiating alcohol use, liver diseases, thalassemia, kidney diseases and sickle cell disease [22,29,30].

Blood volume increases in pregnancy by more than 50%, leading to hemodilution [7]. This increase is greater than the associated increase in the red blood cell mass resulting in physiological anemia (associated with low RBC, Hb, Hct, MCH, MCHC levels) [3]. The increase in blood volume during gestation is attributed to increased atrial-natriuretic peptide levels and increased plasma renin activity [12].

Red blood cells

Red blood cells (RBCs) are the most abundant cells in blood [27]. The average number per µL is 5.2 million (range: 4.4-6.0 million). RBCs are enucleated-biconcave corpuscles filled with hemoglobin [31]. They transport oxygen from lungs to tissues and CO2 from tissues to lungs [32]. Erythrocytes have life span of 120 days, after which their amino acids and iron are recycled. Reduced oxygen (hypoxia) triggers the kidney to release erythropoietin (EPO), a hormone responsible for erythropoiesis [13].

Polycythemia vera, high altitude, smoking, blood loss, alcoholism, liver disease, congenital heart disease and chronic obstructive pulmonary disease (COPD) creates hypoxic conditions leading to polycythemia (high RBC count) [33,34]. Conditions that reduce body

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Hemoglobin (Hgb) is an iron-containing protein complex which binds oxygen and carbon dioxide for transport by RBCs [31]. It forms about 33% [31].

Pregnancy increases the proportions of serum, making the RBCs look fewer in number (pseudo-anemia) [20,36]. With a life expectancy of 120 days, erythrocytes are an excellent long term marker for anemia [19,36].

Anemia (low RBC count) is induced by hemorrhage, iron deficiency, RBC destruction, malnutrition, thalassemia, aplastic anemia, pernicious or sickle cell anemia, chronic renal failure, anti-infective medications, chemotherapy or radiation, and pregnancy [19,36].

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Hgb varies with gestational age due to hemodilution and the respective compensatory mechanisms [21]. The high Hgb levels in pregnancy are defined by Hgb concentration <11g/dl or Hct<0.33L/L [3]. Similar trends are seen in RBC count and Hct [12].

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Hgb level begins to decline from the 16th week of gestation as a result of increased plasma volume. Similar trends are seen in RBC count and Hct [12].

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Table 1: Comparison of hematological reference ranges for pregnant women from different countries.
Maternal anemia and also high Hbg concentrations leads to preterm birth, perinatal death (abortion), intrauterine growth restriction and low immunity for both mother and child, which exposes them to life threatening infections [3,40]. Low Hgb levels show a poor positive correlation with newborn length but do not show correlation with weight [41]. Women on iron supplementation have stable HB levels throughout the pregnancy [30].

**Hematocrit**

Hematocrit (Hct), also known as Packed Cell Volume (PCV), is the percentage of RBCs in (centrifuged) whole blood [42]. Normal range is 37-54%. PCV has a wide coefficient of variation hence should be viewed together with other red cell indices [17,43,44]. Elevated Hct (Polycythemia) may reflect erythrocytosis. Pregnancy decreases Hct, particularly in the last trimester due to increase in plasma volume. PVC decrease can also be caused by malarial infection, hormonal changes, iron deficiency and conditions promoting fluid retention [9]. Variations in Hct are caused by the same factors as in RBCs and Hgb [14,21]. A Hct <15% and >60% can cause cardiac arrest and spontaneous blood clotting, respectively [29].

**Mean cell volume**

Mean Cell Volume (MCV) is the average volume of single RBC. It is calculated as Hct/RBC and measured in femtolitres (fL). Microcytic, normocytic, and macrocytic are less than 80, 80-100 and > 100 fL, respectively [31]. Microcytosis (low MCV) is caused by iron deficiency, thalassemia, hemolytic anemia, anemia of chronic disease, hereditary spherocytosis and lead poisoning [30,45]. Macrocytosis (high MCV) is caused by reticuloytosis, folate deficiency, vitamin B12 deficiency and drugs such as methotrexate and phenytoin [46,47]. In pregnant women, poor positive correlation has been found between maternal Hgb, Hct and MCV. Thus it is important to keep them within the reference range [9].

There is an increase in MCV during pregnancy (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 [46,48]. 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) [49]. However, MCV does not change significantly during pregnancy and a hemoglobin concentration of 9.5 g/dL in association with a MCV of 84 fL probably indicates co-existent iron deficiency or some other pathology [12].

**Mean cell hemoglobin**

Mean Cell Hemoglobin (MCH) is the average mass (amount) of Hgb/RBC [50]. Elevated MCH values are found in alcoholism, folate deficiency, vitamin B12 deficiency, liver disease and hemochromatosis [12,15]. Decreases MCH values are found in sideroblastic anemia, lead poisoning, iron deficiency anemia, anemia of chronic disease and thalassemia [37]. There is no significant change in MCHC during pregnancy [9].

**Platelets**

Platelets, also known as thrombocytes, are round to spindle-shaped cytoplasmic fragments which contain proenzymes, enzymes, myosin and actin and no nucleus [32,51]. They are produced from megakaryocytes which are large bone marrow cells with lobulated nucleus which buds off forming 2-3 nm platelets [19]. Platelet average number per µL is 350,000 (range: 150,000-500,000). Thrombocytes contribute to hemostasis by clumping together and sticking to vessel walls (platelet phase) which activate intrinsic pathway of coagulation phase [23,24]. Platelets have a lifespan of 7-12 days [51].

Thrombocytosis (high platelet count) is caused by acute blood loss (triggers the release of thrombocytes from spleen), chronic myelogenous leukemia (CML), iron deficiency, pregnancy, infection, injury, bone marrow disorder, polycythemia vera, and hypersplenism (missing or malfunctioning spleen) [16,40,52]. Thrombocytopenia (low platelet count) is caused by idiopathic thrombocytopenic purpura, HELLP syndrome, hemolyticuremic syndrome and disseminated intravascular coagulation [5,22,48]. Large spleen can lower the platelet count [46].

There is a significant decrease in platelets count with gestational age [2]. During pregnancy, the uterine wall continuously expands to accommodate fetal growth. This causes laceration of blood vessels at the uterus leading to massive hemorrhage. The primary hemostatic plug where these tears occur is formed by platelets [12,13]. Thrombocytopenia occurs in 8% of all pregnancies, and is the second common hematological disorder after anemia [20]. Thrombocytopenia is defined by platelet count <150*10⁹/L. Gestational thrombocytopenia is due to increased platelet destruction by their activation and increased clearance [12]. Hemodilution also contributes to gestational platelet reduction. The immune system responds by synthesizing newer and larger platelets. Levels of clotting factors and fibrinogen also increase while fibrinolytic activity decreases. These changes are meant to protect the expectant mother from hemorrhage at delivery [11]. However, the increased platelet aggregation, especially in the third trimester makes, makes gestation a hypercoagulable state prone to thromboembolism [2,3]. Gestational thrombocytopenia needs no medical intervention and remises after delivery. However other causes such as immune thrombocytopenia, megaloblastic anemia, liver disorders thrombotic microangiopathy syndromes and eclampsia must be excluded [27,41].

Women with twins may have lower platelet count compared with singleton pregnancies, probably due to higher thrombin generation. Thrombocytopenia in pregnancy is generally mild, with only few life threatening cases [2].

**Mean platelet volume**

Mean Platelet Volume (MPV) is the calculated measurement of mean platelet size. Platelet size often increases with increased production [42,50]. Elevated MPV is diagnostic of immune thrombocytopenic purpura (ITP), myeloproliferative disease, Bernard-Soulier syndrome or pre-eclampsia [31,41]. Reduced MPV is diagnostic of aplastic anemia, cytotoxic drug therapy or viral infections [36].

**White blood cells**

White blood cells (WBC) are classified into agranulocytes (lymphocytes and monocytes) and granulocytes (eosinophils neutrophils, and basophils) [5]. Granulocytes, also referred to as
polymorphonuclear cells, are the most abundant and highly motile [26]. Leukocytes play a large role in the acute phase of inflammation (especially bacterial infections) through phagocytosis. They also supply antibodies [11,12]. WBC are synthesized in the bone marrow and destroyed after 14 to 21 days in the lymphatic system [53]. Leukocytes average number per µL is 7000 (range: 5000-10,000). A patient with leukocytes <500 risks fatal infection while a patient with leukocytes >30,000 has serious disease like leukemia) or massive infection [18,37].

Etiologies for leukocytosis (high leukocyte count) are: Trauma, inflammation, dehydration, acute infection, hemocoencentration, cancer (such as leukemia) and medications such as corticosteroids [43,44]. Etiologies for leukopenia (low leukocyte count) include: Bone marrow disorders, cancer, infections and medications such as chemotherapy, antibiotics and anticonvulsants [28,37].

Normal pregnancy is accompanied by leukocytosis, caused by physiological stress. A complex physiological process increases leucocyte counts during pregnancy. Serial changes occur in endocrine system, metabolic processes and genital system. Therefore, leucocytes increase because they accept stimulatory signals as pregnancy progresses [10,11]. Studies have shown that gestational leukocytosis is as a result of leucocytes release from marginal pools [2,41]. Leukocytosis begins in the first trimester and remains high throughout pregnancy [21]. The white blood cell count during normal pregnancy is between 6×10^9 and 16×10^9/L [3]. The WBC count normalizes 4 weeks after delivery [7,12]. The leukocytosis-inducing physiological stress is attributed to elevated inflammatory response due to immunomodulation, immunosuppression and selective immune tolerance of fetus. However, Yu et al. [2016] suggests that leukocytosis occurs after normal delivery [9,52]. While Tzur et al. [54] associates leukocytosis in first trimester with complicated pregnancy. Thus correct interpretation and correlation of leucocyte count is important during antenatal care and postnatal [20]. Amongst leucocytes, preponderance of neutrophils on differential counts during pregnancy is due to impaired neutrophilic apoptosis [34]. The neutrophil count can be twice its postpartum values [45]. Bone marrow hyperplasia during the last trimester is associated with neutrophilic leukocytosis [21]. There is a significant increase in white blood cell and neutrophil count on day one postpartum which then decreases and normalizes by fifth day. This should be considered to avoid unnecessary use of antibiotics. WBC count peak at delivery hence is a limited marker for infection during normal birth. The increase in leucocyte count is mainly from increased neutrophil and lymphocyte counts [12,41].

**Neutrophils**

Neutrophils, also known as polymorphonuclear leukocytes, are the main phagocytic leucocytes which engulf and digest pathogens or debris in tissues and release cytotoxic enzymes and chemicals (such as bactericides, prostaglandins and leukotrienes) [17,55]. Neutrophil average number per µL is 4150 (range 1800-7300) with a differential count of 50-70%. They are round cells with 3 to 5- lobed nucleus with large, pale inclusions in the cytoplasm [13,56]. They move into tissues after a few hours and may survive for days depending on tissue activity. They are produced in red bone marrow. Etiologies for neutrophilia (high neutrophil count) are: acute bacterial infection, acute stress, burns, leukemia, steroids, rheumatoid arthritis [23,46,57-59]. Etiologies for neutropenia (low neutrophil count) are: folate/ vitamin B12 deficiency, aplastic anemia, chemotherapy and medications such as chloramphenicol and sulfonamides [17,22,25]. Neutrophils increases during pregnancy [3]. Neutrophilia in pregnancy is probably as a result of impaired neutrophilic apoptosis. Pregnant woman serum has inhibitory factors which depress neutrophil chemotaxis and their phagocytic activity [11].

**Eosinophils**

Basophils are named so because they stain well with eosin. They are round cells with, generally, bi-lobed nucleus. They engulf antibody-labeled cells and debris, release cytotoxic enzymes and reduce inflammation [25,43]. Basophil average number per µL is 165 (range:0-7000) with a differential count of <1%. Causes of eosinophilia (high eosinophil count) include allergies, parasitic infections, leukemia polyarthritis nodosa autoimmune disease [51]. Eosinopenia (low eosinophil count) has no specific cause, 0% eosinophil is considered normal [22]. Eosinopenia is observed with gestational age [46].

**Basophils**

Basophils are named so because they take up basic dyes well. Basophils release histamine in damaged tissues to promote inflammation [17,22]. Basophil average number per µL is 44 (range: 0-1500) with a differential count of <1% [25]. Basophilia (high basophil count) is caused by allergies, Hodgkin’s disease, chronic myelogenous leukemia, oral contraceptives [51]. Basopenia (low basophil count) has no specific cause, 0% basophils is considered normal [48]. Basophils declines with gestational age [46].

**Monocytes**

Monocytes are the largest WBCs, involved in chronic inflammation, stored in spleen and are very motile [41,53]. They are large cells with kidney bean-shaped nucleus and abundant pale cytoplasm. Monocytes enter tissues to become macrophages [31]. Their main roles are: phagocytosis, antigen presentation and cytokine production [26]. Monocytes average number per µL is 456 (range: 200-950) with a differential count of 2-8% [23,25]. Monocytosis (high monocyte count) is caused by chronic inflammation, viral infection, bacterial infection such as tuberculosis, sarcoidosis and Cushing’s syndrome [22,28]. Monocytopenia (low monocyte count) is caused by aplastic anemia, glucocorticoids and myelotoxic drugs [12]. Monocytosis is prevalent during pregnancy [46].

**Lymphocytes**

Lymphocytes are round cells, slightly larger than RBCs, with round nucleus and very little cytoplasm. They are the defensive cells of lymphatic system. They can survive for decades, circulating between blood and tissues [15,31]. There are three main types of lymphocytes; T cells, B cells and Natural Killer (NK) cells. T cells mature in the thymus. There are multiple T cells, the most common are: Helper T cells which help other cells mature, activate and function through cytokine production; cytotoxic T cells which cells destroy infected with viruses, and memory T cells which remembers the antigens of past infections [27,43]. B cells are formed in bone marrow. There are two types of B cells: plasma B cells which produce antibodies and memory B cells which remember past infections. NK cells kill infected or cancer cells [22,51]. Lymphocytes average number per µL is 2185 (range: 1500–4000); differential count: 20-30% [25]. Lymphocytosis (high lymphocyte count) is caused by viral infections, leukemias and adrenal insufficiency. Lymphocytopenia (low lymphocyte count) is caused by; HIV virus which destroys T cells (CD4), aplastic anemia, glucocorticoid, rheumatoid arthritis among others [43,56].

A review by Okpokam et al. [39] found that lymphocytes increases during pregnancy probably due to bacterial infections. However, Elado et al. [3] observed lymphocyte suppression with gestational age.
Chandra et al. [46] observed decrease in lymphocyte count during the first and second trimester and an increase in the third semester. The observed lymphopenia during pregnancy may be due to monocytes which help prevent fetal alloreactive rejection during the first trimester. The above dysregulation among and within different immune system components is central in maternal adaptation to pregnancy [11,60].

Conclusion

Normal pregnancy is accompanied by significant hematological changes which includes physiological anemia, thrombocytopenia, and neutrophilia. Thus, using non-pregnant women reference ranges for clinical evaluation of pregnant women is not appropriate and may lead to misdiagnosis. Additionally, these parameters vary between populations.

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