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Dynamic haematological adaptation: Exploring the physiological shifts during pregnancy

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Abstract
Numerous physiological and haematological changes that occur during pregnancy non-pathologically which may seem abnormal to non-pregnant individuals. Pregnancy-related hematologic alterations are frequent and may be brought on by foetal or maternal death. This haematological modification mainly necessary to fulfill the demands of the growing foetus and placenta, which even involves significant changes in blood volume. Pregnancy-related anaemia is most frequently caused by iron deficiency anaemia (IDA). Not only that, but thrombocytopenia is currently the second most prevalent hematologic disorder in pregnancy, following postpartum haemorrhage-causing anaemia. Thrombocytopenia in pregnancy can have a variety of causes, ranging from benign to potentially fatal, requiring early detection and intervention. These disorders include immunological thrombocytopenia, pregnancy-associated atypical haemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, and gestational thrombocytopenia. These indicate that in order to prevent negative consequences, pregnant women's haematological parameters should be monitored at all stages of the pregnancy. The majority of these modifications, including those to the haemostatic profile, platelets, red blood cells and white blood cells, and the scientific basis for them, are emphasized in this review.

Keywords: Foetal death, haemorrhage, iron deficiency anaemia, pregnancy, thrombocytopenia

Introduction
Almost every organ and system undergoes significant alterations during a normal pregnancy in order to meet the needs of the fetoplacental entity [1]. The physiological shifts in platelet count and hemoglobin concentration [HGB] that occur during a typical pregnancy are well-known occurrences. It is also among the physiological states that have the power to significantly alter haematological characteristics. Numerous factors affect a pregnancy, some of which are socioeconomic position, culture, environment, and access to healthcare. The course and outcome of pregnancy are also influenced by the haematological parameters [2].

A person's overall health is mostly reflected in their haematological indicators. A unique kind of connective tissue called blood is made up of formed components in a fluid matrix. Numerous factors, including sex, seasonal variation, lactation, pregnancy health, and dietary condition, affect several of the hematological indices [3]. It is also recognized that in order to improve diagnostic precision, normal differences resulting from sex, age, and breed must be taken into account when comparing individuals and reference data in a clinical diagnostic setting [4].

Numerous studies have found that a pregnant woman's haematological indices are one of the elements influencing pregnancy, and that in a normal pregnancy, an individual's haematological indices largely reflect their general health [5] A common haematological problem [6] is anemia (Low hemoglobin), which is also linked to unfavorable pregnancy outcomes [7].

Two typical measures are used to identify anemia in pregnant women: a hemoglobin concentration of less than 11.0 g/dL or the haemotocrit or hemoglobin concentration 5th percentile in a healthy reference population. Tests evaluating many variables are used to make this assessment possible. This work is significant because the quality and quantity of haematological indices determine the effectiveness of systems that are monitored during prenatal care in an effort to predict and/or enhance pregnancy outcome [8].

Aims of this study

The study's goal is to assess various important haematological indicators' values in healthy pregnant subjects. In order to diagnose problems or difficulties during pregnancy, this study focuses on the diagnostic examination of a variety of situations, particularly the function of variation in white blood cell (WBC) count, hemoglobin, packed cell volume (PCV), granulocytes, lymphocytes, and platelets.

Changes in Plasma

The total volume of blood expands by around 1.5 liters throughout pregnancy, primarily to meet the needs of the developing vascular bed and make up for blood lost during birth. Of this, the uterus and the placenta's maternal blood compartments hold about one liter of blood. As a result, increased blood volume is more noticeable in situations involving multiple pregnancies and iron deficiency [9]. The plasma volume expands by 10–15% between weeks 6 and 12 of pregnancy. Pregnancy tends to cause a small decrease in atrial natriuretic peptide levels and an increase in plasma renin activity [10]. Rather than a result of actual blood volume expansion, which would have produced the opposite hormonal profile (low plasma renin and elevated atrial natriuretic peptide levels), this suggests that the elevation in plasma volume during pregnancy is a response to an underfilled vascular system caused by systemic vasodilatation and an increase in vascular capacitance [11].

Changes in Erythrocytes

Hemoglobin concentration decreases as a result of a rise in maternal erythropoietin production in plasma volume, which is accompanied by a relatively smaller increase in red cell mass. As a result, dilutional anemia exists. By the late second trimester, hemoglobin levels usually drop by 1-2 g/dL; this decrease then stabilizes in the third trimester, when maternal plasma volume decreases (Due to an increase in atrial natriuretic peptide levels). Since women who take iron supplements grow their red blood cell mass more proportionately than those who do not, their hemoglobin fluctuations are less noticeable.

Studies have shown that pregnancy causes minimal changes in the red blood cell indices. Nonetheless, in an iron-replete woman, there is a slight increase in mean corpuscular volume (MCV) of 4 fl on average. This rise peaks between weeks 30-35 of pregnancy and does not indicate a folate or vitamin B12 shortage. Reasonably, the increased MCV can be explained by increased RBC production to satisfy the demands of pregnancy because of a higher proportion of newborn RBCs which are larger in size). Nonetheless, MCV remains relatively constant during pregnancy, and a hemoglobin level of less than 9.5 g/dL combined with a mean corpuscular volume of less than 84 fl most likely signifies the presence of coexisting iron shortage or an additional disease [12].

Following pregnancy, diuresis causes the plasma volume to drop, and the blood volume recovers to levels seen before pregnancy. As a result, hematocrit and hemoglobin levels rise. Two to five days later, plasma volume rises once more, most likely as a result of increased aldosterone secretion. Later on, it falls once more. Measuring hemoglobin at 6-8 weeks postpartum and 4–6 months postpartum has shown a significant rise, indicating that it takes at least 4–6 months postpartum to restore the physiological decrease in hemoglobin to the non-pregnant values [13].

Changes in Leucocytes

Pregnancy causes an increase in white blood cell count, with 6,000/cumm being the usual lower limit of the reference range. Pregnancy-related leucocytosis is brought on by the physiological strain that being pregnant places on the body. The predominant leucocyte type on differential counts is neutrophils. This is probably because pregnancy interferes with neutrophilic apoptosis. Toxic granulation is visible in the cytoplasm of neutrophils. Reduced phagocytic activity and neutrophil chemotaxis are caused, mostly by inhibitory substances found in a pregnant woman's serum [14, 15].

Additionally, there is proof that during pregnancy, neutrophils' oxidative metabolism is elevated. Pregnant healthy women may have immature forms in their peripheral blood film called myelocytes and metamyelocytes, which have no clinical relevance. All they show is a sufficient response of the bone marrow to the elevated erythropoesis drive that occurs during pregnancy [16].

During the first and second trimesters of pregnancy, total the number of lymphocytes falls and in the third trimester, it rises. Absolute monocytosis occurs throughout pregnancy, particularly in the first trimester, although it diminishes as the pregnancy goes on. By penetrating the decidual tissue (7th–20th week of gestation), monocytes may be able to prevent fetal allograft rejection through PGE2-mediated immunosuppression [17]. During pregnancy, the ratio of monocytes to lymphocytes rises noticeably. However, throughout pregnancy, eosinophil and basophil levels do not dramatically alter [18].

Severe leucocytosis may result from the stress of delivery alone. Healthy women have been reported to have a WBC count ranging from 9,000 to 25,000/cumm a few hours after giving birth. Typical WBC ranges by 4 weeks postpartum are comparable to those of healthy non-pregnant women.

Changes in Thrombocytes

The platelet count does drop throughout pregnancy, especially in the third trimester, according to many cross-sectional studies conducted on healthy pregnant women. The term "gestational thrombocytopenia" refers to this. Hemodilution has a role, as does enhanced platelet activation and quicker clearance. Babies with severe thrombocytopenia (Platelet count $\leq$20,000/cumm) do not experience issues associated with thrombocytopenia attributable to gestational thrombocytopenia [19].

Therefore, it has been suggested that 1.15 lac/cumm be used as the lowest limit of platelet count in late pregnancy. For the previously mentioned reasons, the platelet volume distribution width grows dramatically and constantly as gestation progresses. Therefore, as gestation progresses, the mean platelet volume ceases to be a sensitive indicator of platelet size. In response to and as a compensation for increased platelet consumption throughout the delivery process, the post-delivery platelet count rises [20].

Changes in Haemostatic changes

The hemostatic profile is significantly altered during pregnancy. As gestation goes on, there is a noticeable increase in the activity of ristocetin co-factor, fibrinogen, coagulation factors VII, VIII, X, XII, vWF, and other factors. Rising estrogen levels cause greater protein

synthesis, which in turn causes higher amounts of coagulation factors. Pregnant plasma has been shown to be capable of increasing thrombin production in *in vitro* tests [21].

Pregnancy is therefore a prothrombotic condition. Pregnancy causes an increase in factor VIII that is mostly affected by hormones, which can shorten the aPTT by up to 4 seconds in the third trimester. But there are no discernible changes in either PT or TT. Additionally, there are modifications to the natural anticoagulants' levels and activities. Protein C levels and activity stay constant and fall within the same range as those of women of a comparable age who are not pregnant. As gestation progresses, levels of both total and free (i.e., physiologically accessible) Protein S gradually decline. Antithrombin activity and levels are typically constant during pregnancy, decrease during labor, and then quickly return following birth. Pregnancy has been linked to acquired activated Protein C (APC) resistance, even in the absence of Factor V Leiden and antiphospholipid antibodies. The low amounts of free Protein S and the strong activity of factors VIII and V have been ascribed to this. Therefore, during pregnancy, the APC sensitivity ratio is not a useful screening tool for Factor V [22]. Up to 8–12 weeks after childbirth, coagulation factors are still increased, and tests for them may come out falsely negative at this time.

Discussion

The current results clearly show that the third trimester was when the RBC count decreased the most. In contrast, the second trimester produced the lowest HB and HCT readings as well as the highest MCV, MCH, MCHC, and RDW readings. Several earlier publications have documented a progressive decrease in red blood cell count as pregnancy progresses. Conversely, the second trimester showed the lowest values of HB and HCT [23]. Throughout the course of the pregnancy, the RBC count and HB concentration continuously dropped, but the HCT significantly dropped in the second trimester and stayed unchanged after that [24]. While MCH increased till the conclusion of the pregnancy, the maximum MCV was reached in the second trimester. When compared to the results of international records, the average HB concentration and HCT were determined to be significantly lower. Similarly, there was a greater decrease in the first trimester than in the third, both in terms of HB concentration and HCT. It is challenging to provide a physiological explanation for the notable decrease in HB concentration and HCT between the first and third trimesters, which points to a cause other than the typical hematological reaction to pregnancy [25].

The study focuses on the notable increase in the total WBC count from the first trimester to the last two thirds of pregnancy. The trend of change in lymphocyte counts was the opposite; they were similar in the first two trimesters but drastically decreased in the third. On the other hand, over the course of the three trimesters, the numbers of monocytes and granulocytes remained similar [26]. Several earlier publications corroborate the somewhat higher overall WBC count seen in the current results. International research indicates that during pregnancy, the total WBC count is almost always greater than 7000/mm3. More research is needed to determine the precise reason of relative leukocytosis during gestation, however potential factors include decreased neutrophil apoptosis and the psychological and physical stress of pregnancy [27]. Comparably, another study showed that the lymphocyte count was somewhat elevated at the beginning of the pregnancy but gradually decreased over the course of the next three trimesters. According to a long-term study, an increase in neutrophil counts corresponded with a rise in the total WBC count. The study found that as pregnancy progressed, there was an increase in monocytes and a decrease in lymphocytes, eosinophils, and basophils [28].

Data from a different study indicated that while pregnancy progressed, MPV remained constant, PDW increased, and PCT and platelets count steadily decreased. PCT and a decreased platelet count were frequently observed during a typical pregnancy. Pregnancy-related thrombocytopenia was linked to increased platelet activation and clearance as well as plasma volume expansion [29]. Theoretically, pregnancy-related hemodilution and platelet activation can cause platelets to expand, form pseudopodia, and hence raise MPV and PDW [30].

Conclusion

Thus, it may be concluded that among women experiencing a normal pregnancy, there are trimester-specific variations in the reference range for hematological profile. The RBC, WBC, and platelets indices' reference ranges are primarily in line with global records. In this aspect, the trimester pattern of hematological profile change among is similar to earlier publications. The major causes of changes in hematological profiles during pregnancy appeared to be the growth of plasma volume, the physiological stress of pregnancy, and preferential increased hematopoiesis of certain blood forming constituents, but not of others.

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