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Research Article

Haematological Changes during Pregnancy: Insight into Anaemia, Leukocytosis, and Thrombocytopenia

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Abstract: Background: The hematologic system undergoes a series of adaptive changes in preparation for fetal hematopoiesis and wellbeing while also serving as a cushion against expected blood loss at delivery. Objectives: The aim of the present review was to high light on the haematological disorders during pregnancy in pregnant women. The haematological changes during pregnancy are range from the increased plasma volume and red blood cell mass, leucocytosis and adaptive immunological changes to the relative hypercoagulable state of pregnancy. The increase in total blood volume at term, serves as a reserve against normal blood loss at delivery and peripartum hemorrhage. Anaemia is the most common hematological problem in pregnancy, followed by thrombocytopenia. Hemoglobin level below 11g/dl in pregnant women constitutes anemia and hemoglobin below 7g/dl is severe anemia. Up to 56% of all women living in developing countries are anemic. About 20 % of maternal deaths occur due to anaemia. The most common causes of anaemia in pregnancy include iron deficiency, folate deficiency, vitamin B_{12} deficiency, hemolytic diseases, bone marrow suppression, chronic blood loss and underlying malignancies. Prevalence of several maternal risk factors which are associated with low birth weight, increased perinatal, maternal morbidity and mortality are higher among anaemic women. Also, leukocytosis is almost always associated with pregnancy. A pregnancy related leukocytosis with an increase in neutrophils has been seen from the second month of pregnancy with an upward trend observed as pregnancy advances. Lymphocyte count was decreased in pregnant women. 10% lower platelets level at term compared with at pre-pregnancy . The mechanisms for this are thought to be due to dilution effects and accelerated destruction of platelets passing over the often scarred and damaged trophoblast surface of the placenta. 75% of cases of platelets changes are due to gestational thrombocytopenia, 15%–20% secondary to hypertensive disorders, 3%–4% due to an immune process, and the remaining 1%–2% comprises rare constitutional thrombocytopenias, infections, and malignancies . Conclusion: It can be concluded that pregnancy induces a number of physiologic changes that affect the hematologic indices, either directly or indirectly. The main haematological disorders were anaemia, thrombocytopenia, and leucocytosis. Further studies should be conducted to decrease the prevalence of these haematological disorders during pregnancy to avoid their risks on mothers and their newborn infants.

Keywords: Anemia, Thrombocytopenia, Leukocytosis, Pregnant women, Blood disorders

INTRODUCTION

Pregnancy is influenced by many factors, some of which include culture, environment, socioeconomic status, and access to medical care (Purohit, G. *et al.*, 2015) .

Hematological profile is considered one of the factors affecting pregnancy and its outcome. The hematologic system undergoes a series of adaptive changes in preparation for fetal haematopoiesis and wellbeing while also serving as a cushion against expected blood loss at delivery. These changes range from the increased plasma volume and red blood cell mass, leucocytosis and adaptive immunological changes to the relative hypercoagulable state of pregnancy and tend to commence as early as the 6th week of gestation with resolution by the 6th week postpartum Akinlaja, O. (2016).

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Anemia is the most common hematological problem in pregnancy, followed by thrombocytopenia. Leukocytosis is almost always associated with pregnancy) Akinbami, A.A. *et al.* (2013). Anemia affects the lives of more than two billion people globally, accounting for over 30% of the world's population. It is a global public health problem occurring at all stages of the life cycle but the burden of the problem is higher in pregnant women (Gebre, A. & Mulugeta, A. 2015). It affects half a billion women of reproductive age worldwide. In 2011, 29% (496 million) of non-pregnant women and 38% (32.4 million) of pregnant women aged 15-49 years were anaemic (Stevens, G. *et al*., 2013). In developing countries, it is a cause of serious concern as, besides many other adverse effects on the mother and the fetus it contributes significantly high maternal mortality. According to world health organization estimates, up to 56% of all women living in developing countries are anemic (Sharma, J.B. & Shankar, M. 2010). About 20 % of maternal deaths occur due to anaemia (Jiji, D.B. & Rajagopal, K. 2014).

Pregnancy is usually accompanied by leukocytosis, but the full sequential changes of the various cell types responsible for this observed leukocytosis have not been clearly determined in all geographical locations and physiological conditions (Akinbami, A.A. *et al*.,2013; Onwukeme, K.E. & Uguru, V.E. 1990). A pregnancy related leukocytosis with an increase in neutrophils has been seen from the second month of pregnancy with an upward trend observed as pregnancy advances (Akinlaja, O. 2016; Pramanik, S.S. *et al*., 2007). Lymphocyte count was decreased in pregnant women compared to non pregnant women as pregnancy proceeded (Dhariwal, S.K. *et al*., 2016).

The platelets count is slightly lower in pregnant than in non pregnant women (Abbassi-Ghanavati, M. *et al*., 2006). Most studies report an approximate 10% lower platelets level at term compared with at pre-pregnancy (Boehlen, F. *et al*., 2000; Jensen, J.D, *et al*., 2011). The majority of pregnant women still have levels within the normal range; however, if the pre-pregnancy level is borderline or there is a more severe reduction, this may fall below the normal range. The mechanisms for this are thought to be due to dilution effects and accelerated destruction of platelets passing over the often scarred and damaged trophoblast surface of the placenta (Fay, R.A. *et al*., 1983). Platelets counts may also be lower in women with twin compared with singleton pregnancies, possibly due to greater thrombin generation (Tsunoda, T. *et al*., 2002). Although most cases of thrombocytopenia in pregnancy are mild, with no adverse outcome for mother or baby, occasionally a low platelets count may be part of a complex disorder with significant morbidity and be rarely life-threatening (Akinbami, A.A. *et al*., 2013). Overall, about 75% of cases of platelets changes are due to gestational thrombocytopenia, 15%–20% secondary to hypertensive disorders, 3%–4% due to an immune process, and the remaining 1%–2% comprises rare constitutional thrombocytopenias, infections, and malignancies Burrows, R.F. & Kelton, J.G. 1990 .

OBJECTIVES

The prevalence of anemia, thrombocytopenia, and leukocytosis in pregnant women were done worldwide and reported varying magnitude of the problem especially in developing countries. Therefore, the aim of this study was to high light on the haematological disorders during pregnancy in pregnant women.

Effect of Pregnancy on Blood Volume

The total plasma volume at term is 4700-5200mls due to a gain of about 1100-1600mls and an average of 10-15% increase in plasma volume by 6-12 weeks gestation with a progressive rapid rise till the 34th week (Akinlaja, O. 2016; Lund C.J. & Donovan, J.C. 1967). The result is a plasma volume that is about 30-50% above that of the non-pregnant, which later regresses to about 10-15% above that of the non-pregnant by the 3rd week postpartum and is at normal non-pregnant level by the 6th week (Akinlaja, O. 2016). Possible reasons that have been espoused for the increased plasma volume include a response to the under-filled vascular system resulting from systemic vasodilatation, reduced systemic vascular resistance and blood pressure as well as increased cardiac output associated with sodium and water retention (Akinlaja, O. 2016). The maternal blood volume at term is about 50% above the non pregnant level in normal pregnant women, averaging about 100ml/kg and the presence of a fetus is not needed for the hematological changes as an increase in blood volume have been seen in women with hydratidiform mole (Akinlaja, O. 2016; Jansen, A.J. *et al*., 2005). The increase in total blood volume at term, which averages about 47% (+/- 15) above the non-pregnant serves as a reserve against normal blood loss at delivery and peripartum hemorrhage (Akinlaja, O. 2016; Zeeman, G.G. *et al*., 2009).

During pregnancy, plasma renin activity tends to be increased and atrial natriuretic peptide levels are slightly reduced. This suggests that the rise in plasma volume is in response to an underfilled vascular system caused by systemic vasodilatation and the 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) (Schrier, R.W. 1988; Nadel, A.S. *et al*., 1988).

Anaemia

Anaemia is one of the most common disorders principally characterized by a decline in the concentration of circulating erythrocytes or hemoglobin

in the blood and a concomitant impairment of oxygen transportation that does not meet the body's physiological need (McLean, E. *et al*., 2009; WHO/UNU/UNICEF. 2001; Melku, M. & Agmas, A. 2015). According to WHO, hemoglobin level below 11g/dl in pregnant women constitutes anemia and hemoglobin below 7g/dl is severe anemia. The center for disease control and prevention (1990) defines anemia as less than 11g/dl in the first and third trimester and less than 10.5gm/dl in second trimester (World Health Organization. 1993; Centers for Disease Control. 1989). The prevalence of anaemia was highest in south Asia and central and west Africa (Stevens, G. *et al*., 2013).

The most common causes of anaemia in pregnancy include iron deficiency, folate deficiency, vitamin B_{12} deficiency, hemolytic diseases, bone marrow suppression, chronic blood loss and underlying malignancies (Sharma, J.B. & Shankar, M. 2010; Reveiz, L. *et al*., 2007). 30-50% of woman become anaemic during pregnancy, with iron deficiency being the most common form of anaemia in more than 90% of the cases (Milman, N. 2008; Johnson, T.A. 2010)**.** Anaemia is an indicator of both poor nutrition and poor health. Prevalence of several maternal risk factors which are associated with low birth weight, increased perinatal, maternal morbidity and mortality are higher among anaemic women (Melku, M. & Agmas, A. 2015; Prema, K. *et al*., 1981). It is, therefore, possible that coexisting obstetric problems contribute, at least in part, to the adverse obstetric outcome reported among anaemic women. Anaemic women should, therefore, be treated as a high risk obstetric group (Kalaivani, K. 2009). Immune depression due to anaemia and consequent increased morbidity due to infection, especially urinary tract infection, might be one of the factors responsible for low birth weight babies in anaemic women. Screening for, and effectively treating infections in anaemic women might therefore result in improved foetal and maternal prognosis (Ramachandran, P. 1992).

Classification of Anaemia

Anaemia can be classified as physiological (e.g. pregnancy), according to the etiology and red blood cell morphology. Classification based on red cell morphology classifies anaemia based on the size and shape of the red blood cell, (normocytic MCV80-90fl, macrocytic MCV>100fl, microcytic MCV<80fl), as well as pigmentation (normochromic, hypochromic) (Oliver, E. & Olufunto, K. 2012). The Centers for Disease Control and Prevention has defined anemia as hemoglobin levels of less than 11 g/dL (hematocrit less than 33 percent) in the first and third trimesters and less than 10.5 g/dL (hematocrit less than 32 percent) in the second trimester (Centers for Disease Control. 1989; Oliver, E. & Olufunto, K. 2012). The World Health Organization defines anemia in pregnant women as hemoglobin <110 g/L (11 g/dL) or hematocrit (33 percent) (WHO/UNU/UNICEF. 2001). Severe anemia in pregnancy is defined as hemoglobin <70 g/L (7 g/dL) and requires medical treatment. Very severe anaemia is defined as hemoglobin <40 g/L (4 g/dL) and is a medical emergency due to the risk of congestive heart failure (Bauer, K.A. *et al*., 2011).

Classification of Anaemia Based on Aetiology
(Oliver, E. & Olufunto, K. 2012**)**

Blood loss: a. Acute (Antepartum haemorrhage (eg. placenta praevia , abruption placenta), and Intrapartum haemorrhage). b. Chronic (Hookworm infestation, Bleeding hemorrhoids, and Peptic Ulcer Disease)

1. Nutritional Anaemia (Iron deficiency, Folate deficiency, and B12 deficiency).
2. Bone marrow failure (Aplastic anaemia, Isolated secondary failure of Erythropoiesis, and Drugs (e.g. Chloramphenicol, Zidovudine)).
3. Haemolytic : a. Inherited (Haemoglobinopathies (e.g. Sickle cell disorders, Thalassemia), Red cell Membrane defects (e.g. Hereditary spherocytosis, elliptocytosis), and Enzyme deficiencies (eg G6PD deficiency, Pyruvate kinase defeciency).

Acquired (Immune Haemolytic anaemias (eg autoimmune, alloimmune, drug induced), Non- Immune Haemolytic anaemias (Acquired membrane defects (e.g. Paroxysmal nocturnal Haemoglobinuria), and Mechanical damage (eg. Micro-angiopathic haemolytic anaemia), Secondary to systemic disease (eg. Renal diseases, liver disease), and Infections (Malaria, Sepsis, HIV).

Morphological Classification of Anemia and Causes
(Oliver, E. & Olufunto, K. 2012**)**

a) Hypochromic Microcytic (Iron deficiency, Thalassemia, Sideroblastic anemia, Anaemia of chronic disorders, Lead poisoning).
b) Macrocytic (Folic acid deficiency, vitamin B12 deficiency, liver disease, myxoedema, chronic obstructive pulmonary disease, myelodysplastic syndromes, and blood loss anemia).
c) Normocytic Normochromic (Autoimmune haemolytic anaemia, systemic lupus erythomatosis, collagen vascular disorders, hereditary spherocytosis, haemoglobinopathies, bone marrow failure, malignancies, myelodysplasia, blood loss anemia, and anemia of chronic disease).

Classification of Anaemia by Degree of Severity

Anaemia can be classified according to severity as mild (Hb(9-11g/dl), moderate (Hb (7-9g/dl), severe (Hb (4 -7g/dl) and very severe((Hb <4g/dl). Recent estimates suggest that up to 60% pregnant women in developing countries may be anaemic and nearly 7% of pregnant women are severely anaemic (Van den Broek, N.R. 2003). Mild, anemia may not have any effect on pregnancy and labour except that the

mother will have low iron stores and may become moderately to severely anemic in subsequent pregnancies. Moderate anemia may cause increased weakness, lack of energy, fatigue and poor work performance. Severe anemia, however, is associated with poor outcome. The woman may have palpitations, tachycardia, breathlessness, increased cardiac output leading to cardiac stress which can cause de-compensation and cardiac failure which may be fatal (Sharma, J.B. & Shankar, M. 2010; Malhotra, M. *et al*., 2002; Sharma, J.B. 2003). Increased incidence of pre-term labour (28.2%), pre-eclampsia (31.2%) and sepsis have been associated with anemia (Sharma, J.B. & Shankar, M. 2010; Indian Council of Medical Research. 1989). At a global level, anemia prevalence is a useful indicator to monitor the impact of widespread or highly effective interventions and to track the progress made toward the goal of reducing anemia during pregnancy and maternal mortality (Melku, M. & Agmas, A. 2015; Kraemer, K. & Zimmermann, M.B. 2007).

As a result of the normal physiological changes in pregnancy, plasma volume expands by 46–55%, whereas red-cell volume expands by 18–25%. The resulting haemodilution has, perhaps wrongly, been termed 'physiological anaemia of pregnancy'. There are in fact insufficient data to give accurate physiological limits for the expected haemodilution. In most published studies, the mean minimum normal haemoglobin in healthy pregnant women living at sea level is 11.0-12.0 g/dl. The mean minimum by WHO criteria is taken to be 11.0 g/dl in the first half of pregnancy and 10.5 g/dl in the second half of pregnancy (World Health Organization. 1993).

Women with mild anaemia in pregnancy have decreased work capacity. They may be unable to earn their livelihood if the work involves manual labour. Women with chronic mild anaemia may go through pregnancy and labour without any adverse consequences, because they are well compensated (Kalaivani, K. 2009).

Women with moderate anaemia have substantial reduction in work capacity and may find it difficult to cope with household chores and child care. Available data from India and elsewhere indicate that maternal morbidity rates are higher in women with Hb below 8gm/dl (prema, k. *et al*., 1981). They are more susceptible to infections and recovery from infections may be prolonged. Premature births are more common in women with moderate anaemia. They deliver infants with lower birth weight and perinatal mortality is higher in these babies (prema, k. *et al*., 1981).

Three distinct stages of severe anaemia have been recognized - compensated, decompensated, and that associated with circulatory failure. Cardiac decompensation usually occurs when Hb falls below 5.0 g/dl. The cardiac output is raised even at rest, the stroke volume is larger and the heart rate is increased. Palpitation and breathlessness even at rest are symptoms of these changes. These compensatory mechanisms are inadequate to deal with the decrease in Hb levels. Oxygen lack results in anaerobic metabolism and lactic acid accumulation occurs. Eventually circulatory failure occurs further restricting work output. Untreated, it leads to pulmonary oedema and death. When Hb is <5 g/dl and packed cell volume (PCV) below 14, cardiac failure is seen in a third of cases (Lawson, J.B. 1967).

Studies estimated that anaemia may be responsible for as much as 20% of all maternal deaths in Sub –Saharan Africa through three main mechanisms. Firstly anaemia makes women more susceptible to deaths from haemorrhage by lowering their haematological reserves for blood loss especially at birth. Severe anaemia is associated with increased susceptibility to infection due to lowered resistance to disease, and Hb<4g/dl is also associated high risk of cardiac failure, particularly during delivery or soon after, making the women likely to die if unable to reach good health facilities immediately (Buseri, F.I. *et al*., 2005).

Gebre & Mulugeta, (2015) reported that the over all prevalence of anemia (hemoglobin < 11 g/dL) among the pregnant women in North Western Zone of Tigray, Ethiopia was 36.1% (95% CI = 32.7%–39.7%) of which 58.5% were mildly, 35.7% moderately, and 5.8% severely anemic. In pregnant women, rural residence, no education/being illiterate, absence of iron supplementation during pregnancy, and meal frequency of less than two times per day were the independent predictors for increased anemia among the pregnant women.

Effect of Pregnancy on Total Body Iron Content

The normal total body iron content in a non-pregnant woman is about 2g, which is about half that of men while the iron stores are only about 300mg (Akinlaja, O. 2016; Pritchard, J.A. & Mason, R.A. 1964). Iron supplementation is needed for the replacement of the approximately 1000mg needed during pregnancy, about 500mg of which is expended in the development of the maternal red blood cell mass, while the fetus and placenta utilize about 300mg. Approximately 200mg of iron is excreted via the skin, urine and gastrointestinal tract. It is absorbed in the duodenum in the ferrous form and about 30mg of daily elemental Fe is needed as prophylaxis and more may be required depending on the degree of maternal anemia. An average of 3-4mg of iron needs to be absorbed per day during pregnancy although this is non-uniform as about 6-7mg is needed daily in the late second to third trimester (Akinlaja, O. 2016; Pritchard, J.A. & Scott, D.E. 1970; Michael, J.P. & Hossain, N. 2010). Iron supplementation is usually given as 325mg of oral tablets, in the form of ferrous sulfate with 65mg of

elemental iron, ferrous gluconate with 35mg and ferrous fumarate with 107mg of elemental Iron (Akinlaja, O. 2016).

Effect of pregnancy on Folic acid

All women of reproductive age are advised to consume 0.4 mg of folic acid daily, because folate deficiency is associated with neural tube defects and possibly other birth defects as well as macrocytic anemia (Michael, J.P. & Hossain, N. 2010). In addition, 400-800mg of folic acid is recommended daily during pregnancy for the increased red blood cell production while about 50-100 mg/d is needed pre-pregnancy (Akinlaja, O. 2016).

Effect of Pregnancy on Leukocytes:

A pregnancy related leukocytosis with an increase in neutrophils has been seen from the second month of pregnancy with an upward trend observed as pregnancy advances ((Akinlaja, O. 2016; Pramanik, S.S. *et al*., 2007). Neutrophils range between 5-12,000/µl with up to 15,000/µl seen in the third trimester and during labor and the puerperium; levels of 25,000/µl or more have been attained (Akinlaja, O. 2016; Taylor, D.J. *et al*., 1981). Leucocyte levels have been demonstrated to correlate with cervical dilation and labor progress and should resolve by the 6^{th} day postpartum, if associated with pregnancy (Akinlaja, O. 2016; Acker, D.B. *et al*., 1985).

Lymphocytes and monocytes do not demonstrate a significant change while eosinophils and basophils might either be slightly decreased in number or remain the same (Akinlaja, O. 2016). Pregnancy is associated with leukocytosis, primarily related to increased circulation of neutrophils (Kuvin, S.F. & Brecher, G.(1962). Data from two series reported mean white blood cell counts in laboring patients of 10,000 to 16,000 cells/microL, with an upper level as high as 29,000 cells/microL (Acker, D.B. *et al*., 1985; Molberg, P. *et al*., 1994); the mean count increased linearly with the duration of elapsed labor (Acker, D.B. *et al*., 1985).

Effect of Pregnancy on Platelets

Pregnancy is a relatively hypercoagulable state with an increased platelet activity and consumption (Valera, M.C. *et al*., 2010). This combined with the hemodilution state leads to a mean platelet count that is slightly lower than that in the non-pregnant state (Matthews, J.H. *et al*., 1990). An increased platelet production can be inferred from the increase in circulating platelets width and volume. There is also an increase in thromboxane A_2 with an increased tendency for platelets aggregation in pregnancy (Hayashi, M. *et al*., 2002). It is usually asymptomatic or mild, tends to present without a prior history and has been described in about 5% of pregnancies. A platelet level between 70,000 and 150,000/mm3 was described by Burrows and Kelton in about 8% of pregnancies but mostly resolves by 4 weeks postpartum (Burrows, R. & Kelton, J. 1988; Burrows, R.F. & Kelton, J.G. 1993).

Thrombocytopenia was considered present when the platelet count was less than $150x10^9$/L (Boehlen, F. *et al*., 1999) but, Severe thrombocytopenia was defined as under 50 $x10^9$/L (Stamilio, & Macones, 1999). It affects up to 10% of all pregnancies, and may result from a number of diverse etiologies. While some of these are not associated with adverse pregnancy outcomes, others are associated with substantial maternal and/or neonatal morbidity and mortality (McCrae, K.R. 2003).

Thrombocytopenia in the pregnant patients may result from many causes. These causes include gestational thrombocytopenia; immune thrombocytopenic purpura; drug-induced; type IIB von Willebrand disease, and congenital (McCrae, K.R. *et al*., 1992), hypertensive disorders such as preeclampsia; the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP); uncommon disorders such as thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome; and acute fatty liver of pregnancy (McCrae, K.R. 2007). Gestational, or incidental, thrombocytopenia affects approximately 5% of all pregnant women, and accounts for > 75% of all cases of pregnancy-associated thrombocytopenia (McCrae, K.R. *et al*., 1992; Shehata, N. *et al*., 1999).

Olayemi and Akuffo, (Olayemi, E. & Akuffo, F.W. 2012) reported that the prevalence of thrombocytopenia in pregnant Ghanaian women in this study was 15.3% compared with 4% in controls. Most cases of thrombocytopenia were mild (76%), only 4% of the women with thrombocytopenia had severe thrombocytopenia.

Shamoon *et al*. (2009) reported that the mean platelet count in pregnant women was significantly lower than in non-pregnant women in Erbil City, Iraq. Thrombocytopenia affected 8% of cases, with peak incidence during the third trimester. Gestational thrombocytopenia was found to be the principal cause (73.8%); hypertensive disorders caused thrombocytopenia in 23% of cases and two cases (4%) were due to immune thrombocytopenic purpura.

Mbanya *et al*. (2009) were studied the factors associated with thrombocytopenia among pregnant women in Cameroon. The major factors associated with thrombocytopenia were anaemia (29.8%), history of inter menstrual bleeding (25.7%), history of preeclampsia (23.3%), current hypertensive disorders (23.2%), malaria (22.3%), HIV infection (21.0%) and the absence of antimalaria prophylaxis (16.2%). Thrombocytopenia was not significantly associated with third-trimester bleeding or with a history of postpartum haemorrhage (Mbanya, D. *et al*., 2007).

CONCLUSION

Many hematologic problems develop in pregnancy or can be triggered by the pregnant state. Normal physiologic changes during pregnancy can alter hematologic indices during pregnancy and make recognition of pathologic states difficult. These haematological disorders were anaemia, thrombocytopenia, and leucocytosis. These conditions are a significant source of morbidity and mortality during pregnancy that has implications for both the mother and the fetus. Further studies should be conducted to decrease the prevalence of these haematological disorders during pregnancy to avoid their risks on mothers and their newborn infants.

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