Review Article

Hematological changes in pregnancy – the preparation for intrapartum blood loss

Abstract

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. 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.

Keywords: Hematological Changes, Pregnancy, Prevention, Intrapartum blood loss, Hypercoagulable state, Postpartum

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Introduction

Pregnancy is associated with various physiological changes, which tend to affect most of the body system and some of these begin immediately after conception continuing through delivery to the postpartum period in order to accommodate both the maternal and fetal needs.

The hematologic system adapts to make provision for fetal hematopoiesis, ensuring adequate blood supply to the enlarged uterus and its content thereby protecting both mother and fetus against the effects of impaired venous return in both the supine and erect positions in addition to safeguarding against bleeding at delivery.

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.[1,2]

Major hematological changes seen can be broadly categorized under:

1. Physiologic Anemia
2. Leukocyte and Immunological function
3. Mild Thrombocytopenia
4. Coagulation and fibrinolysis

Physiologic anemia

This is also referred to as dilutional ane mia and it results from an increased plasma volume to red blood cell ratio. It is detected between the late second and third trimester with peak at 30–34weeks GA.[3]

Its absence has been associated with an increased tendency for stillbirths while its presence conveys benefits related to decreased blood viscosity and reduced resistances to blood flow culminating in increased perfusion of the placenta.[4]

Maternal hemoglobin level tends to increase by the third day postpartum and there is a diuresis–induced resolution of pregnancy–induced anemia by the 6th week postpartum.

The average hemoglobin level is about 12.5g/dl at term and according to the World Health Organization (WHO), anemia is hemoglobin level less than 11g/dl. It is classified as severe, when less than 7g/dl and hemoglobin level less than 4g/dl is very severe necessitating urgent treatment to prevent the development of congestive heart failure.[5] The United States Center for Disease Control (CDC) denotes anemia as hemoglobin less than 10.5g/dl in the 2nd trimester and less than 11g/dl in the 1st and 3rd trimesters.[6]

The frequent use of iron supplementation in pregnancy has been associated with a reduction in maternal anemia at delivery and only about 6% of pregnant women on Iron supplementation should present with a hemoglobin level less than 11 g/dl.[7] The postpartum hematocrit is usually similar to the prelabor hematocrit by the 7th day postpartum in the absence of excess blood loss or disease states such as preeclampsia.[8]

Plasma volume changes

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.[1,9]

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.

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.

Red blood cell changes

The erythrocyte volume is about 250–450mls higher at term in women on iron supplements compared to those not supplemented and about 20–30% higher than that in the non–pregnant state.[1] A 15–20% increase in red blood cell mass is seen in non–iron supplemented pregnant women bearing in mind that 1ml of red blood cell mass has about 1.1mg of elemental iron.[10]

A progressive increase occurs from 8–10 weeks gestation till the end of pregnancy but the average red blood cell life span is slightly reduced.[1] The average mean corpuscular volume is about 4 fl higher in healthy pregnant women but decreases to an average of 80–84 fl in those not on Iron supplements.[11]

Erythropoietin levels are 50% higher due to the higher metabolic oxygen requirement and this accounts for the moderate bone marrow erythroid hyperplasia and elevated reticulocyte count. There is also an increased transportation of oxygen across the placenta due to the combination of a reduced maternal RBCs oxygen affinity from an elevated 2,3 Diphosphoglycerate and a low maternal pCO_2.[12]

Physiologic effects of hypervolemia and anemia

A reduced resistance to flow from the decreased blood viscosity results in an increased placental perfusion and reduced cardiac work. 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.[13]

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Blood loss at delivery range from 500mls at normal singleton vaginal delivery, 1000mls at twin delivery and cesarean section to 1500mls at cesarean hysterectomy.[1]

The increased cardiac output to the placenta leads to an increased supply of nutrients to the fetus and those to the kidney and skin encourages excretion of maternal and fetal waste products and control of maternal temperature while a reduction in large cerebral blood flow has also been reported.[14]

A lack of the hypervolemic changes and physiologic hemodilution has been shown to be associated with an increased risk of stillbirths especially small for gestational age associated stillbirths.[4]

Pregnancy requirements

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.[15]

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.[16] 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. In addition 400–800mcg of Folic acid is recommended daily during pregnancy for the increased red blood cell production while about 50–100mcg is needed pre–pregnancy.

Chronic severe anemia and consequences

Possible sequelae of inadequate Iron stores and folate deficiency derived from reduced intake and chronic hemolytic states, such as malaria and sickle cell disease are as listed in box 1 while box 2 encompasses standard laboratory tests.

Box 1

A. Spontaneous abortion

B. Low birth weight infants

C. Prematurity

D. Reduced amniotic fluid volume

E. Fetal cerebral vasodilation

F. Non Reassuring Fetal heart tracing

G. Increased neonatal mortality and

H. Increased maternal mortality

Box 2

Standard laboratory Evaluation

a. Complete Blood count

b. Reticulocyte count

c. Peripheral smear review

d. Serum Iron level

e. Total Iron–binding capacity

f. Serum Ferritin level and

g. Hemoglobin electrophoresis, if applicable

In areas where iron deficiency is prevalent, offsprings have demonstrated a positive correlation between prenatal iron/folic acid supplementation and intellectual functioning but fetal red blood cell production is not impaired even in the presence of severe maternal iron deficiency anemia.[17,18]

Leukocyte and immunological function

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.[19] 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.[20]

Leucocyte levels have been demonstrated to correlate with cervical dilation and labor progress and should resolve by the 6th day postpartum, if associated with pregnancy.[21] Lymphocytes and monocytes do not demonstrate a significant change while eosinophils and basophils might either be slightly decreased in number or remain the same.

Complement factors C3 and C4 are noted to be increased in the 2nd and 3rd trimesters while C–reactive protein (CRP) level, a serum acute phase reactant has also been found to be elevated during pregnancy with further increase noted during labor.[22,23] In order for the maternal body to accept the fetal graft, there is various changes in the immunological function, which generally leads to a decreased cell mediated immunity and an increased humoral or antibody–mediated immunity.[24]

The suppression of T–helper 1 and T–cytotoxic 1 cells leads to decreased Interleukin –2, Tumor necrosis factor, interferon gamma

and alpha. Up–regulation of T–helper 2 and T–cytotoxic 2 cell function do lead to an increased Interleukin 4, 6 and 13.[25] There is an increased ratio of CD8 to CD4 T–lymphocytes and an increased peak level of Immunoglobulin A and G has also been reported.[26]

The spleen is about 50% enlarged by term relative to its size in the first trimester in a normal pregnancy and about 68% larger than its size in non–pregnant controls.[27,28]

Platelets

Pregnancy is a relatively hypercoagulable state with an increased platelet activity and consumption.[29] This combined with the hemodilution state leads to a mean platelet count that is slightly lower than that in the non–pregnant state.[30] An increased platelet production can be inferred from the increase in circulating platelets width and volume. There is also an increase in thromboxane A2 with an increased tendency for platelets aggregation in pregnancy.[31]

Gestational thrombocytopenia

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.[32,33]

Coagulation and fibrinolysis

Pregnancy is regarded as a procoagulant state. The coagulation cascade is in an activated state with about 20–200% increase in fibrinogen and factors II, VII, VIII, X and XII while the level of factors XI and XIII decrease.[34,35] Fibrinogen level increases from about 300mg/dl pre–pregnancy to as much as 600mg/dl at term, averaging about 450mg/dl.[36]

There is an increased Von Willie brand factor, increased fibrinolytic inhibitors such as plasminogen activator inhibitor type 1 and 2 (PAI–1 & 2) and thrombin cleavage products.[37,38] An increased resistance to activated protein C has been seen, while the anticoagulant protein S and fibrinolysis are reduced.

The free protein S antigen level is used for screening for protein S in pregnancy.[39]

Factors V, IX, antithrombin and protein C are relatively unchanged while thrombin level progressively increases throughout pregnancy.[34,40,41] The whole blood clotting time and bleeding time are unchanged but there is about 20% decrease in the prothrombin and plasma thromboplastin times.

D–Dimer and the erythrocyte sedimentation rate are elevated in pregnancy and this limits their diagnostic usefulness during pregnancy. The hitherto D–dimer concentration threshold of 0.50 mg/L cannot be used to rule out venous thromboembolism (VTE) in the third trimester.[42]

Overall, the coagulation profile change indicates a substantially increased production in relation to the physiological increase in plasma volume and tends to prevent postpartum hemorrhage due to thrombus formation in addition to the myometrial contraction.[43]

Adverse effects include an increased risk of venous thromboembolism (VTE) in pregnancy and the postpartum period with VTE occurring in 0.7/1000 women. It is about 3–4x higher in the puerperium than in the non–pregnant thereby making close monitoring and the institution of preventive measures as well as early treatment especially important in women with inherited thrombophilia.[44] Persistent hypercoagulation has been demonstrated during the first 3 weeks of delivery, however, pregnancy related hypercoagulable state should resolve by 6–8 weeks postpartum.[45]

Conclusion

Clinicians' familiarity with these pregnancy related physiological changes in the hematologic system will encourage an optimal management of pregnancies in addition to facilitating the use of simple explanatory terms to aid the parturient in understanding the course of pregnancy.

Acknowledgments

None.

Conflicts of Interest

None.

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