INTRODUCTION

The normal platelet count in adults ranges from 150,000 to 450,000/mm^3, with mean value of 237,000 and 266,000/mm^3 in male and female respectively ***(Buckley et al., 2000).***

Thrombocytopenia is defined as a platelet count less than 150,000/mm^3. Thrombocytopenia, or a low blood platelet count, is encountered in 7-8% of all pregnancies with normal platelet function; thrombocytopenia is rarely the cause of bleeding unless the count is less than 50,000/mm^3. Thrombocytopenia should always be confirmed by examination of a peripheral smear. It can be caused by decreased platelet production, increased destruction, sequestration, or a combination of these causes ***(Francisca & Jose, 2006)***.

Primary hemostasis begins when platelets adhere to the site of endothelial disruption, leading to platelet clumping. This is followed by platelet activation, which is characterized by release of granules containing von Willebrand factor, adenosine 5'-diphosphate (ADP), and serotonin. This serves to recruit other platelets into the growing platelet plug, which acts to stop the bleeding. Simultaneously, the synthesis of thromboxane A_2 and release of serotonin leads to vasoconstriction to reduce blood loss at the site of vascular injury ***(Bonnefoy et al., 2006).***

The secondary hemostatic phase begins when the coagulation pathway is activated on the surface of the activated platelets to form a fibrin meshwork, which serves to reinforce the platelet plug ***(Andre et al., 2000).***

Average platelet count in pregnancy is decreased (213,000/mm^3 vs 250,000/mm^3) change in platelet count is due to haemodilution, increased platelet consumption and increased platelet aggregation driven by increased levels of thromboxane A_2 ***(Kadir & Mclintock, 2011).***

Classification of thrombocytopenia in pregnancy is arbitrary and not necessarily clinically relevant:

- Mild thrombocytopenia is 100,000-150,000/mm^3.
- Moderate thrombocytopenia is 50,000-100,000/mm^3.
- Severe thrombocytopenia is <50,000/mm^3 ***(Magan & Martin, 1999).***

In normal pregnancies, 7.6% of women present with mild thrombocytopenia during pregnancy, and 65% of them will not be associated with any pathology. Any pregnant patient with a platelet count of less than 100,000/mm^3 should undergo further clinical and laboratory assessment ***(Kadir & Mclintock, 2011).***

Regional anesthesia is currently a standard of practice for labour pain relief in most obstetric units, and all efforts towards its safe use should be encouraged. However, the safety of

regional anesthesia in the presence of thrombocytopenia has been controversial, due to the risk of neuraxial hematoma and neurological sequelae. It is therefore of utmost importance that anesthetists continue to investigate the safety of regional or general anesthesia in this subset of patients.

AIM OF THE WORK

Is to enable practitioners to make informed evidence based decisions on the diagnosis, clinical management, and anesthetic management of thrombocytopenia with pregnancy.

Chapter (I)

HEMATOLOGICAL CHANGES WITH PREGNANCY

Normal pregnancy is characterized by profound changes in almost every system to accommodate the demands of the fetoplacental unit.

The most significant hematological changes are:

- Physiologic anemia.
- Neutrophilia.
- Mild thrombocytopenia.
- Increased procoagulant factors.
- Diminished fibrinolysis.

Plasma Volume

Plasma volume increases by 10 to 15% at 6 to 12 weeks of gestation then expands rapidly until 30 to 34 weeks, after which there is only a modest rise ***(Bernstein et al., 2001).***

The total gain at term averages 1100 to 1600 mL and results in a plasma volume of 4700 to 5200 mL, 30-50% above that found in non pregnant women and the red blood cell volume increases only by 20-30% ***(Whittaker & Lind, 1993).***

During pregnancy, plasma renin activity is typically increased and atrial natriuretic peptide levels are slightly reduced, suggesting that the increase in plasma volume represents underfilling due to systemic vasodilatation and the ensuing 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, 1989).***

Furthermore, the degree of sodium retention is physiologically regulated, as increasing sodium intake does not produce further volume expansion ***(Bernstein et al., 2001).***

Red Blood Cells

Red blood cell mass begins to increase at 8–10 weeks of gestation and steadily rises by 20–30% (250–450 mL) above nonpregnant levels by the end of pregnancy in women receiving iron supplementation, among women not on iron supplements, the red cell mass may only increase by 15–20%, erythrocyte life span is slightly decreased during normal pregnancy ***(Lurie and Mamet, 2000).***

Erythropoietin levels increase by 50% in normal pregnancies and vary according to the presence of pregnancy complications ***(Harstad et al., 1992).***

The increased plasma erythropoietin induces the rise in red cell mass, which partially supports the higher metabolic requirement for oxygen during pregnancy ***(Milman et al., 1997).***

Mean corpuscular volume decreases during pregnancy and averages 80– 84 fL in the third trimester (***Whittaker et al., 1996).***

Physiological anemia

A greater expansion of plasma volume relative to the increase in hemoglobin mass and erythrocyte volume is responsible for the modest fall in hemoglobin levels (i.e., physiological or dilutional anemia of Pregnancy) observed in healthy pregnant women. The greatest disproportion between the rates at which plasma and erythrocytes are added to the maternal circulation occurs during the late second to early third trimester. “Lowest hematocrit is typically measured at 28–36 weeks” ***(Whittaker, 1996).***

Nearer to term, hemoglobin concentration increases due to cessation of plasma expansion and continuing increase in hemoglobin mass. Conversely, the absence of physiologic anemia appears to be a risk factor for stillbirth ***(Stephansson et al., 2000).***

Determining a good definition of anemia in pregnant women is not straightforward, given the pregnancy-associated changes in plasma volume and red cell mass, normal differences in hemoglobin concentrations between women and men, ethnic variation between white and black women, and the frequent use of iron supplementation in pregnancy. The Centers for Disease Control and Prevention has defined anemia as hemoglobin levels of less than 11 g/dL (hematocrit less than 33%) in the first and third trimesters and less than 10.5 g/dL (hematocrit less than 32%) in the second trimester, women with hemoglobin values below these levels can be considered anemic and should undergo a standard evaluation ***(Bailit et al., 2007).***

Sixteen to twenty nine percent of pregnant women become anemic in the third trimester. Severe anemia with maternal hemoglobin below 6 g/dL has been associated with reduced amniotic fluid volume, fetal cerebral vasodilatation, and non reassuring fetal heart rate patterns ***(Carles et al., 2003).***

Increased risks of prematurity, spontaneous abortion, low birth weight, growth restriction, and fetal death have also been reported ***(Sifakis and Pharmakides, 2000)***

White Blood Cells

Pregnancy is associated with leukocytosis, primarily related to increased circulation of neutrophils. The neutrophil count begins to increase in the second month of pregnancy and plateaus in the second or third trimester, at which the total white blood cell counts ranges from 9,000 to 15,000 cells/uL, data from two series reported mean white blood cell counts of 10,000–16,000 cells/uL in laboring patients, with an upper level as high as 29,000 cells/uL ***(Molberg et al., 1994).***

In healthy women with normal pregnancies, there is no change in the absolute lymphocyte count and no significant changes in the relative numbers of T and B lymphocytes ***(Kuhnert et al., 1998).***

Coagulation

Coagulation proteins include:

i. Fibrinogen
ii. Prothrombin
iii. Tissue factor
iv. Calcium ions
v. Labile factor (Cofactor for activation of prothrombin to thrombin).

vii. Proconvertin.

viii. Antihemophilic factor.

ix. Christmas factor.

x. Stuart-Prower factor.

xi. Plasma thromboplastin antecedent.

xii. Hageman factor.

xiii. Fibrin stabilizing factor

Also:

- High-molecular-weight kininogen (Fitzgerald, Flaujeac, or William factor).
- Prekallikrein (Fletcher factor).

The proteins involved in the formation of the fibrin clot. Factors II, VII, IX, and X (as well as proteins C, S, and Z) are the zymogen forms of vitamin K-dependent serine proteases ***(Kato, 2002).***

Normal pregnancy is a prothrombotic state**.** The circulating levels of several coagulation factors change during pregnancy:

Protein S activity and free protein S antigen decrease due to estrogen induced increases in the complement 4b binding protein and possibly due to other mechanisms related to the hormonal changes of pregnancy. Resistance to activated protein

C increases in the second and third trimesters. Fibrinogen, factors II, VII, VIII, von Willebrand factor, and X increase by 20–200%. Factors V and IX remain unchanged and factor XI levels decrease by 30% (***Esmon, 1993).***

Activity of the fibrinolytic inhibitors, thrombin activatable fibrinolytic inhibitor (TAFI), PAI-1, and PAI-2 increase ***(Ku et al., 2003).***

Protein S

Protein S (PS) is a vitamin K-dependent glycoprotein with several anticoagulant functions. In the presence of PS, activated protein C inactivates factor Va and factor VIIIa, resulting in reduced thrombin generation. PS also serves as a cofactor for protein C enhancement of fibrinolysis. PS has a direct anticoagulant effect independent of its co-factor function with activated protein C. It prevents the binding of surface phospholipids with factors such as Va, Xa, and VIIIa, thereby decreasing the activation of the factors (***Dahlback, 1991).***

Pregnancy is associated with decreased levels of PS activity and free PS antigen ***(Paidas et al., 2004).***

The significance and degree of decrease in PS levels commonly seen in pregnancy has not been vigorously evaluated ***(Paidas et al., 2005).***

Factor X

Factor X, its activation to FXa and participation in the activation of prothrombin, is a central element in the generation of thrombin ***(Prager et al., 1995).***

Protein Z

Protein Z (PZ) is a 62 kDa vitamin K-dependent plasma protein that serves as a co-factor for a PZ-dependent protease inhibitor (ZPI) of Factor Xa ***(Kemkes and Matthes, 2001).***

It is a component in the regulation of factor Xa activity in addition to tissue factor pathway inhibitor ***(Broze, 2001).***

Activation Markers

Activation markers are often increased in pregnancy. Normal pregnancy is associated with both increased thrombin activity, increased soluble fibrin levels (9.2–13.4 nmol/L) and increased thrombin–antithrombin complexes (3.1–7.1 mcg/L), and fibrinolysis, as evidenced by increased levels of fibrin D-dimer (91–198 mcg/L***) (Bremme et al., 1992).***

Mechanism of Blood Coagulation:

There are two theories for blood coagulation. There are the classic and the modern theories

(A) The Classic Theory:

When blood vessel is injured and gets in contact with wounded tissues or with foreign surface, clotting reactions start. The damaged tissues and platelets release a substance called thrombokinase which converts the inactive prothrombin into active thrombin in the presence of calcium ions (Ca^{2+}). Thrombin converts soluble fibrinogen into insoluble fibrin. Fibrin forms a network having blood cells in meshes then forms a red jelly like mass called blood clots. The clot then retracts i.e. decreases in volume due to contraction of fibrin filaments and squeezes out clear yellow liquid called serum ***(Michiels, 2003).***

$$\text{Prothrombin} \xrightarrow{\text{Thrombokinase \& Ca +2}} \text{Thrombin}$$

$$\text{Fibrinogen (Soluble)} \xrightarrow{\text{Thrombin}} \text{Fibrin (Insoluble)}$$

(B) Modern (Enzymatic Cascade) Theory:

It is essentially an extension of the classical theory. More factors are needed in this theory. It is the most accepted theory of blood coagulation ***(Hoffman & Monroe, 2001).***

This theory suggests 4 stages for clot formation. These stages are:

I) Stage I:

It is the stage of formation of active thromboplastins which are prothrombin activators. There are two independent systems or pathways for formation of active thromboplastins. These systems are:

1. **Intrinsic or Platelet System (Pathway) of Thromboplastin Formation (4-8 Minutes):**

As shown in Figure 1 in contact with a foreign surface or injured blood vessels, platelets stick together and disintegrate to release certain phospholipids collectively known as platelet factor 3. This factor and factor XII, XI, IX, VIII, X and V interact to activate each other in certain order till activated factor V is obtained. Platelet factor 3 reacts with activated factor V to produce active platelet thromboplastins (prothrombin activators). Ca^{2+} is needed for these reactions except during activation of factor XII (the first step) which is activated by contact with the foreign surface ***(Kato, 2002).***

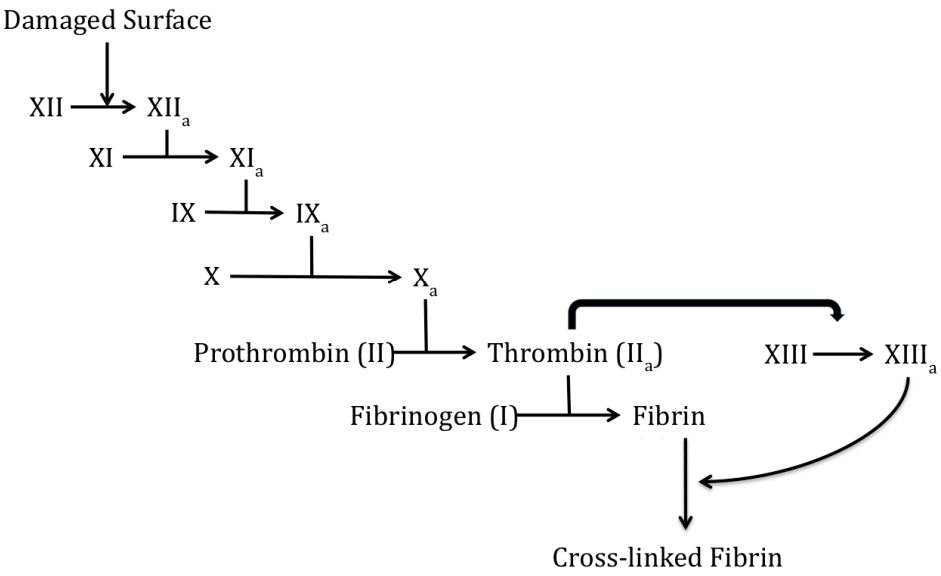

Figure (1): The intrinsic clotting pathway. Damaged surface of tissue triggers clotting factor XII (Hageman Factor), which proceeds through a series of reactions to result in afibrin clot.

2- Extrinsic or Tissue System (Pathway) of Thromboplastin Formation (12-20 Seconds):

Tissue damage releases tissue juice containing a tissue factor which activates factor VII. Activated factor VII activates factor X, then the remaining reactions are the same as for intrinsic pathway Figure 1.

So, both systems (intrinsic and extrinsic) activate factor X and when the activated factor X is formed, the coagulation mechanism proceeds rapidly and in a common pathway to get the two different types of active thromboplastin (platelet and tissue thromboplastin) ***(Kato, 2002).***