International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 10-12-2018; Accepted: 12-01-2019
www.medicalsciencejournal.com
Volume 5; Issue 2; February 2019; Page No. 28-36

Reactive thrombocytosis after caesarean section and normal vaginal delivery: Implications for maternal thromboembolism and its prevention

Dr. Suha Abduljaleel Wadi[1*], Dr. Ahmed Rifat Shakr[2], Dr. Farah Muayyed Gebriel Shammas Youisif[3]
[1-3] Senior Specialist in Obstetrics and Gynaecology, Al-Elwiya Maternity Teaching Hospital, Baghdad, Iraq

Abstract
Objective: To assess the duration and severity of reactive thrombocytosis after caesarean section and after normal vaginal delivery.
Design: A prospective study.
Setting: Al-Elwiya Maternity Teaching Hospital -Baghdad -Iraq.
Materials and Methods: Seventy pregnant women who were admitted for delivery at Al-Elwiaya Maternity Teaching Hospital were recruited into the study, the platelets count was measured at the time of first visit in the antenatal period. The second sample was taken just before normal vaginal delivery or caesarean section, followed by postnatal blood samples on days: 3, 8, 12, 16, 20 and 24 for the measurement of platelets count. Seventy pregnant women were recruited and forty completed the study, twenty of whom were delivered by normal vaginal delivery and twenty by caesarean section. This study compared the platelets counts within and between the two groups (normal vaginal deliveries group and caesarean sections group) to assess the severity and timing of reactive thrombocytosis.
Results: Antenatally: there were no statistically significant differences in platelets count measurement in the first antenatal visit and the pre delivery visit between the two groups. There was a slight fall in the pre-delivery platelets count in both groups compared with first visit platelets count but this fall was not significant. Postnatally: I. in the normal vaginal deliveries group; the platelets count continued to fall until the third postnatal day, then it rose, reaching peak values, compared with first visit and pre-delivery values at days 8 and 12 of the postnatal period which was statistically significant. The mean platelets count decreased gradually thereafter. II. In the caesarean sections group; the platelets count gradually increased, the rise started from the third post-operative day reaching a significantly high value, compared with first visit and pre-delivery values at day 8 of the postnatal period. The platelets count peaked at days 12 and 16 of the postnatal period. The platelets counts remained significantly higher than the first visit and pre-delivery values for 24 days after the caesarean section.

Keywords: postpartum. Thromboembolism, prevention, postpartum reactive thrombocytosis

1. Introduction

In vivo action of the clotting mechanism is balanced by limiting reactions that normally prevent clots from developing in uninjured blood vessels and maintain the blood in a fluid state. During pregnancy and early puerperium, this balance between coagulation and fibrinolysis is disturbed. The maintenance of normal haemostatic function requires the successful interaction of three main Components: Intact blood vessel wall, intact platelets function system, intact plasma coagulation and fibrinolytic components [1]. Platelets are central to normal haemostasis and to all thromboembolic disease [4]. Platelets are the smallest cellular elements present in human blood. They are granulated non-nucleated, 2-4 μm in diameter [1] with a concentration from 150,000-400,000/μL [4, 5].

While in their resting state, the circulating platelets maintain a discoid shape. Platelets are formed from the megakaryocytes. The megakaryocytes are polypoid cells which, in turn, were differentiated from the erythropoietic stem cell. The vast majority of megakaryocytes are present in bone marrow and a minority of them are present in the lung. Each mature megakaryocyte ultimately fragments to release approximately 7000 platelets into the blood [1, 4]. The platelets have a life span of about ten days. There are two humoral materials affecting the regulation of platelets production from the megakaryocytes: Meg-CSA (Megakaryocyte-colony-stimulating activity) which affects the proliferation of platelets and thrombopoietin (TPO). TPO: is a glycoprotein hormone produced by the liver and kidneys which regulates the production of platelets, it stimulates the production and differentiation of megakaryocytes, the bone marrow cells that bud off large numbers of platelets [4, 5]. The normally functioning platelet appears to be necessary for the first phase of haemostasis i.e. the formation of the initial plug (temporary haemostatic plug)[1, 4]. Within seconds from vasospasm response of the injured blood vessel wall, platelets stick to the exposed collagen of the damaged endothelium. This results in: platelets adhesion to the site of injury, platelets aggregation; the activated platelet will undergo a shape change, becoming flattened and release its contents. By the release of these substances, the platelets attract other platelets and a loose plug of aggregated platelets is formed, platelets surface clotting, with subsequent repair of the injured site, platelets consolidation, hence the formation of the white thrombus [1, 4, 5]. Pregnancy and early puerperium are hypercoagulable states as is obvious by the following changes: 1. Increase in platelets activity, this is measured by: A. Platelets count. B. Platelets aggregation and adhesion [6, 7]. A. Platelets count: indeed mild, non clinical, thrombocytopenia (platelets 100-150 × 10^6/L), is observed in up to 10% of all pregnancies. It is likely that this is largely a haemodilution effect that results from the maternal blood

volume expansion. The decrease in platelets count is accompanied by an increase in mean platelets volume and a notable change in the granule content. Many indices of platelets activation have been shown to correlate with gestational age, though some, such as platelets responsiveness to agonist stimulation, peak at weeks 30-36 and decline thereafter. Only few studies have assessed platelets function at multiple time points throughout pregnancy and so, information is limited regarding the absolute indices of platelets activation and their temporal relationship to gestational events. However, in general it can be concluded that platelets are hyperactivated from as early as gestational week 10, in the first trimester of pregnancy. B. Platelets aggregation and adhesion: during pregnancy and early puerperium, there is increased adhesive property of platelets. Various possibilities can be considered regarding the mechanism of activation of platelets in pregnancy. Some of these could be activation by immune complexes or by endothelial cell injury in the systemic circulation. The possibility of in vivo activation is supported by the finding that pregnant subjects also have a significantly higher number of circulating platelets aggregates when compared to non pregnant controls. These findings therefore suggest the possibility that pregnancy is associated with the activation of platelets, which leads to their in vivo clumping and aggregation. Recently, enhanced activity of the platelets thromboxane pathway has been shown to occur in normotensive and hypertensive pregnancies (thromboxane is a vasoconstrictor and pro-aggulatory substance) [6]. In the early puerperium, both, number and adhesiveness of platelets are increased, the net result is that total platelets activity is increased during this period [7]. It is the time of greatest danger to develop thromboembolic complications [13]. 2. Increase in plasma fibrinogen, it approaches double that of the non- pregnant level, of (2.5-4) to 6 gm/L during late pregnancy, labour and early puerperium [12]. 3. Increase of several other clotting factors and there is a depressed fibrinolytic activity. The result of these physiological changes will alter the usual balance between the pro-coagulants and anticoagulants in favour of the factors promoting blood clotting. Following the initial phase of a hypercoagulable state in the early puerperium, the coagulation and fibrinolytic systems gradually revert to normal and all tests are within the normal non-pregnant range six weeks after delivery [7, 13]. A normal platelets count ranges from 150,000 to 450,000 platelets per micro liter of blood. Thrombocytosis, or thrombocythemia, generally is defined as platelets persisting in number greater than 450,000 Platelets/ µL. It presents in two forms: Primary and Secondary Thrombocytosis. Primary (Essential) Thrombocytosis [16]: It is a myeloproliferative disorder that accounts for most cases in which platelets counts exceed l million platelets/ L [17]. Secondary (Reactive) Thrombocytosis [16]: In this type, platelets counts seldom exceed 800,000 Platelets/ µL [17]. The common causes of reactive thrombocytosis are: Puerperal reactive thrombocytosis: following delivery (vaginally or by caesarean section) [7], post-operative reactive thrombocytosis; which has been shown to occur after a variety of surgical and orthopedic operations, specially if the operation is associated with haemorrhage, anaemia, and infection and other causes include: malignant tumours, 1ron deficiency, hemorrhage, inflammatory diseases and connective tissue disorders [17]. Thrombocytosis usually is asymptomatic, but arterial and venous thromboses may develop [l6]. Increased platelets activity (number and adhesiveness) after delivery (spontaneous or operative) may be due to the following: 1. increased thromboxane biosynthesis [13]. Thromboxane A2 (TXA2) is a pro-aggregatory substance released by the platelets themselves, it has a powerful platelet-aggregatory properties, [5] it also causes vasoconstriction, hence the action of thromboxane lowers cAMP concentration and promotes platelets adhesion. Prostacyclin (PGI2) is an anti-aggregatory substance secreted by an intact blood vessel endothelium, it also causes vasodilatation, it raises the cAMP and prevents platelets adhesion [19]. In an intact vascular endothelium, there is a balance between actions of PGI2 and TXA2. If there is any imbalance between these two substances, the end results can be a predisposition to either bleeding or thrombosis [5]. Intact vascular endothelium does not attract platelets because of the high concentration of PGI2 in the intima. However sub-intimal tissues contain little PGI2 and immediately they are exposed to the circulation by a breach in the intima [4, 5]. In normal pregnancy, TXA2 biosynthesis is increased. The increase is mainly platelets derived and is consistent with increased platelets activation throughout normal pregnancy. In pregnancy also, under the influence of gestational progesterone, endothelial cells produce less NO and PGI2 and platelets produce more TXA2. This tilts the hemostatic balance towards platelets activation and thrombosis. Any tendency for platelets to aggregate is however balanced by the local production of high concentrations of PSG1 (it is a Protein Coding gene and it is a major product of the syncytiotrophoblast cells of the placenta), which prevents integrin mediated platelets aggregation[6]. When the vascular intima is damaged by hypertensive disease, surgery like caesarean section and local or blood born infection which may follow any delivery (spontaneous or operative), then platelets under the influence of thromboxane adhere and aggregate leading to the formation of atheromatous plaques [5, 6, 11, 15, 20]. Atheromatous plaques do not generate prostacyclin, which could explain platelets adhesion at the sites of intimal lesions [4, 5]. 2. Increased thrombopoietin (TOP) levels after surgery: TPO is the main regulator of thrombocytopoiesis (formation of platelets), it is a probable candidate to play a role in thrombocytosis that is frequently seen after surgery. Thus, increased TPO levels after surgery like caesarean section (possibly resulting from enhanced TPO production under the influence of IL-6 (interleukin-6) or other inflammatory cytokines), are involved in an enhanced thrombocytopoiesis, also these inflammatory cytokines exhibit significant colony stimulating activity (Meg-CSA) [5, 20]. These findings could explain why caesarean section, especially when there is extensive tissue damage is associated with more prominent thrombocytosis and is considered as the main risk factor in the genesis of thromboembolic disease in the postpartum period. In the early puerperium, total platelets activity is increased as part of generalized coagulopathy during this period, this may encourage thromboembolism at the time of early postpartum period [7, l3]. The following conditions are associated with a high incidence of post-operative thromboembolic complications: acute blood loss during the operation, chronic blood loss post-operatively, anemia, dehydration and infection. These factors are known to significantly increase the post-operative platelets count. As these factors are frequently associated with caesarean section, therefore women who had undergo caesarean section are at increased risk of thromboembolism in the post-operative

period [9, 17]. This study will demonstrate the presence, duration and severity of reactive thrombocytosis following uncomplicated caesarean section as well as after normal vaginal delivery in a systematic way. Thromboembolic disease can coexist in three forms: 1. Superficial thrombophlebitis (STP) 2. Deep vein thrombosis (DVT) 3. Pulmonary embolism (PE). Superficial thrombophlebitis (STP): Thrombosis is limited strictly to the superficial veins of the saphenous system (veins located near the surface of the skin of the lower limbs)[18]. Deep vein thrombosis (DVT); it is of two types: Distal leg DVT (Isolated calf vein thrombosis) in this type the clotting occurs in the venous plexuses (sinuses) within the soleus muscle of the calf, it's the most common primary site for DVT, the majority of thrombi form in the deep veins below the popliteal trifurcation (distal DVT) most likely to resolve spontaneously with no symptoms, this type poses a lower risk of pulmonary thromboembolism. Proximal leg DVT (pelvic vein thrombosis): Most patients present with symptoms when distal DVT extend to the popliteal and femoral veins and other proximal vein. There is a 50% chance that patients with untreated symptomatic proximal leg DVT will develop symptomatic PE. DVT can lead to complications such as postphlebitic syndrome, PE and death [22]. Pulmonary embolism (PE): Is a blockage of an artery in the lungs. The most common cause of the blockage is a blood clot [23]. A pulmonary embolus is most often caused by a blood clot that develops in a vein outside the lungs. The most common blood clot is one in a deep vein of the thigh or in the pelvis (hip area) (proximal DVT). The blood clot breaks off and travels to the lungs where it lodges [32]. Rudolf Virchow was the first to mention a triad of factors which are involved in the pathogenesis of VTE disease (Virchow's triad): Venous stasis; Hypercoagulable state and Local venous intimal injury. Venous stasis: the speed of venous flow along the lower limbs during pregnancy and delivery is decreased [2]. Venous flow in the legs is also much reduced in the post-operative period (following caesarean section), as a result of inactivity, poor muscle tone and loss of the pump action of the calf muscles [11]. Hypercoagulable state: the need for the relative physiological hypercoagulation in pregnancy and delivery is particularly apparent at the time of placental separation. However, a disadvantage to the potentially life-saving physiological adjustment of hypercoagulation, as pregnancy and the puerperium are associated with substantially increased risks of thromboembolic problems [24]. The causes of these physiological hypercoagulable state are probably hormonal and humoral changes in pregnancy and early puerperium. They include rise in the levels of Serum progesterone and estradiol [6], serum hydrocortisone, thrombopoietin (TPO) and thromboxane. Serum hydrocortisone: there is a physiological increase in serum hydrocortisone concentration during pregnancy reaching three times their non pregnant concentration at term. Hydrocortisone demonstrated antifibrinolytic properties at physiologic concentrations in pregnancy, suggesting that there may be a role for hydrocortisone in the prothrombotic tendency associated with pregnancy and early puerperium [25, 26]. Thrombopoietin (TPO): Increased TPO levels after surgery are involved in post-operative thrombocytosis [20]. Thromboxane (TXA2): Thromboxane biosynthesis is increased in pregnancy, the increase is mainly platelets derived. TXA2 is a potent stimulator of platelets aggregation [6]. Venous intimal injury: The normal vascular endothelial cell is not thrombogenic, and circulating blood platelets and clotting factors do not normally adhere to it to an appreciable extent. However when a blood vessel is damaged, the endothelium is disrupted and underlying layer of collagen is exposed. Collagen attracts platelets[1], within seconds, platelets stick to the exposed collagen of the damaged endothelium, a white thrombus, then forms initially by adherence of circulating platelets to areas of abnormal endothelium. This white clot is adherent and less likely to produce pulmonary embolism. This localized stasis triggers fibrin formation, a red thrombus can form around a white thrombus, initially by adherence of platelets but followed promptly by other processes of haemostasis so that the bulk of the thrombus forms a long tails consisting of a fibrin network in which red cells are enmeshed (red thrombus). These tails become detached easily and travel as emboli to the pulmonary arteries [4]. So the clot which shifts to enter the pulmonary arteries is not one which is established and giving evidence of its presence in the veins of the legs. It is an unstable one, newly formed or a new extension of the original. For this reason embolism can occur before there is any sign of venous thrombosis [8]. Blood vessel can be damaged by: Trauma, Inflammation, Hypertensive disease of pregnancy and malignancy. Trauma: by obstetrical complications like difficult forceps, ventouse delivery, operative surgery in the pelvis like (caesarean section) and haemorrhage; especially if it is associated with extensive tissue damage [3]. Inflammation: pelvic septic infection leads to pelvic septic thrombophlebitis (which usually occurs post-operatively and leads to vascular endothelial damage), resulting in thrombus formation with subsequent invasion by pelvic pathogens. This process may progress to embolization [27]. Blood vessel may be damaged by hypertensive disease of pregnancy. Pregnancy is a state of chronic intravascular coagulation, and preeclampsia is apparently the exaggerated state of this phenomenon, most probably due to enhanced platelets activity and the damage to the blood vessels by the disease process of hypertension [6]. So according to these findings, puerperal thromboembolic disease is often associated with anemia, pelvic infection, toxaemia of pregnancy, difficult delivery with extensive tissue damage [11, 15]. The overall incidence of VTE is approximately 1 in 1000 Maternities (Pregnancy and Puerperium), it can develop at any time during pregnancy, but the risk is highest during the first 6 weeks after birth, when it increases 20-fold [28]. Pregnancy is associated with a five- to 10-fold increased risk of VTE compared with nonpregnant women; however, during the postpartum period, this risk could increase to 20-80-fold [32]. The majority of deaths from venous thromboembolic disease occur in the puerperium and are more common after caesarean section than after vaginal delivery [14, 31]. There are many factors involved in the pathogenesis of puerperal thromboembolic events. One of these factors is the occurrence of reactive thrombocytosis. This study aims to demonstrate the presence, severity and the timing of reactive thrombocytosis in the postpartum period. This study intends to clarify the following: The association of reactive thrombocytosis following caesarean sections and uncomplicated normal vaginal deliveries with an increased incidence of thromboembolic complications. Comparison of platelets counts measurements within and between uncomplicated caesarean sections group and uncomplicated normal vaginal deliveries group. Women who have been delivered by caesarean sections are assessed prior

to surgery for their risk of developing thromboembolic complications. So, if they are at moderate or high risk, certain preventive measures from post-operative thromboembolic complications will be considered for them.

2. Patients and Methods

This study was done in Al-Elwiya Maternity Teaching Hospital, Baghdad-Iraq. In cooperation with the Department of Haematology in the same hospital, during the period from the 1st of June 2017 to the 1st of August 2018.

From the ethical point of view, the project of this work has been submitted to the local ethical committee which allowed to perform it and a consent form from each pregnant woman has been signed concerning the obtaining the blood samples.

2.1 Patients

Selection of patients: Seventy pregnant women were recruited into the study during the antenatal visits to the antenatal care unit in the mentioned hospital. They had an age-range of 19-39 years (mean 31 years). Primiparous as well as multiparous women were included. The patients chosen were those who were committed to deliver in the mentioned hospital and agreed to take part in the study after explaining its aims to them. They had to comply with the following criteria: Gestational age was confirmed by history, clinical examination and ultrasonography done at 8-14 weeks of gestation. They had regular antenatal care, no major pregnancy complications, no history of essential hypertension or diabetes mellitus, no history of any medical disorder affecting the platelets count. The following pregnant women were excluded from the study: women with medical disorders affecting the platelets count such as thrombocytopenia, women with history of malignant disease, genetic blood disorders like antithrombin III deficiency.

Questionnaire: A questionnaire was made for each woman and it was in two parts: antenatal part and postnatal part. Serial blood samples were taken for the measurement of platelets count in the antenatal and in the postnatal periods.

2.2 Antenatal blood samples

After a written consent was obtained, the first blood sample was taken at time of first visit to the antenatal clinic between 8-14 weeks of gestation. This first sample included also a request for full blood count and haemoglobin concentration. This sample was called first visit sample. The study was continued, and each pregnant woman had regular antenatal visits, the second blood sample was taken just before delivery (by normal vaginal delivery or caesarean section). This sample was called pre-delivery sample.

At the time of taking the second sample, women with:

- Protein uric hypertension or history of APH in her current pregnancy; should be excluded from the study. The study was continued, the pregnant women were admitted for delivery in Al-Elwiya hospital. Labour was managed according to the unit guidelines.

Each woman had an individual obstetric assessment to decide about the mode of delivery, whether vaginally or by caesarean section (elective or emergency).

2.3 Postnatal blood samples

Following delivery, general urine examination (GUE) and (Hb) concentration were done for each woman. Seventy pregnant women were recruited, thirty were excluded and forty women completed the study. Twenty of whom were delivered by a normal vaginal delivery and twenty of whom were delivered by an uncomplicated caesarean section (either elective or emergency). Those forty puerperal women who were delivered (either vaginally or by caesarean section) were chosen to complete the study and they had the following criteria: They had normal blood pressure, normal Hb%, GUE was normal with no sugar or protein or evidence of infection and they had no history of postpartum haemorrhage.

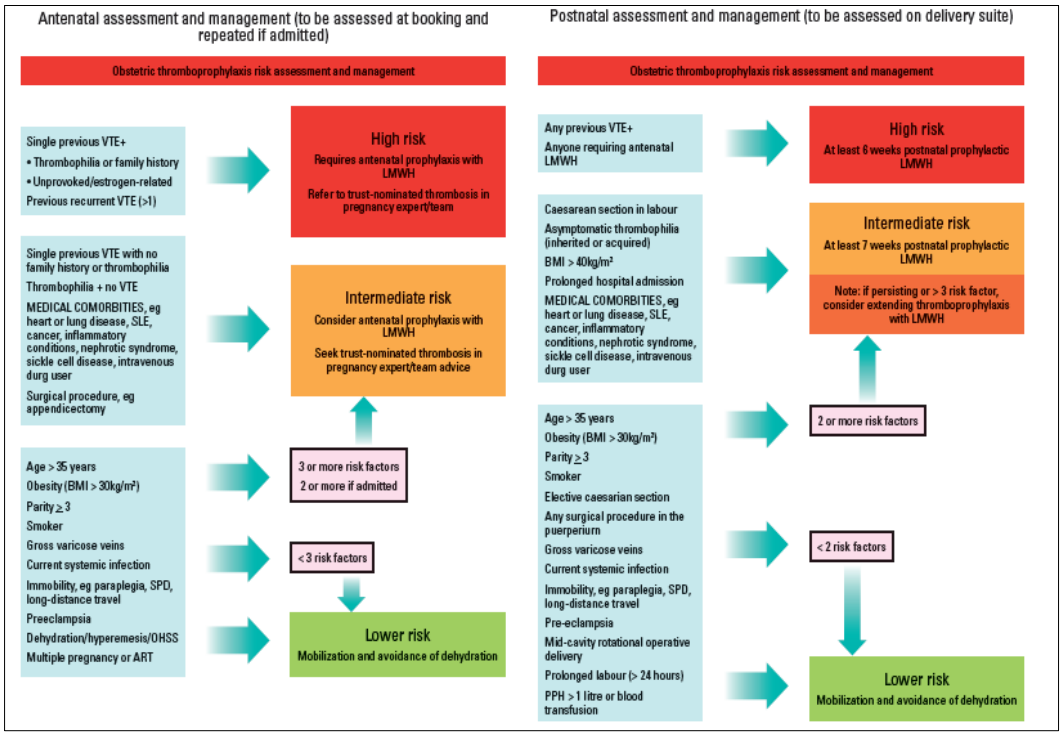

Fig 1: Obstetric thromboprophylaxis risk assessment and management

The following puerperal women were later excluded from the study: women who were delivered by instrumental delivery like forceps or ventouse, those who suffered from postpartum haemorrhage of an estimated blood loss more than 1000 ml, those with anaemia (Hb less or equal to 11g/dl). All women who were delivered by caesarean sections whether elective or emergency, were assessed prior to surgery for their risk of developing thromboembolic complications in the peripartum period. A risk factor scoring system was used to determine patients at low, moderate or high risk for developing perioperative thromboembolic disease.

After that it would seem reasonable to use some form of prophylactic measures for women at low, moderate or high risk of developing thromboembolic complications in the peripartum period (Figure 1) [15]. Serial of blood samples were taken in the postpartum period on days 3, 8, 12, 16, 20, and 24 following delivery for the measurement of platelets counts in both groups of women (caesarean sections group or normal vaginal deliveries group). These samples were called postnatal samples.

2.4 Methods of samples taking from the patients

- **Antenatal samples:** The first visit sample was taken while the patient was attending the antenatal care centre of Al-Elwiya Maternity Hospital. At that time, discussion with the pregnant woman about the purpose of this study and the importance of antenatal visits which is to maintain the mother and her fetus in the best possible state of health and to give the mother and her partner information and reassurance about pregnancy and labour. The second pre-delivery sample was taken just before labour.
- **Postnatal samples:** For the caesarean sections group, a platelets count was done on the third postnatal day after which the women were usually discharged home. Day 8 blood sample was taken at the time of removal of wound stitches. The rest of postnatal blood samples for the measurement of platelets count were taken during regular postnatal visits on days 3, 8, 12, 16, 20, and 24 made by the puerperal women to the hospital. Discussion with each woman was made about the importance of these postnatal visits, explaining to them that the aim of the study was to make them comfortable and to identify problems like thromboembolism whether actual or potential at an early stage and instituting appropriate management to minimize their complications. During these postnatal visits, history was taken and examination was done to determine that the mother is well and whether she had returned to her pre-pregnant state of health (this usually would take six weeks after delivery whether vaginal or abdominal by caesarean section). These postnatal visits were important to determine that the baby is well and if any contraceptives were required. Advice also could be given about postnatal physiotherapy and early ambulation. If there was difficulty in making the patient attending the hospital in the post-partum period, then home visits were done for some of the patients discussing with them that this test is part of their post-partum management and follow-up and is an indicator for any potential risk of thromboembolic disease.

2.5 Statistics

A random effects model was used to analyze the platelets counts and to allow for the correlation between the repeated measures of platelets counts. Using this model, this study compared the platelets counts within and between the two groups (normal vaginal deliveries group and caesarean sections group) to assess the severity and the timing of reactive thrombocytosis. The statistical significance of the difference between mean values was assessed by the student's (t) test probability value (p-value). Values of <0.05 were considered significant.

3. Results

Seventy pregnant women were recruited in the study and forty pregnant women completed the study. Those forty pregnant women were divided into two groups: Normal vaginal deliveries group (twenty patients) and Caesarean sections group (the other twenty).

Antenatal platelets counts (first visit and pre-delivery platelets counts) of all women in both groups were within the normal range (150- 400x 10^9 L.) (Table 1).

Table 1: The mean & range of platelets counts of first visit and pre delivery counts in the two groups.

Time of blood sample taking	Normal vaginal deliveries group (mean & range of platelets counts) (x10^9/L)	Caesarean sections group (mean & range of platelets counts) (xl0^9/L)	p-value (Caesarean sections counts compared with vaginal deliveries counts)
1st Visit	259.2 (157-393)	280.5 (145-385)	0.30
Pre-delivery	254.15 (138-384)	261.2 (136-370)	0.72
p-value (pre-delivery counts compared with 1st visit count)	0.81	0.32	

There were no statistically significant differences in the first visit and pre-delivery platelets counts between the two groups. There was a slight fall in the pre-delivery platelets count in both groups compared with 1st visit platelets count but this fall was not statistically significant (Table 1).

I. In the normal vaginal deliveries group: The platelets count continued to fall until the third postnatal day, this fall was not statistically significant. The platelets count increased rapidly after the third postnatal day, reaching peak values at eighth and twelfth days of the postnatal period. These peak values were statistically significant compared with first visit and pre-delivery values. The platelets count exceeded the upper limit of normal range (400x10^9/L) in seven women (35%). The mean platelets count decreased gradually after the twelfth postnatal day (Table 2).

Table 2: The mean & range of platelets counts in the normal vaginal deliveries group.

Time of blood sample taking	Normal vaginal deliveries group (The mean & range of platelets count x 10^9/L)	p-value compared with 1st visit platelets count	p-value compared with pre-delivery platelets count
Antenatal blood samples:			
1st Visit	259.2 (157-393)		
Pre-delivery	254.15 (138-384)		
Postnatal blood samples:			
Day3	250.2 (132-424)	0.2	0.3
Day8	373.55 (264-650)	0.000001 **	0.000001 **
Day 12	378.3 (277-522)	0.000002**	0.000003**
Day 16	327.4 (235-420)	0.0003*	0.0002*
Day 20	321.6 (234-392)	0.0004*	0.0003*
Day24	291.5 (176-393)	<0.05*	0.04*

* Significant difference
** Highly significant difference (peak values)

II. In the caesarean sections group: Reactive thrombocytosis began on the third post-operative day, but the rise was not significant. A significant high value of the platelets count was reached on the eighth post-operative day, compared with first visit and pre-delivery counts. Peak values of platelets counts were reached at twelfth and sixteenth post-operative days. These peak values were statistically significant higher levels, compared with the first visit count and pre-delivery count. The platelets counts remained statistically higher than the first and pre- delivery values for 24 days of the postnatal period. So the rise in platelets count was continued for a longer period than in the normal vaginal deliveries group.
The platelets count exceeded the normal range (400xl0^9/L) in sixteen women (80%) (Table 3, Figure 2).

Table 3: The mean & range of platelets counts in the caesarean sections group.

Time of blood sample taking	Normal vaginal deliveries group (The mean & range of platelets count x 10^9/L)	p-value compared with 1st visit platelets count	p-value compared with pre-delivery platelets count
Antenatal blood samples:			
1st Visit	280.5(145-385)		
Pre-delivery	261.2(136-370)		
Postnatal blood samples:			
Day 3	288.95(148-421)	0.6	0.1
Day8	462.55(269-635)	0.003*	0.002*
Day 12	537.15(282-910)	0.0000002**	0.0000007* *
Day 16	542.3(286-1107)	0.000003**	0.000001 **
Day20	475.95(264-690)	0.005*	0.001 *
Day 24	430.3(194-798)	0.002*	0.005*

* Significant difference
**Highly significant difference (peak values)

There was a greater rise in the platelets counts in the caesarean section group compared with the normal vaginal delivery group.
The platelets counts in women delivered with caesarean section were significantly higher than in women delivered normally from day 12 to day24 of the postnatal period (Table 4).

Table 4: The mean & range of platelets counts in the caesarean section group compared with normal vaginal delivery group.

Time of blood sample taking	Normal vaginal deliveries group (The mean & range of platelets count x 109/L)	Caesarean sections group (The mean & range of platelets count x 109/L)	p-value (Caesarean section s counts compared with vaginal delivery counts)
Antenatal blood samples:			
1st Visit	259.2(157-393)	280.5(145-385)	0.31
Pre-delivery	254.15(138-384)	261.2(136-370)	0.73
Postnatal blood samples:			
Day3	250.2(132-424)	288.95(148-421)	0.09
Day8	373.55(264-650)	462.55(269-635)	0.01
Day 12	378.3(277-522)	537.15(282-910)	0.001*
Day 16	327.4(235-420)	542.3(286-1107)	0.0001 *
Day20	321.6(234-392)	475.95(264-690)	0.00005*
Day24	291.5(176-393)	430.3(194-798)	0.005 *

* Significant difference

Significant thrombocytosis occurred at days 8 and 12 after normal vaginal deliveries and caesarean sections. In the normal vaginal deliveries group, the mean platelets count decreased gradually thereafter. In the caesarean sections group, however, thrombocytosis continued till the sixteenth day. It stayed at significantly higher level than in the normal vaginal deliveries group for 24 days after delivery. The platelets counts in women in the caesarean sections group

were significantly higher than in women in the normal vaginal deliveries group from day 12 to day 24 of the postnatal period (Table 5, Figure 2).

Table 5: The mean & range of platelets counts in the normal vaginal delivery group & caesarean section group (Summary of the results).

Time of blood sample taking	Normal vaginal delivery group (The mean & range of platelets counts (x109/L))	p-value (Vaginal deliveries counts compared with antenatal counts)	Caesarean sections group (The mean & range of platelets counts (x109/L))	p-value (Caesarean sections counts compared with vaginal deliveries counts)	p-value (Caesarean sections counts compared with antenatal counts)
Antenatal blood samples:				-	
1st visit	259.2(157-393)		280.5(145-385)		
Pre-delivery	254.15(138-384)		261.2(136-370)		
Postnatal blood samples:					
Day3	250.2(132-424)		288.95(148-421)		
Day5	373.55(264-650)	0.000001 *	462.55(269-635)		0.002*
Day 12	378.3(277-522)	0.000002*	537.15(282-910)	0.001**	0.0000007*
Day 16	327.4 (235-420)		542.3(286-11 07)	0.0001 **	0.000001 *
Day20	321.6(234-392)		475.95(264-690)	0.00005**	0.001 *
Day24	291.5(176-393)		430.3(194-798)	0.005**	0.005*

* Statistically significant high value compared with 1st visit & pre-delivery platelets counts.
** Statistically significant high value compared with normal vaginal delivery group.

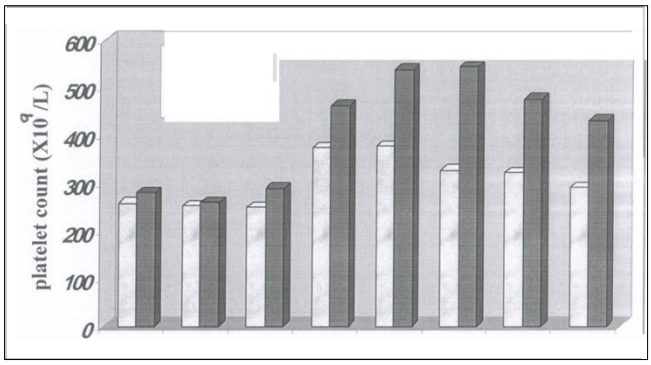

Fig 2: Mean of platelets counts in the Normal Vaginal Deliveries group (NVD) and Caesarean Sections group (C-S).

4. Discussion

Previous studies about this subject: Reactive (secondary) thrombocytosis (elevated platelets count > 450,000/µl and usually < 1,000,000/µl) [17]. P Saha, D Stott, R Atalla (2009) studied thrombotic changes during the postnatal period up to 6 weeks after delivery and assess the extent of risk period. In their study the mean platelets counts were low on pre delivery days and rose sharply to a peak on day 11, and continued to be elevated until 25 days after delivery. Women with complication such as anemia, preeclampsia, postpartum hemorrhage, infection, present or past history and family history of thrombophilia may attain an even higher hypercoagulable state. The time to peak values is between (7-15) days, usually at a time when the patients are discharged from hospital. They also demonstrated that fibrinogen concentration from a pre delivery mean of 5.4 G/L, fibrinogen levels peaked to 6.1 G/L at day 3 with a subsequent full appearing to stabilize after day 25 to levels around 3.4-3.6 G/L. All means values of fibrinogen from pre delivery to day 15 were significantly elevated, then gradually diminished. Their prospective study, showed that some women recruited antenatally in the vaginal delivery group required C-S. The coagulation parameters of women have been separately analysed in both groups (vaginal and cesarean), the result was that platelets counts and fibrinogen levels were significantly high till day 25 and 15 postpartum, respectively, after delivery (in C-S and VD groups). Reactive thrombocytosis that has been found to be a common occurrence during postpartum period is associated with an increased incidence of thrombosis. Increased fibrinogen is considered to contribute to hypercoagulable state as well. Also their study shows an exaggerated change towards hypercoagulability in cesarean sections group compared with vaginal deliveries group [7]. Susan Blackburn (2014) founded that fibrin degradation products increases after placental delivery. Fibrinolytic activity returns to normal ranges as early as 1 hour after delivery and fibrinolysis to non pregnant levels by 24 to 48 hours. Return to normal levels reflects removal of the fibrinolytic inhibitors produced by the placenta [13]. The results of this current study demonstrated that reactive thrombocytosis was more prominent in the caesarean sections group, it began earlier than normal vaginal deliveries group on the 3rd post-operative day, reaching a statistically significant high value on the 8th post-operative day, peaked at days 12 and 16 of the postnatal period. In the normal vaginal deliveries group, thrombocytosis was noted after the 3rd postnatal day, the platelets count peaked significantly at days 8 and 12 of the postnatal period and decreased gradually thereafter. However, in the caesarean sections group, the platelets counts remained at a significantly high level for 24 days following the operation. The platelets counts values were higher in the caesarean sections group than those in the normal vaginal deliveries group from the 3rd postnatal day up to 24 days following delivery. In addition, the platelets counts were significantly higher in the caesarean sections group than those in the normal vaginal deliveries group from day 12to day24 of the postnatal period.

The overall incidence of VTE is approximately 1 in 1000 Maternities (Pregnancy and Puerperium) [28] The puerperal period is the highest risk period for VTE [31]. Compared to pregnancy, the risk of VTE is even higher postpartum. [10, 31]. Risk for postpartum venous thromboembolism is highest during the first 3 weeks after delivery [9]. During the first 6 weeks postpartum, the risk is 20-80-fold higher and in the first week, the risk is 100-fold higher [10]. Women with obstetric complications are of highest risk for postpartum venous thromboembolism [9]. The risk is greater in women who undergo c-section and is about 3 in 1000. Women who had a planned c-section were twice as likely to develop a blood clot as those who delivered vaginally. The risk was

between 3-4 times higher for women who underwent an emergency (unplanned c-section) [29]. Cesarean section was associated with a four-fold greater risk for symptomatic postpartum venous thromboembolism (VTE) compared with vaginal delivery [30]. What is more important that the frequency of the thrombosis and the risk of fatal PE development are 10 times higher after cesarean delivery compared with normal vaginal deliveries in the postpartum period (as observed by autopsies) [31, 11]. Though, caesarean section was highlighted as the main risk factor for TE, anaemia, infection and postpartum haemorrhage, which are known to cause reactive thrombocytosis, were also additional risk factors [7, 9, 17]. On the basis of the results of our study and other studies, it has been shown that the time of development of thromboembolic complications coincides with the time of significant reactive thrombocytosis, which was more prominent in the caesarean sections group. So there must be an association between reactive thrombocytosis and the increased incidence of thromboembolic complications, especially after operative delivery. Clinical presentation of postpartum VTE perceived to be rare and does not reflect the true incidence of silent venous thrombosis and many episodes of thrombotic events occur after discharge from hospital. 70-80% of PE are clinically silent and the diagnosis been made after autopsy [7, 14]. Thrombosis and thromboembolism continue to be the leading cause of direct death in UK and the rate has not changed significantly, with a mortality rate of 1.01 per 100,000 maternities [21]. Of these deaths, 61.6 % deaths occurred during postpartum period. 61% of these postpartum deaths occurred after 7 days of delivery [7, 14], despite wide spread use of thromboprophylaxis. There is a strong suggestion that inadequate thromboprophylaxis is a major cause of this preventable condition. Pregnant women become more susceptible to VTE due to a variety of factors, including venous stasis and trauma associated to delivery. Also, hemostatic changes drive increases in some coagulation factors, while decreasing bleeding inhibitors, but for some reason these changes seem to be worse for women who deliver via C-S. "In the postpartum period specifically, women following C-S exhibit greater activation of coagulation than women following VD, as reflected by greater D-dimer levels," explained Dr. Blondon. D-dimer levels indicate that blood clots may be forming or breaking down in the body. "This outcome may be a result of the conditions leading to the C-S or to the procedure itself, similar to the increased VTE risk following non-obstetric surgery. Furthermore, physical activity is reduced following C-S compared with following VD, with delayed recovery of mobility occurring in the first two days following delivery. This could partly explain why the risk of puerperal thromboembolic event is four times greater following caesarean section than normal vaginal delivery [11].

5. Conclusion

Our study data indicate that puerperium is a high-risk period for the development of TED. A significant thrombocytosis occurred at day 8 and day 12 after NDV and C-S. In NVDs group, the mean platelet count reaches peak values at 8th and 12th days of the puerperium and decreased gradually after the 12th postnatal days. In the C-Ss groups thrombocytosis continued till the 16th day. It stayed at significantly higher level than in normal vaginal deliveries group for 24 days after delivery. Such reactive (postpartum) thrombocytosis is associated with a hypercoagulable state and increase risk of TED and it is more prominent in the C-S group compared to the VD group where it extended up to 24 days postpartum. C-S was highlighted as the main risk factor for thromboembolism in the postpartum period. This could partly explains why the risk of puerperal thromboembolic events is about four times greater following C-S than following NVD and these events are more common ten days or more after delivery.

6. Recommendation

TE which is accepted as a complication, is a preventable one. Our recommendation is to consider anticoagulant prophylaxis for at least 21-25 days after delivery. Perhaps this would reduce the incidence of postpartum venous thrombosis and hence maternal morbidity and mortality. It is the task of the gynaecologic surgeon to identify patients at risk for development of a perioperative VTE and to apply the safest, most effective, and most cost-efficient method of prophylaxis to decrease the risk of thrombus development.

7. Acknowledgment

DR. S.A. WADI Author thanks Mr. HAYDER SAAD MAHDI for his exerted efforts in this study.

8. References

1. Barrett K, Brooks H, Boitano S, Barman S. Cardiovascular Physiology: Blood as a Circulatary Fluid and the Dynamics of Blood and Lymph Flow. Ganong's Review OF Medical Physiology. 23th Edition. 2010; 32(4):523-524; 531-534.
2. Kristine Krafts MD. Coagulation, Hematopathology: Virchow's triad. Pathology Student, 2009.
3. Bahl R, Strachan BK, Murphy DJ. Operative Vaginal Delivery. RCOG; Green-top Guideline. 2011; 26:11,12.
4. Katzung BG, Masters SB, Trevor AJ. Drugs Used in Disorders of Coagulation. BASIC AND CLINICAL PHARMACOLOGY. 11th Edition. 2009; 34(4):587-588.
5. Boundless. Cardiovascular System: Blood; Hemostasis. Platelets. Boundless Anatomy and Physiology. Book Version. 2013; 29(16):4-5.
6. AL Obaidly M, Regan C, Lwaleed B, Moran M. A Role For Platelets in Normal Pregnancy. 2015; Ch 2, 3, 4, 5, 8.
7. Saha P, Stott D, Atalla R. Haemostatic changes in the Puerperium, 6 weeks postpartum (HIP Study)-implication for maternal thromboembolism. 2009; 1,4,5,6,7,10.
8. Ouellette DR, Mosenifar Z. Pulmonary Embolism: Practice Essentials, Background, Anatomy, 2017.
9. Tepper NK. Postpartum venous thromboembolism: incidence and risk factors, 2014.
10. James AH. Epidemiology of Pregnancy-associated thrombosis. Pregnancy-associated thrombosis. ASH Hematology. The Education Program, 2009.
11. Glenview IL. Cesarean Section Carries Increased Risk For Postpartum Venous Thromboembolism (VTE). 2016.
12. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Reference Values for Fibrinogen in Pregnancy. Reference Values During Pregnancy. Perinatology. com; Pregnancy and Laboratory Studies : a reference table for clinicians. Obstet Gynecol. 2009; 114(6):1326-31.
13. Susan Blackburn. Adaptation in Major Body Systems in the Pregnant Woman, Fetus, and Neonate. Haematologic

and Haemostatic Systems. Maternal, Fetal, & Neonatal Physiology. 2014; 2(8):224-225.
14. Morris JM, Algert CS, Roberts CL. Incidence and risk factors for pulmonary embolism in the Postpartum period. Jonral of Thrombosis and Haemostasis. PDF, 2010.
15. RCOG. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium. Green-top Guideline. 2015; 36(9):33.
16. Mayo Clinic. Essential thrombocythemia causes, 2017.
17. Liesveld J, James P, Reagan P. Reactive Thrombocytosis (Secondary Thrombocythemia). Blood Disorders. MSD MANUAL, 2016.
18. Nagarsheth KH. Superficial Thrombophlebitis, 2017.
19. Nelson RJ, Kriegsfeld LJ. Prostoglandins. An Introduction to Behavioral Endocrinology. Fifth Edition, 2016.
20. Simon J. Davidson. Inflammation and Acute Phase Proteins in Hemostasis. 2013; 2:15-16.
21. Payne J. Mortality rates and main causes of death. Maternal Mortality, 2016.
22. Moheimani F, Jackson DE. Venous Thromboembolism: Classification, Risk Factors, Diagnosis, and Management. 2011; 1:2.
23. Goldhaber SZ, Kline JA, Morris TA, Fedullo PF. Pulmonary embolus. Medline plus. Home- Medical Encyclopedia, 2017.
24. Thornton P, Douglas J. Coagulation in Pregnancy. Best Practice & Research-Clinical Obstetrics and Gynaecology. 2010; 24(2):339-352. 1, 2 of 14 PDF.
25. Jung C, Clin J. A longitudinal study of Plasma and Urinary Cortisol in Pregnancy and Postpartum. Endocrinology Met. 2011.
26. Coelho MCA, Santos CV, Neto LV, Gadelha MR. Adverse effects of glucocorticoids: Coagulopathy. 2015; 1 of 11 PDF.
27. Cafasso J. Medically reviewed by Janine Kelbach, RNC-OB. Septic Pelvic Vein Thrombophlebitis. Infections in Pregnancy, 2016.
28. Troy Brown RN. Guidelines Updated on Thromboembolic Disease in Pregnancy, 2015.
29. Norton A. C-Section Raises Risk of Blood Clots After Childbirth: Review, 2016.
30. Boyles S. C-Section: Independent Risk Factors for Postpartum VTE, 2016.
31. Ozsoy S, Akduman B, Karapirli M, Tugcu H. Death induced by pulmonary thromboembolism after caesarean section. Romanian Journal of Legal Medicine. 2012; 2(4):261.
32. Izadi M, Javad M. Advanced Biomedical Research. Do pregnant women have a higher risk for venous thromboembolism following air travel, 2015.