Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Physiology

Evaluation of Fibrinogen Level and Platelet Count among the Apparently Healthy Pregnant Women at 3rd Trimester

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DOI: 10.36347/sjams.2024.v12i03.014 | **Received:** 12.02.2024 | **Accepted:** 15.03.2024 | **Published:** 20.03.2024

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Abstract **Original Research Article**

Background: Different physiological changes affect normal coagulation and fibrinolytic system during pregnancy. Hemostatic abnormalities are often associated with various complications of pregnancy. ***Objectives:*** This study was aimed to evaluate the fibrinogen level and platelet count among pregnant women at third (3rd) trimester as compared to non-pregnant healthy women. ***Methods:*** This cross-sectional study was conducted at the Department of Physiology, Rajshahi Medical College (RMC), Rajshahi, Bangladesh, from July 2016 to June 2017 on 60 healthy women, out of them 30 were apparently healthy pregnant women of third trimester in the age group of 20-35 years (cases), and 30 were age matched non-pregnant healthy women (controls). Their detailed case history was taken and relevant clinical examinations were done. Plasma fibrinogen level and platelet count were measured using auto analyzer. Data were analyzed and compared by statistical test. ***Results:*** The mean±SD age of the pregnant women was 27.27±3.72 years and that was 27.13±4.01 years in non-pregnant healthy women. The maximum (40.0%) study women were in 26-30 years age group followed by 38.3% was in 20-25 years age group and 21.7% was in 31-35 years age group. Most of the cases were primipara [22(36.66%)] and majority women in the control group were multiparous [17(28.33%)]. Mean±SD body mass index (BMI), pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were nearly similar between the groups. Plasma fibrinogen level was significantly high ($p<0.001$) and platelet count was relatively low among women at 3rd trimester of pregnancy in comparison to non-pregnant healthy women. ***Conclusion:*** Plasma fibrinogen level is significantly high and platelet count is relatively low at 3rd trimester of pregnancy. Coagulation parameters are altered in a balanced way during normal 3rd trimester pregnancy.

Keywords: Coagulation Parameters, Plasma Fibrinogen Level, Platelet Count, Pregnancy, Third (3rd) Trimester.

1. INTRODUCTION

During pregnancy different physiological changes affect normal coagulation and fibrinolytic system [1]. Normal pregnancy is accompanied with hemostatic abnormalities results in a hypercoagulability state that are likely due to hormonal changes, which ultimately increase the risk of thromboembolism [2]. These changes are often associated with various complications of pregnancy [3]. Pregnancy, delivery and puerperium are well-established risk factors for venous thromboembolism especially in the 3rd trimester of pregnancy, with an incidence of 4-5 times higher compared to non-pregnant women [4]. Normally pregnancy is associated with significant changes in all aspects of the Virchow's classical triad: venous stasis, endothelial damage and a tendency to enhanced coagulation resulting in a shift of the hemostatic balance towards hypercoagulability [5, 6, 7]. This is one of the protective mechanisms involved in avoiding serious bleeding complications at delivery and puerperium [4]. Fibrinogen is a soluble plasma glycoprotein and a

positive acute phase protein, act as a blood coagulation factor, which produced in the liver by hepatocytes [8]. Normal activity of plasma fibrinogen usually indicates normal blood clotting ability [8]. Decreases fibrinogen activity may impair the body's ability to form a stable blood clot [8]. It is helpful in diagnosing disseminated intravascular coagulation (DIC) or hyper-fibrinolysis [9, 10]. It was observed that fibrinogen increased progressively throughout the pregnancy [4, 7]. However, another study found no significant difference in fibrinogen level between pregnant and non-pregnant women [11]. It is still obscure to what extent pregnancy affects the fibrinogen of pregnant women. Therefore, estimation of plasma fibrinogen level during pregnancy is helpful to early diagnosis of hemostatic failure, which also useful to guide the replacement therapy of decreased fibrinogen [12]. Circulating platelet plays an important role in hemostasis by forming hemostatic plug when blood vessels are injured [13]. A decrease in platelet count occurs in normal pregnancy although in most cases it remains within normal limits [14], and thrombocytopenia occurs in 6-10% of all pregnancies [15, 16]. Thrombocytopenia may occur commonly during all pregnancies, and usually may results from diverse etiologies [15]. Although during pregnancy maximum cases of thrombocytopenia are benign that has no effects on pregnancy outcomes but in few occasions, it may be complicated with significant morbidity and sometimes life threatening [16, 17]. Olorunshola KV *et al*., showed lower platelet count during labor and one-hour post-partum than non-pregnant control subjects [13]. A lower platelet count may occur in pregnancy for many reasons, ranging from the relatively benign, gestational thrombocytopenia to more sinister conditions, such as HELLP syndrome [6]. However, Durotoye IA *et al*., observed no significant difference in platelet count between pregnant and non-pregnant women [18]. The previous reports on coagulation parameters during pregnancy are inconsistent and not conclusive [2, 5-7, 9-11]. Moreover, most of the reference values established by laboratories about coagulation parameters are based on samples obtained from non-pregnant women. Therefore, this present study was aimed to evaluate the plasma fibrinogen level and platelet count during normal 3rd trimester pregnancy and compare the values with healthy non-pregnant women.

2. METHODOLOGY

This cross-sectional analytical study was carried out at the Department of Physiology, Rajshahi Medical College (RMC), Rajshahi, Bangladesh, from July 2016 to June 2017. A total of 60 women were enrolled as study population; of them 30 were apparently healthy pregnant women and rest 30 were age matched non-pregnant healthy women. The study protocol was approved by the Ethical Review Committee (ERC) of Rajshahi Medical College, Rajshahi, Bangladesh. Study subjects were selected by simple random sampling technique following selection criteria. Apparently healthy pregnant women in 3rd trimester (≥28 weeks of gestation) and age between 20-35 years (cases) and apparently healthy non-pregnant women of that age group (controls) were included. Women with known case of bleeding disorders, presence of hypertension/diabetes mellitus/varicose veins, women using anticoagulant/oral contraceptive and non-steroidal anti-inflammatory drugs (NSAIDs), known cases of pre-eclampsia/eclampsia, chronic kidney disease (CKD), chronic illness, fibrinogen deficiency disorder and subjects having severe malnutrition were excluded from this study.

Study Procedure

After selection of the study subjects (cases and controls), the aim/objectives, risk/benefits and procedure of this study were explained to each woman. Informed written consent was taken from each study women prior to enrollment. Thereafter a detailed case history was taken and relevant clinical examinations were performed. Their blood pressure (BP), pulse rate (beat/minute) height (in centimeter), weight (in kilogram) was measured and the body mass index (BMI) was calculated. The gestational age of the pregnant women was evaluated by the last menstrual period, bimanual examination and ultrasonogram (USG) report. Absence of pregnancy in control group was confirmed by urine for human chorionic gonadotrophin (hCG) test and ultrasonogram (USG) report.

Sample Collection and Estimation of Plasma Fibrinogen Level

With all aseptic precautions 5 ml venous blood was collected by venae-puncture and the blood sample was transferred immediately into an anti-coagulate containing tube. Then blood sample was centrifuged for 15 minutes at 3000 rpm in room temperature (22°C-24°C) and the plasma was separated. The separated plasma was transferred in a clean and dry test tube and was tested within 2-3 hours of blood collection. Sysmex Automated Blood Coagulation Analyzer CA-500 was used for the estimation of fibrinogen in the Biochemistry laboratory, Rajshahi Medical College, Rajshahi, Bangladesh.

Sample Collection and Estimation of Platelet Count

Venous blood (5 ml) without undue stasis was collected from a peripheral vein by venae-puncture under aseptic conditions. K2-EDTA was used as an anti-coagulant to prepare the anti-coagulant blood sample (the dose of K2-EDTA was 1.5 mg/ml blood). Anti-coagulant blood was mixed up. Auto-analyzer (cell-counter) was used for the estimation of platelet count.

Normal Values

According to the Biochemistry laboratory, Rajshahi Medical College, Rajshahi, Bangladesh; normal range of plasma fibrinogen level is 200-400 mg/dl and normal range of platelet count is 1.5 lac to 3 lac/cu mm of blood.

Statistical Analysis of Data

All collected data were cleaned, verified and compiled then entered into the computer to analyze. Data were analyzed by a windows-based software program Statistical Package for Social Sciences (SPSS) version 26. All qualitative data were expressed as mean with standard deviation (SD) and all quantitative data were expressed as frequency (n) with percentage (%). The test of significance was calculated by using unpaired student-t test and Chi-Square test as appropriate. Probability value (p) <0.05 was taken as the significant value.

3. RESULTS AND OBSERVATIONS

The current study was intended to investigate the plasma fibrinogen level and platelet count during normal 3rd trimester pregnancy and compare the values with healthy non-pregnant women. A total of 60 women were enrolled, of them 30 were pregnant women at 3rd trimester (cases) and rest 30 were age matched non-pregnant healthy women (controls). The mean±SD age of the cases was 27.27±3.72 years and that was 27.13±4.01 years in control group. Mean±SD body mass index (BMI), pulse rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 24.20±1.21 kg/m^2, 73.37±3.21 beats/minute, 123.00±9.15 mm of Hg and 78.67±8.60 mm of Hg in case group; which were 23.73±1.65 kg/m^2, 72.40±4.70 beats/minute, 119.00±9.95 mm of Hg and 75.30±13.92 mm of Hg respectively in control group, no significant difference (p>0.05 in all instances) was observed between the groups (Table- 1). Among the study population; highest number [24(40.0%)] was in 26-30 years age group followed by 23(38.3%) were in 20-25 years age group and 13(21.7%) subjects were in 31-35 years age group (Figure- 1).

Table- 1: Demographic profile in both groups of study population (N= 60)

Variables	Pregnant women [Cases (n= 30)] (mean±SD)	Non-pregnant women [Controls (n= 30)] (mean±SD)	p-value
Age (years)	27.27±3.72	27.13±4.01	0.889
Body Mass Index [BMI (kg/m^2)]	24.20±1.21	23.73±1.65	0.213
Pulse rate (beats/min)	73.37±3.21	72.40±4.70	0.230
Systolic blood pressure (mm of Hg)	123.00±9.15	119.00±9.95	0.111
Diastolic blood pressure (mm of Hg)	78.67±8.60	75.30±13.92	0.264

Data were expressed as mean±SD. The significance of difference was calculated using unpaired "t" test. N= total study population, n= number of study subjects in each group

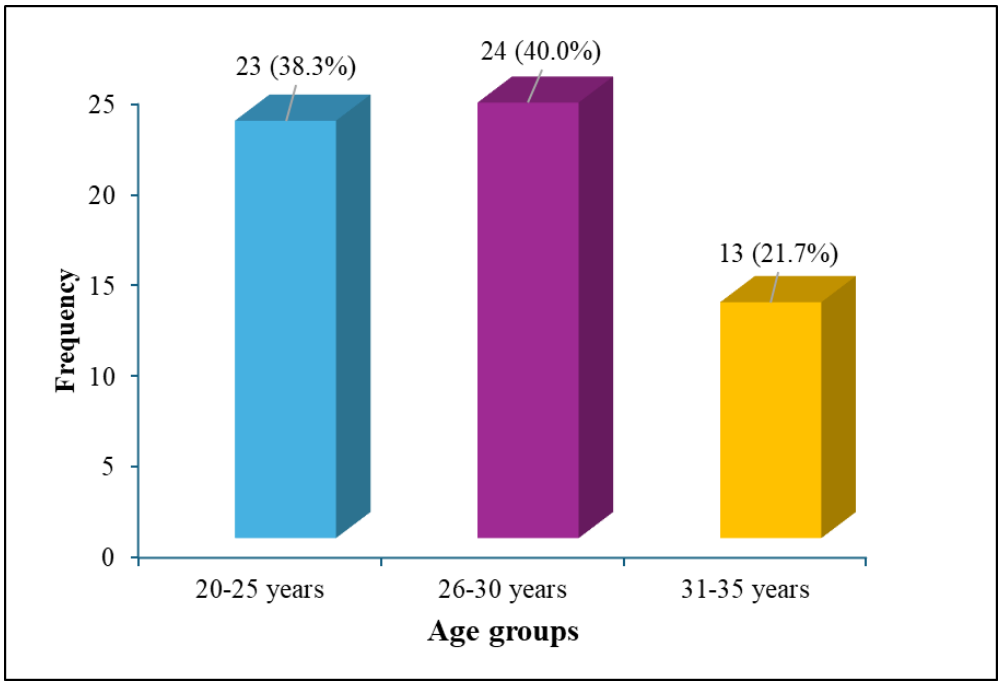

Figure-1: Age distribution of the study population (N= 60)

On the basis of Body Mass Index (BMI); majority [26(43.3%)] of the pregnant women (cases) had normal body weight and only 4(6.7%) had over weight. Among the non-pregnant women majority [28(46.7%)] had normal body weight and only 2(3.3%) had over weight (Table- 2).

Table- 2: Distribution of study population according to the body mass index (BMI) categories (N= 60)

Body mass index (BMI) categories	Pregnant women [Cases (n=30)]	Non-pregnant women [Controls (n=30)]	p-value
Normal body weight (18.5-24.9 kg/m^2)	26(86.7%)	28(93.3%)	0.389
Overweight (25-30 kg/m^2)	4(13.3%)	2(6.7%)	
Obese (>30 kg/m^2)	00	00	

Data were expressed as frequency (n) with percentage (%). The significance of difference was calculated using Chi-Square test. N= total study population, n= number of study subjects in each group

In this study among the cases, most of them were primipara [22(36.66%)] followed by multiparous [8(13.33%)], On the other hand in the control group, multiparous [17(28.33%)] was higher than nulliparous [13(21.66%)] (Table- 3).

Table- 3: Distribution of study population on the basis of their parity (N= 60)

Parity distribution	Pregnant women [Cases (n= 30)]	Non pregnant women [Controls (n= 30)]	Total (N=60)
Nulliparous	0(00%)	13(43.3%)	13(21.7%)
Primipara	22(73.3%)	0(00%)	22(36.7%)
Multipara	8(26.7%)	17(56.7%)	25(41.7%)
Total	30(50.0%)	30(50.0%)	60(100.0%)

Data were expressed as frequency (n) with percentage (%). N= total number of study population. n= number of study subjects in each group

It was observed that, mean±SD plasma fibrinogen level was significantly increased among pregnant women at 3rd trimester in comparison to non-pregnant healthy women (p<0.001). However, mean±SD platelet count was non-significantly decreased among women in 3rd trimester pregnancy compare to non-pregnant women (p= 0.078) (Table- 4).

Table- 4: Fibrinogen and platelet count in pregnant women and non-pregnant women (N= 60)

Variables	Pregnant women [Cases (n= 30)] (mean±SD)	Non-pregnant women [Controls (n= 30)] (mean±SD)	p-value
Fibrinogen level (mg/dl) Range (minimum-maximum)	328.07±79.76 (204-497.2)	265.70±56.71 (186-386)	<0.001
Platelet Count (lac/cu mm) Range (minimum-maximum)	2.33±0.50 (1.00-3.00)	2.54±0.40 (1.90-3.60)	0.078

Data were expressed as mean±SD. The significance of difference was calculated using unpaired "t" test. N= total number of study population. n=number of study subjects in each group

4. DISCUSSION

Pregnancy is a complicated physiological process and several physiological changes occur in different system of the body [4]. Normal pregnancy is associated with some hemostatic changes; with features of increasing in several clotting proteins including fibrinogen, decreasing in the concentration of natural anticoagulants and less fibrinolytic activity [11]. These changes result in a hypercoagulable state, which may increase the risk of thrombosis [4, 11]. This present study was aimed to measure fibrinogen and platelet count during normal 3rd trimester pregnancy and compare these values with the age-matched healthy non-pregnant women.

A total of 60 healthy women were enrolled, out of them 30 were apparently healthy pregnant women at 3rd trimester pregnancy (cases), and rest 30 were non-pregnant healthy women (controls), between the age ranged 20-35 years. The mean±SD age of the cases was 27.27±3.72 years and that was 27.13±4.01 years in control group. The maximum study women were in 3rd decade of life. Among the study population most of them were primipara followed by multiparous. The demographic parameters like- age, body mass index (BMI), pulse rate, and blood pressures (BP) were almost similar between the groups. It was documented that blood level of the coagulation factors are increase maximally at the 3rd trimester of pregnancy [19], which was the reason of choosing subjects at 3rd trimester of pregnancy in our study.

In this study it was observed that, plasma fibrinogen level was increased significantly (p<0.001) among pregnant women at 3rd trimester of pregnancy in comparison to non-pregnant women. This finding was

compatible with a couple of related studies [18, 20-22]. In this context, Amilo GI *et al*., observed progressive rise of fibrinogen from first to third (3rd) trimester pregnancy [8]. According to Hui C *et al*., during normal pregnancy, the hemostatic balance tilts in the direction of hypercoagulability which helps to reduce bleeding complications during delivery [23]. Estrogen and progesterone hormones are increase several folds during pregnancy [24]. Estrogen stimulates hepatocytes, thereby, increasing the production of virtually all coagulation factors [25]. Progesterone has been found to increase the decidual tissue factor and also increase the synthesis of plasminogen activator inhibitor type- 1 [24]. Elevation of the levels of certain coagulation factors and the fibrinolytic inhibitors occur in practically all healthy pregnant women [23]. Therefore, the elevated fibrinogen concentration observed during pregnancy might be due to increased protein synthesis by the hepatocytes [24]. Moreover, the increase might also be due to depressed fibrinolytic system during pregnancy [20]. Durotoye IA *et al*., documented that elevated level of fibrinogen was an important factor in pregnancy as it assists in preventing postpartum hemorrhage, with 5-10% of the total circulatory fibrinogen being deposited at the placental site [19].

In this current study, it was found that the platelet count was relatively lower among pregnant women at 3rd trimester in comparison to non-pregnant women. This finding was an agreement with similar previous studies [17, 18]. It was suggested that the occurrence of thrombocytopenia in labor or pre-partum might be related to the low grade "Physiologic DIC" that might accompany normal delivery [18]. Various physiological changes that occur during different system in pregnancy are responsible for the hypercoagulability state of pregnancy [4, 11, 18]. However, there is a balance between coagulation and fibrinolytic activities which limits the likelihood of actual thrombosis [18]. Furthermore, changes in the hemostatic system during pregnancy may be more marked in the uteroplacental than in the systemic circulation and thus the pregnant women may be relatively well protected against the thrombotic effects of a hypercoagulable state [18]. In addition, decrease platelet count can be explained by haemo-dilution and increased consumption of platelet during pregnancy [18]. Olorunshola KV *et al*., observed that gestational thrombocytopenia is more apparent during the 3rd trimester of pregnancy and normalizes within 2 to 12 days after delivery [13]. It was found that high prevalence of sticky platelets is responsible for pregnancy loss [26]. Therefore, low platelet count during pregnancy is physiological and may be a protective mechanism.

Although we have included only healthy women in our study, and it was possible to detect any minute change of hemostatic parameters due to pregnancy, our study was done on a small sample size. In this study only pregnant women at 3rd trimester were included, and therefore, trimester variation regarding to the changes of hemostatic parameters couldn't be studied. Moreover, we couldn't do the d-dimer assay due to lack of facilities, and therefore, we couldn't assess the fibrinolytic activity in pregnancy, which is essential to conclude the lower platelet count and other altered coagulation activities in pregnancy. In addition, prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time are also essential to assess the coagulation activity in pregnancy [4, 8, 11].

5. CONCLUSION

This study showed that, a physiological hypercoagulable state with an increased level of plasma fibrinogen and decreased platelet count occurs in normal 3rd trimester pregnancy. Pregnancy is a physiological process in women but it may be associated with certain risks to the health and life of both the mother and the child. Coagulation parameters are altered as well as balanced during normal 3rd trimester pregnancy. If this balance is disrupted, adverse outcome may occur. This study concluded that estimation of coagulation parameters plays an important role in the diagnosis of some diseases and the evaluation of risk factors related to coagulation disorder during pregnancy.

Conflict of Interest: All authors declared that they have no conflict of interest regarding this publication.

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