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Assessment of various parameters of haemostatic assay amongst pre-eclamptic and normotensive pregnancies-A comparative study

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Abstract

Background: Pregnancy is considered to be a state causing physiological changes/alterations in all the organ /systems of the body along with the coagulation system, converting it to be a hyper coagulable state and is normally linked with significant changes in all aspects of the classic triad of Virchow: endothelial damage, venous stasis and enhanced coagulation, to a significant extent that the procoagulant effect turns out to be dominant. Aggregation of platelets is increased with gestational age while the platelets count is decreased. Depending on the morphologic changes that occur during the activation of platelets, several platelet indices have been measured like platelet count (PC), mean platelet volume (MPV) and platelet distribution width (PDW).

Material and methods: In this study, a total of 108 pregnant women, 54 normotensive and 54 pre eclamptic was recruited from the obstetric department. Routine examination and investigations were done along with platelet count, platelet distribution width, mean platelet volume, serum LDH, serum fibrinogen and d-dimer and the observations were compared.

Results and conclusion: The development of the disease from normotensive to mild pre-eclampsia and its progression from mild to severe pre-eclampsia was also seen as well as the alterations in values haemostatic parameters in this progression was seen. Platelet count decreased in pre-eclampsia but had no significant difference when compared to normotensive women Mean platelet volume, Platelet distribution width, Serum fibrinogen, D-dimer showed significant difference (p value <0.01) in pre-eclamptic patients. With increasing severity of blood pressure in pregnant women changes were noted in the haemostatic parameters.

Keywords: pre-eclampsia, normotensive, Platelet count, Platelet distribution width, Mean platelet volume, Serum fibrinogen, D-Dimer

Introduction

The Utopian objective of maternal care quotes "Every pregnancy should culminate in a healthy mother and a healthy baby who is mentally and physically healthy".

Obstetrics is a preventive science, mostly achieved in appropriate ante-, intra- and post-partum period. A vital component of obstetrics is Antenatal care and assessment aiming at identifying pregnancies at risk for maternal as well as fetal complications. Adequate and timely maternal care gives the opportunity to create awareness, advice and counsel. It also helps to detect deviations from normality, select population at risk and abnormalities well in time. Since years, research has been going on to identify risk markers to detect high risk pregnancies as early as possible. Pregnancy is considered to be a state causing physiological changes/alterations in all the organ /systems of the body along with the coagulation system, converting it to be a hyper coagulable state and is normally linked with significant changes in all aspects of the classic triad of Virchow: endothelial damage, venous stasis and enhanced coagulation, to a significant extent that the procoagulant effect turns out to be dominant.[1]

This phenomenon is due to hormonal changes which protect the woman from fatal haemorrhage during parturition. There are significant data suggesting that oestradiol-induced triglyceride alteration is responsible for these changes in coagulation and fibrinolysis.[2] During normal pregnancy, both coagulation and fibrinolysis are augmented but remain balanced to maintain hemostasis. Evidence of activation includes increased concentrations of all clotting factors, except factors XI and XIII, and increased levels of fibrinogen complexes.

Aim To predict the development of pre-eclampsia and evaluate its severity.

Objectives

To compare the parameters of hemostatic assay like Platelet count, Mean platelet volume, Platelet Distribution Width, Serum Fibrinogen, Serum Lactate dehydrogenase (LDH) and D-dimer in normotensive pregnancies and pregnancy complicated with pre-eclampsia.

Material and methods

This study was conducted in the Department of Obstetrics and Gynaecology, Bhagat

Phool Singh Government Medical College for Women Khanpur Kalan, Sone pat, Haryana,

India.

In this study, a total of 108 pregnant women, 54 normotensive and 54 pre eclamptic was recruited from the obstetric department.

Inclusion criteria

- Age 20-30 years
- Gestational age 24 weeks to 40 weeks
- Pregnancy with singleton live foetus
- No previous history of hypertension

Exclusion criteria

- Those women with
- Hydatidiform Mole
- Multi foetal Pregnancy
- Intrauterine Foetal Demise
- Diabetes Mellitus(Gestational or Overt)
- Other Medical Conditions

On admission, a detailed history of present pregnancy, past medical and obstetric history was taken. General physical examination and obstetrical examination was done to ascertain fundal height, lie, presentation and foetal heart rate. Informed consent was taken from the subjects willing to participate in the study. At the time of admission, gestational age was calculated from the reliable menstrual history dates and the parameters of the earliest ultrasound.

Routine hematological investigations like Haemoglobin, total leucocyte count, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin concentration,

peripheral smear, blood grouping and Rhesus typing, Glucose challenge test (as per DIPSI (Diabetes In Pregnancy Societies of India) method:), Viral markers and Urinalysis (routine, microscopy, total protein and albumin (Using dipstick)) and other investigations as per requirement along with platelet count, platelet distribution width, mean platelet volume, serum LDH, serum fibrinogen and d-dimer was done. After this patient were allocated groups according to the ACOG 2002 criteria.[3]

Group A: Normotensive pregnant women with a period of gestation 24-40 weeks.

Group B: Pregnancy complicated with Pre-eclampsia

Pre-eclampsia (PE): Preeclampsia is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mm Hg or more with proteinuria after the 20th week in a previously normotensive and non proteinuric woman.

Mild pre-eclampsia (mPE): Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure normal blood pressure.

Proteinuria: 300 mg or more per 24-hour urine collection (or this amount extrapolated from a timed collection) or Protein/creatinine ratio of 0.3 mg/dL or more.

Severe preeclampsia (sPE): if systolic blood pressure (SBP) is ≥160mm Hg or diastolic blood pressure (DBP) is ≥110mm Hg or at least one of the following clinical symptoms occurred: renal insufficiency, pulmonary edema, micro vascular disease, thrombocytopenia, impaired liver function, and peripheral severe organ involvement (visual impairment and headache).[3]

The primary outcome of the study was to assess if there are alterations in the various parameters of haemostatic assay in pre-eclamptic women as compared to normotensive pregnancies and to determine if these parameters are useful in the prediction of the severity of pre-eclampsia.

Observations and results

This study was conducted for the duration of 12 months during year 2020-2021 and 108 patients who fulfilled the inclusion criteria were enrolled. Patients were further divided in two groups: Group A: 54 patients who were normotensive and in Group B: 54 patients who had pre-eclampsia. Out of the 54 patients of pre-eclampsia group 37 patients were found to have mild pre-eclampsia and 17 patients were having severe pre-eclampsia.

Table 1: correlation of patients between two groups according to parity

			Primigravida	Multigravida	Total	p-value
Groups	Group a	N	21	33	54	0.04
		%	38.9%	61.1%	100.0%	
	Group b	N	36	18	54	
		%	66.7%	33.3%	100.0%	
Total		N	57	51	108	
		%	52.8%	47.2%	100.0%	

- Table No 1 shows the distribution of patients according to parity.
- There are 21(38.9%) women in group A who are primigravida while the group B includes 36(66.7%) women who were primigravida.
- Multigravida consisted of 33(61.1%) women in group A and 18(33.3%) in group B.
- The p value came out to be 0.04 which is significant.
- Thus there is significant difference between the parity of the women in two groups i.e. pre-eclampsia is more common in primigravidae than multigravida.

Graph 1: correlation of patients between two groups according to parity.

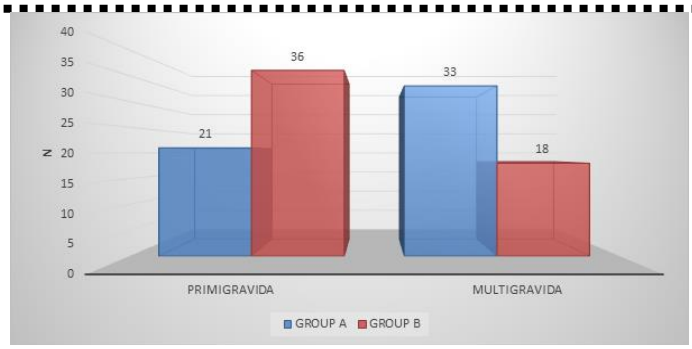

Table 2: correlation of haemostatic assay between two groups.

Haemoststic Parameters	Groups	N	Mean	Std. Deviation	P-value
Platelet count (lakh/cumm)	Group a	54	1.73	±0.62	0.88
	Group b	54	1.71	±0.73	
Mean platelet volume(fl)	Group a	54	8.89	±0.94	**0.001**
	Group b	54	12.34	±1.44	
Platelet distribution Width (%)	Group a	54	12.8	±1.23	**0.001**
	Group b	54	17.77	±1.24	
Serum ldh(u/l)	Group a	54	440.13	±165.176	**0.001**
	Group b	54	832.89	±145.274	
Serum fibrinogen(g/l)	Group a	54	4.1552	±1.33	**0.001**
	Group b	54	5.4426	±0.96	
D dimer(ng/ml)	Group a	54	405.37	±91.274	**0.001**
	Group b	54	1025.98	±589.765	

- Table no. 2 shows the correlation of haemostatic parameters in two groups.
- The mean platelet count was 1.73 lakh/cumm with standard deviation of 0.62 lakh/cumm in group A and 1.71 lakh/cumm with standard deviation of 0.73 lakh/cumm in group B. The p value was 0.88 which was statistically not significant.
- The average mean platelet volume was 8.89 ±0.94 fL. in group A and 12.32 fL. ±1.44 fL. in group B. The p value was 0.001 which was statistically significant.
- The platelet distribution width was 12.8±1.23% in group A and 17.77±1.24% in group B. The p value was 0.001 which is statistically significant.
- In group A, Serum LDH was 440.13±165.176 (U/L) while in group B it was 832.89±145.274 (U/L). The p value was 0.001 which was statistically significant.
- Serum fibrinogen in group A was 4.1552±1.33g/L and 5.4426±0.96g/L in group B. The p value was 0.001 which was statistically significant.
- In group A, D-Dimer came out to be 405.37±91.274 ng/ml and 1025.98±589.765 ng/ml in group B. The p value came out to be 0.001 which was statistically significant.

Graph 2: correlation of haemostatic assay between two groups

Graph 3:

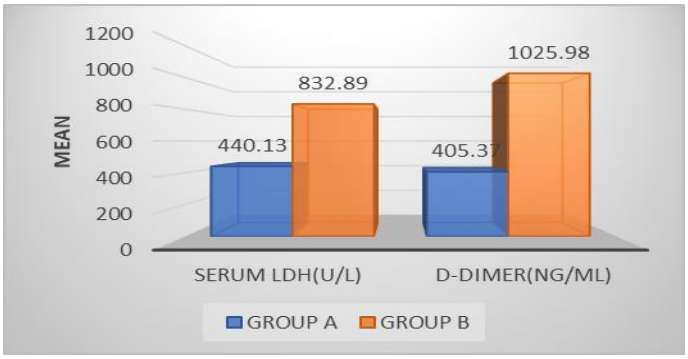

Table 3: distribution of women according to mode of delivery between two groups

Mode of delivery		Caesarean section		Vaginal delivery	Total	ᵡ2-value
Groups		Emergency	Elective			
Grou	N	11	6	37	54	

p a	%	11.1 %	20.5%	68.5%	100 %	0.19
Grou p b	N	18	7	29	54	
	%	33.3%	13.0%	53.7%	100 %	

- Table 3 shows the distribution according to the mode of delivery in two groups
- There were 11 (11.1%) patients in group A who had undergone emergency caesarean section and 6 (20.5%) patients who had to be taken for elective caesarean section.
- While 18(33.3%) patients were taken for emergency caesarean section and 7(13%) patients who had to be taken for elective caesarean section in group B.
- 37(68.5%) patients in group A and 29(53.7%) patients in group B delivered vaginally.
- The p value in this case came out to be 0.19 which is non-significant.
- Though the result was statistically non-significant the rate of caesarean section was more in pre-eclamptic group than in normotensive group and the most common indication being non-reassuring foetal testing.

Discussion

Pre-eclampsia (PE) is a pregnancy complication characterized by new-onset hypertension and signs of abnormal metabolism or organ dysfunction.[4] It can lead to severe or even fatal complications for both mother and the fetus. Hence, accurate and timely identification of the pregnant women who are at risk of developing PE is crucial as they require close prenatal monitoring and treatment to achieve better pregnancy outcomes.

The incidence of pre-eclampsia occurs more in nulliparous women as compared to multiparous women.[5] In the present study 38.9% and 66.7% were primigravida while 61.1% and 33.3% were multigravida in normotensive and pre-eclamptic groups respectively. The percentage of primigravida is more in cases with pre-eclampsia and the difference between the two groups was statistically significant. On the contrary, in a study conducted by Duan et al[6], there was no significant difference found between the parity of women who were studied. A similar study was conducted by MO been et al[7] in December 2019 and two groups were normotensive patients and patients with pre-eclampsia and according to their study there was no significant difference in the parity of women studied in both the groups.

Platelet count

In our study mean platelet count was 1.73 lakh/cumm with in normotensive women and 1.71 lakh/cumm in pre-eclamptic women. The p value was 0.88 which was statistically not significant. Although platelet count remained well above the lower limit (>1.5 lakh/cumm), it was noted that the platelet count in our study decreased. Our findings regarding platelet count are consistent with the study by Hongmei et al[8].They too did not report a significant difference between normal and mild preeclampsia and severe preeclampsia patients and suggested that decreased platelet count may be due to the gestation itself, rather than the pre-eclampsia. Thus, the platelet count, though an important parameter in pre-eclampsia, cannot be used as a definitive marker for the same. Our results are also consistent with the study conducted by Thalor et al[9] in which there was no significant difference between normotensive and preeclampsia patients.

Mean platelet volume

In our study the mean platelet volume was 8.89 ±0.94 fl in normotensive women and 12.32 fl ±1.44 fl in pre-eclamptic women. The p value was 0.001 which was statistically significant. The mean platelet volume gradually rises from normotensive pregnant women to

mild pre-eclamptic and severe pre-eclampsia in the present study which correlated with other studies. This increase in MPV in pre-eclampsia probably indicates hyper destruction of platelets due to shorter platelet half-life. Thus, it can be suggested that the MPV can be used as a valuable marker in the diagnosis and prediction of preeclampsia, as well as in the prognosis of the disease. Our results are comparable with the other studies shown in table no 4 and the results were found to be significant.

Table 4: Correlation of mean platelet volume in the present study with the other studies.

	Thalor et al[9]	Giles et al[10]	Present study
Normotensive	10.5±2.8 fl	8.7 fl	8.89 ±0.94 fl
Pre-eclampsia	11.8 ±1.7fl	9.9 fl	12.32 ±1.44 fl
p-value	**0.01**	**0.01**	**0.001**

Platelet distribution width

In the present study the platelet distribution width in normotensive women was 12.8±1.23% and 17.77±1.24% in pre-eclamptic women. The p value was 0.001 which is statistically significant.

There was an increase in PDW from normotensive pregnant women to pre-eclampsia in the present study which correlated with the study conducted by Tygart et al.[11] This probability reflects increased platelet turnover which would support the idea that platelet survival time is decreased resulting in increased destruction of platelets.

Our results are also consistent with the results of MO been et al[7] which showed a significant reduction in platelet distribution width between normotensive and pregnant women.

Our results are comparable with the other studies and showed significant results as shown in table no 5.

Table 5: Correlation of platelet distribution width in the present study with the other studies.

	Thalor et al[9]	Giles et al[10]	Present study
Normotensive	13.3%	12%	12.8%
Pre-eclampsia	16.1%	16%	17.77%
p-value	**<0.001**	**<0.001**	**0.001**

The increase in both the MPV and PDW, which are the markers of platelet activation, suggests an active turnover of platelet production in the bone marrow due to peripheral consumption.

The increase in values of both the MPV and PDW along with increased BP, further suggests that they are also elevated in severe pre-eclampsia with higher elevations of BP.

Serum ldh

In the present study Serum LDH in normotensive women was found to be 440.13±165.176(U/L) while in women with mild pre-eclampsia was 822.89±162.49(U/L) and in severe preeclampsia was 856.41 ± 98.17(U/L). The p value was 0.001 which was statistically significant.

This shows that higher LDH levels are found in patients with pre-eclampsia and it correlates well with increase in severity of disease. Our results are consistent with the results of other studies shown in table no 6.

Table 6: Correlation of LDH levels in the present study with the other studies.

	Duan et al[6]	Jaiswar et al[12]	Present study
Normotensive	152(U/L)	278.33± 119.25(U/L)	440.13±165.176(U/L)
Mild pre-	183.5(U/	400.45	822.89±162.49(

eclampsia	L)	1±45.21(U /L)	U/L)
Severe pre-eclampsia	200 (U/L)	646.95 401.64	856.41 ± 98.17(U/L)
p-value	**<0.001**	**<0.001**	**0.001**

D-dimer

In the present study D Dimer in normotensive women came out to be 405.37±91.274 ng/ml and 915.19±276.07 ng/ml in mild pre-eclamptic women and 1267.29± 943.59 ng/ml in severe pre-eclampsia. D-Dimer value significantly increases with severity of preeclampsia. Our results are comparable with the results shown in the table 6 which also correlated the level of D-Dimer increases with the severity of pre-eclampsia.

Table 6: Correlation of D-Dimer levels in the present study with the other studies.

	Duan et al[6]	Gulec et al[13]	Present study
Normotensive	1.05mg/l	1.12 ± 0.36 mg/l	405.37±91.274 ng/ml
Mild pre-eclampsia	3.05 (2.25-4.08) mg/l	2.06 ± 1.43mg/l	915.19±276.07 ng/ml
Severe pre-eclampsia	5.65 (2.29-7.71) mg/l	3.04 ± 1.87mg/l	1267.29± 943.59 ng/ml.ng/ml
p-value	**<0.001**	**<0.001**	**<0.001**

There is an activation of the immunologic, inflammatory, and coagulation system in different proportions in pre-eclampsia, which triggers the multi-systemic compromise which is inherent to the disease.

The circulating level of D-dimer is an indirect signal of coagulation and fibrinolysis cascade activation. D-dimer is increased physiologically during pregnancy and does so progressively from the first trimester but with preeclampsia its value further increases and can be correlated with its severity. This shows that D-Dimer can be used significantly in assessing the severity of pre-eclampsia.

Serum fibrinogen

In the present study, mean plasma fibrinogen level was higher in pre-eclamptic women than in normotensive female. This finding was in agreement with those of different researchers of different countries. Literature review suggested that raised plasma fibrinogen and FDP in preeclampsia were due to the exaggerated systemic inflammatory response and fibrinolytic activity.

In the present study Serum fibrinogen in normotensive women was 4.1552±1.33g/L and 5.4426±0.96g/L in women with pre-eclampsia. The p value was 0.001 which was statistically significant.

Mode of delivery

In the present study, 68.5% women who were normotensive and 53.7% women who were pre-eclamptic delivered vaginally while 31.5% normotensive women and 46.3% women with pre-eclampsia were taken for caesarean section. Although the result was not-significant but there were higher number of caesarean section in pre-eclamptic group as compared to normotensive group. A study conducted by Duan et al[6] in 2019 on pre-eclamptic and normotensive women, a significantly higher rate of caesarean section was seen in pre-eclamptic as compared to normotensive women.

Conclusion

There was a statistically significant difference in parity among normotensive and pre- eclamptic women 38.9% women in normotensive group and 66.7% in pre-

eclamptic group were primigravida whereas 61.1% and 33.3% were multigravida in normotensive and pre-eclamptic groups, respectively. Hence primigravidae have shown to have a higher incidence of pre-eclampsia. The difference in mean blood pressure and proteinuria were also found significant in the two groups. Haemostatic assays like MPV, PDW, Serum LDH, Serum fibrinogen and D-dimer showed significant difference in the values between the normotensive and pre- eclampsia patients. Furthermore, some normotensive women who had deranged values of these parameters progressed to pre-eclampsia (mild and severe) and some of the pre-eclamptic women having mild disease progressed to severe disease. Hence according to the present study, the haemostatic parameters could be used as markers for detection of pre-eclampsia, as well as markers for its severity. The rate of caesarean section was found higher in pre-eclamptic women as compared to normotensive women with the main indication being non-reassuring foetal testing.

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