Coagulation Profiles in PIH –a) To Determine Coagulation Index to Distinguish Severe Preeclampsia from Normal Pregnancy b) To Assess the Correlation of Coagulation Parameters in Normal Pregnancy & in Varying Grades of Preeclampsia

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Abstract: _Background_: *PIH is the most common medical complication of pregnancy & it affects 2-10 % of all pregnancies. Thrombocytopenia is the most common finding which ocurrs in 11% to 29% of patients with PIH.It contributes significantly to maternal and perinatal morbidity and mortality.* _Methodology & Results_: *The coagulation index in severe pre-eclampsia = 2.62 ± 2.64. Higher the coagulation index severe is the pre-eclampsia. Thus the coagulation index of more than 1 can be safely taken as cut off value to distinguish between normal pregnancy & severe pre-eclampsia. In severe pre-eclampsia, the platelet count = (105 ±63.65)x 10^3/mm ,PT = (19.6 ± 5.7) sec , APTT =(78.7± 22.7) sec& D dimer(0.48 ± 0.07)was noted.* _Conclusion_: *The degree of thrombocytopenia increases with severity of disease (lower the platelet count, greater are maternal and fetal morbidity and mortality. The coagulation parameters, especially Platelet count, aPTT and D- dimer can be safely used as an early indicator for theassessment of severity of PIH cases and can be used to monitor the progression of gestational hypertention to preeclampsia. So, it is concluded from this study that total platelet count with APTT & D dimer can be taken as an early and rapid procedure for screening preeclampsia cases at admission followed by serial platelet counts while monitoring coagulation indices.*

Keywords: Pre-eclampsia, PIH , D-dimer, Platelet count, Multivariate, PT, APTT

1. Introduction

Pregnancy Induced Hypertension (PIH) is definedas hypertension that occurs in pregnancy for the first time after 20 weeks of gestation and disappears following delivery.PIH is classified into (i) Gestational hypertension/mild PIH (ii) Pre-eclampsia iii) Eclampsia. It is one of the most common medical complications of pregnancy & it affects 2-10 % of all pregnancies. PIH is associated with 16 % of all maternal mortality and 20% of all perinatal mortality in India. Thrombocytopenia is the most common finding which ocurrs in 11% to 29% of patients with PIH.[1]

According to the criteria of the International Society of the Study of Hypertension in pregnancy, Pre-eclampsia is defined as the Blood pressure ≥ 140/90 mm Hg occurring after week 20 of gestation with proteinuria 300 ≥ mg / day or urinary protein/creatinine ratio =30 mg/mmol

Eclampsiais occurrenceof convulsion or coma with signs and symptoms of pre eclampsia.[2]

Based on the classification of American College of Obstetrician &Gynaecologist (ACOG),The pre-eclampsia can be categorized into Mild (140-159 /90-109 mm Hg) and severe (≥160 /110).[2,3,4]

The basic pathology of preeclampsia is endothelial dysfunction, poor placentation and vasospasm of vessels along with alteration of haematological profile of which thrombocytopenia is the most common.

It has been noted in other studies that the degree of thrombocytopenia increases with severity of disease (lower the platelet count, greater are maternal and fetal morbidity and mortality). The dreaded complications of PIH are DIC & HELLP syndrome.

HELLP syndrome is Hemolysis, Elevated liver enzyme, low platelet count.It occurs in 2–12% women with severe pre-eclampsia or eclampsia.[4]Early assessment of severity of PIH is necessary to prevent complications like HELLP syndrome and DIC. This has prompted me to undertake the present study

 The main Objective of this study is to
a) To determine Coagulation index to distinguish severe preeclampsia from normal pregnancy
b) To assess the correlation of coagulation parameters of normal pregnancy with varying grades of preeclampsia.
c) To assess the relationship between total platelet count and severity of preeclampsia.

2. Methodology & Results

This study was undertaken in a tertiary maternity & children hospital. A total of 100 pregnant females with pre-eclampsia constituted cases.

<u>Inclusion criteria</u>

- 100 pregnant females with pre-eclampsia in 3rd trimester, were taken as cases
- 100 normal pregnant females in 3rd trimester without any disease were taken as controls
- Controls were Age &parity matched with cases (controls chosen were of similar age groups & parity as compared to cases with only minor differences)

<u>The preeclamptic women were selected based on the following criteria:</u>

Pregnant women with blood pressure over the baseline ≥ 140 /90 mm of Hg with Proteinuria ≥ 0.3 gm / l or >1 + measured by dipstick. Cases were categorized into Mild (140-159 /90-109 mm Hg) and severe (≥160 /110) based upon classification of American College of Obstetrician &Gynaecologist (ACOG).[4]

a) <u>To determine Coagulation index</u>
1. **Calculation of Deltaplt** = [platelet counts before delivery] - [platelet counts in early gestation]) as an index of changes in platelet counts.
2. **Antithrombin (AT) level**
3. **Thrombin-antithrombin (TAT) complex,**
4. **Fibrin degradation products (FDP)& D-dimer,**
 Coagulation index was calculated using multivariate logistic regression analysis.

In this case we used four parameters & following formula was obtained:

$Y = (-0.019 \times AT$ activity$) + (0.067 \times TAT) + (0.067 \times D$-dimer$) + (-0.064 \times DeltaPlt) + 0.706.$[5]

b) In order to assess the correlation of coagulation parameters of normal pregnancy with varying grades of preeclampsia.
The various coagulation parameters were studied
1) Platelet count
2) PT & PTT
3) D dimer
4) PBS &retic count
5) Antithrombin III

If any of the cases shows features of hemolysis on PBS (fragmented RBCs , increased retic count) then only in such cases Indirect bilirubin, LDH, ALT, AST were done to rule out HELLP syndrome & DIC

<u>Exclusion criteria</u>

Cases with history of hypertension, diabetes mellitus, history, recurrent miscarriages, hepatic or renal disease, ITP were excluded from the study

<u>Statistical analysis of data</u>

All data were expressed as Mean +/ - SD. Statistical analysis was done using unpaired students t test. A level of p value <0.05 was used to indicate statistical significance in all analyses.

3. Results

Total no. of pre-eclampsia cases in 3rd trimester of pregnancy = 100
Mild pre-eclampsia= 65 cases
Severe pre-eclampsia= 35cases (HELLP syndrome= 04 cases & DIC= 08 cases)
Age & parity matched controls = 100

Table 1: To determine Coagulation index

Coagulation parameters	Normal pregnancy (100 cases)	Severe Preeclampsia (35 cases)	P value
Delta PLT = (PLT count before delivery – PLT count in early gestation)	$(4.8 \pm 1.2) \times 10^4$/microL	$(15.9 \pm 1.7) \times 10^4$ /microL	P = 0.03
Antithrombin (AT) level	(91.7 ± 18.8)%	(24.2 ± 17.8)%	P = 0.026
Thrombin-antithrombin (TAT) complex,	(11.8 ± 4.9) ng/ml	(19.7 ± 4.6) ng/ml	P = 0.06
D-dimer	(0.33 ± 0.08) microg/mL	(0.48 ± 0.07) microg/mL	P = 0.07

 Coagulation index was calculated using multivariate logistic regression analysis =
 $Y = (-0.019 \times AT$ activity$) + (0.067 \times TAT) + (0.067 \times D$-dimer$) + (-0.064 \times DeltaPlt) + 0.706.$[5]

The coagulation index in normal pregnant females= -0.59 ± 0.38

The coagulation index in severe pre-eclampsia = 2.62 ±2.64

Table 2: Comparative analysis of coagulation parameters in PIH

Coagulation parameters	Normal pregnancy Control (100)	Mild pre-eclampsia (65) cases	severe pre-eclampsia (35) cases
PLT Count x 10³/mm	$(192 \pm 41.9) \times 10^3$/mm	$(181 \pm 52) \times 10^3$/mm PLT is low in 25% of mild preeclampsia cases	$(105 \pm 63.65) \times 10^3$/mm PLT is low inDIC = 08 65% of severe D dimer++ preeclampsia casesHELLP synd.= 04 cases PBS = fragmented RBCs, Retic ++, Liver enzymes +++
PT (sec)	(10.9 ± 2.1) sec	(11.8 ± 3.2) sec PT is + in 15% of mild preeclampsia cases	(19.6 ± 5.7) sec PT is ++ in 40 % of severe preeclampsia cases

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APTT (sec)	(39.6 ± 1.2) sec	(51.6 ± 11.5) sec PTT is + in 35% of mild preeclampsia cases	(78.7± 22.7) sec PTT is ++ in 78 % of severe preeclampsia cases
D dimer (microg/dl)	(0.33 ± 0.08)	(0.38 ± 0.07) D dimer is + in 15% of mild preeclampsia cases	(0.48 ± 0.07) D dimer is ++ in 65 % of severe preeclampsia cases
Anti Thrombin (AT)	(96.3 ± 20.9)%	(51.0 ± 6.79)%	(24.11 ± 17.21)%,

4. Discussion

Coagulation index takes into account Antithrombin (AT) activity, thrombin-antithrombin (TAT) complex, fibrin degradation products (FDP) D-dimer, and DeltaPlt&it can be used to distinguish severe preeclampsia from normal pregnancy. (DeltaPlt = [platelet counts before delivery] - [platelet counts in early gestation]) was calculated as an index of changes in platelet counts. The coagulation index was calculated using multivariate logistic regression analysis& the formula obtained was   Y = (-**0.019 x AT activity) + (0.067 x TAT) + (0.067 x D-dimer) + (-0.064 x DeltaPlt) + 0.706**

According to this formula, coagulation indices in normal pregnant women and in patients with severe preeclampsia were- **0.59 ± 0.38** and **2.62 ± 2.64** respectively (**p < 0.002**). On follow up of cases it was found that the coagulation index if more than 1.3 then the pregnancies were terminated in cesarean sections. This fact was also confirmed in other studies.[6,7] This suggest that an excessive hypercoagulable state is associated with the termination of pregnancy resulting from the aggravation of preeclampsia.

So 2 important conclusions were drawn
1) Higher the coagulation index severe is the pre-eclampsia. Thus the coagulation index of more than 1 can be safely taken as a cutoff to distinguish between normal pregnancy & severe pre-eclampsia
2) If the coagulation index is > 1.3, then the pregnancies should be terminated by cesarean sectionas there is increased risk of fetal & maternal mortality due to hypercoagulability

Platelet count was low in 25% of mild pre-eclampsia ((**181 ±52)x 10^3/mm**& 65 % 0f severe pre-eclampsia(**105 ±63.65)x 10^3/mm**

The platelet count was significantly reduced in severe pre-eclampsia as compared to normal pregnancy. The platelet gradually reduced with the severity of pre-eclampsia. 8 cases showed features of DIC & 4 showed HELLP syndrome. These results very well correlated with other   studies.[8,9]

Table 3: Platelet count versus other coagulation parameters

PLT COUNT	PT	APTT	D dimer	Mild preeclampsia	Severe preeclampsia
>1.0x10^3/mm	08%	06%	06%	09%	01%
0.5 -1x10^3/mm	08%	19%	09%	05%	07%
<0.5x10^3/mm	06%	25%	22%	02%	14%

There was a strong correlation between APTT and marked thrombocytopenia & also with D dimer APTT is prolonged in more than 50 % of total cases and platelet count were reduced in 38 % of total cases. The platelet count in mild preeclampsia was not significantly lower than that in controls. It was (**181 ±52)x 10^3/mm** with P value > 0.05. It has been seen that the platelet count in severe preeclampsia and eclampsia was very significantly lower than that in normal healthy pregnant controls. The mean platelet count in severe preeclampsia(**105 ±63.65)x 10^3/mm.**

Thrombocytopenia is relatively frequently reported in severe preeclampsia withthe occurrence range of 30-50%.[10,11]The incidence ofthrombocytopenia in our study was 50%. This highincidence probably occurred because we included onlythe cases with severe preeclampsia or eclampsia, many of whom were admitted in the intensive care unit

Table 4: Comparison of platelets in various studies

Authors	Control (x10^3/cmm)	Mild pre-eclampsia (x10^3/cmm)	Severe Pre-eclampsia (x10^3/cmm)
Srivastava[12] (1995)	1.94	1.79	1.64
Jambhulkar et al [13](2001)	2.38	2.3	1.7
Joshi et al.[14] (2004)	2.2	2	1.4
J. Davies et al [2](2007)	2.57	2.3	1.77
Ellora Devi et al.[2](2012)	2.44	1.82	1.42
Present study	(192 ±41.9)	(181 ±52)	(105 ±63.65)

5. Conclusion

This present study along with few other studies showed that the degree of thrombocytopenia increases with severity of disease (lower the platelet count, greater are maternal and fetal morbidity and mortality. Early assessment of severity of PIH is necessary to prevent complications like HELLP syndrome and DIC.

The coagulation parameters, especially Platelet count,aPTT and D- dimer can be safely used as an early indicator for theassessment of severity of PIH cases and can be used to monitor the progression of gestational hypertention to preeclampsia.coagulation index can be used as an effective tool in assessment of severity0f PIH.Higher the coagulation index severe is the pre-eclampsia. **Coagulation index** of more than 1 can be safely taken as to distinguish between normal pregnancy & severe pre-eclampsia. If the coagulation index is > 1.3, then the pregnancy should be terminated by cesarean section as there is increased risk of fetal & maternal mortality due to hypercoagulability.

So, it is concluded from the study that total platelet count with APTT & D dimer can be taken as an early and rapid procedure for screening preeclampsia cases at admission

followed by serial platelet counts while monitoring coagulation indices.

References

[1] Nirmala T, Kumar Pradeep. Study of Coagulation profile in PIH. Indian Journal of Pathology and Oncology. 2015;2(1);1-6

[2] Girija P, Rama M. Assessment of Coagulation profile & its correlation with severity of preeclampsia in women of Odisha. A comparative cross sectional study.International Journal of Basic & Applied Physiology IJBAP, 2014: 3(1); 139-145

[3] World Health Organization. Make Every Mother and Child Count. World Health Report, 2005. Geneva, Switzerland: World Health Organization; 2005.

[4] American College of Obstetricians and Gynecologists Committee on Practice Bulletins Obstetrics. ACOG practice bulletin: diagnosis and management of pre-eclampsiaandeclampsia: number 33, January 2002. Obstetric Gynecol. 2002; 99:159 –167.

[5] Kobayashi T, Sumimoto K, Coagulation index to distinguish severe preeclampsia from normal pregnancy.SeminThrombHemost. 2002 Dec;28(6):495-500.

[6] Brown MA, Lindheimer MD, de Swiet M, van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy.* 2001; 20: IX-XIV.

[7] Cunningham F.G, Kenneth J. Leveno, StevenL. Bloom. Pregnancy induced hypertention. In: Kenneth J. Leveno, StevenL. William's Obstetrics, 23rd ed. New York ; 2010. p.706-56.

[8] Mary P, Jamie S. Laboratory findings in Hypertensive disorders of pregnancy.Journal of Indian medical association. vol 88,(12),794 - 798

[9] Mohapatra B, Pradhan U. Platelet estimation : its prognostic value in Pregnancy induced hypertension. Indian J PhysiolPharmacol 2007; 51(2)

[10] Solomon CG, Ellen W. Seely. Preeclampsia, searching for the cause. N Eng J Med 2004; 350–357.

[11] Baha M Sibai. Hypertension in pregnancy. In :S.G. Gabbe, J.R. Niebyl, J.L. Simpson editors. Obst.Normal and Problem of Pregnancies. 3rdEdn, New York : Churchill Livingstone; 1996; p. 935–991.

[12] Srivastava M; Bali S; Pandey J; Nayar V; Talib VH; Pregnancy induced hypertension and antithrombin III. Indian J PatholMicrobiol 1995 Jul;38(3):257-60.

[13] Jambhulkar S, Shrikhande A, Shrivastava R, Deshmukh K. Coagulation profile in pregnancy induced hypertension. Indian Journal of Hematology & blood transfusion, 2001Mar; 19(1):3-5.

[14] Joshi et al Platelet estimation: its prognostic value in pregnancy induced hypertension. Indian J PhysiolPharmacol 2004; 51 (2): 160–164