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C-REACTIVE PROTEIN AS A PREDICTOR OF PREGNANCY INDUCED HYPERTENSION

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Abstract:

Introduction: As the leading cause of perinatal death and morbidity, hypertension affects 10% of pregnancies and is the most common medical consequence of pregnancy.

Aims: The main objective of this study is to determine the level of C-reactive protein (CRP) in pregnancy induced hypertension (PIH) along with normal pregnant mothers and compare them and to seek a relationship between PIH and serum CRP as an inflammatory biomarker for the predictor of the disease.

Materials and method: It's an observational case control study. It's conducted in Medical College and hospital Kolkata, EDEN building, antenatal ward [GM WARD], outdoor department [OPD], labor room [LRO] from 18 months [March 2019 to August 2020]taking women with pre-eclampsia and normal pregnancy from 28weeks to 40weeks of gestation. Total of 280 samples have been included in this study.

Result: A difference in CRP levels was found in our study between the groups with hypertensive disorders of pregnancy and the healthy group. The serum CRP value in study group as Mean ± SD is 20.0700±8.2155,as compared to the control group of 6.3357±3.0993.

Conclusion: This implies the inflammatory response linked to the presence of dead placental cells in the uterine and placental bed, the immunological activation linked to endothelial dysfunction, and the inflammatory processes that cause vasospasm.

Keywords: Hypertension, Pregnancy, CRP, PIH

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

INTRODUCTION

As the primary cause of perinatal death and morbidity, hypertension is the most common medical complication of pregnancy, affecting 10% of pregnancies. [1] The fatal trifecta of hypertensive problems complicating pregnancy, bleeding, and infection, together account for a significant portion of maternal morbidity and death. Decades of extensive research have not resolved the mechanism by which pregnancy causes or exacerbates hypertension. Undoubtedly, among the most important and fascinating unresolved issues in obstetrics, hypertension diseases continue to exist. [2]

The hypertensive disorder of pregnancy are classified into chronic hypertension, gestational hypertension, preeclampsia-eclampsia,pre-eclampsia superimposed on chronic hypertension. Gestational hypertension is defined as blood pressure more than or equal to 140/90 mmHg after 20weeks of gestation ,documented on two occasions at least 4hours apart in a previously normotensive women, and there is no proteinuria and goes away after delivery and return to normal by twelve weeks post partum, and if it associates with new onset proteinuria, is known as preeclampsia, which affects 3% to 5% of pregnancies. Chronic hypertension in pregnancy is defined as blood pressure more than or equal to 140/90 before pregnancy or in recognition that many women seek medical care only once pregnant, before 20weeks of gestation.Women with chronic hypertension that manufactures evidences of preeclampsia, known as chronic hypertension with superimposed preeclampsia. Eclampsia is the occurrence of seizures in women with preeclampsia . [3]

The past several decades have seen a modest increase in the incidence. Preeclampsia has several complicated and poorly understood causes, including endothelial activation, inadequate placentation, and decreased organ perfusion from vasospasm. Preeclampsia happens with inadequate trophoblastic invasion in early pregnancy ,which leads to increased oxidative stress causing systemic endothelial dysfunction. This endothelial dysfunction causes abnormal immune activation causing release of inflammatory agents like CRP.Preeclampsia most frequently affects women who are nulliparous. On the other hand, preeclampsia risk is higher in multiparous pregnant women with a new partner than in nulliparous women. Pregnant women who have experienced preeclampsia in the past are more likely to experience it in subsequent pregnancies. An additional risk factor is a mother of the father who has a history of preeclampsia. [4]

MATERIAL AND METHODS

A. Study Design: An observational case control study.

B. Place of study: Medical College and hospital Kolkata, EDEN building, antenatal ward [GM WARD], outdoor department [OPD], labor room [LRO].

C. Period of study: 18 months [March 2019 to August 2020]

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

D. Sample Size/Design:

Sample size is 280 with 140 pregnant women in each group divided into case or study group and control group.

Total number of sample = 140+140=280

E. Inclusion Criteria:

1.CASES: Pregnant mothers in third trimester of gestation (28-40weeks), who were diagnosed as having pregnancy induced, hypertension on the basis of clinical history, examination, systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90mmHg.

2. CONTROLS: Apparently healthy normotensive pregnant women in third trimester (28-40 weeks).

3. Without hearing and memory impairment, who cooperated with follow-up and with complete clinical records and gave informed written consent.

4. without familial genetic diseases. And had not received irritant drug therapy in past.

F. Exclusion Criteria:

1. Pregnant women below 18 years
2. with multiple gestations
3. Who recently received blood transfusion therapy
4. with mental disease or physical deficiency.
5. with personal or family history of hypertension, diabetes, ischemic heart disease, any renal or cardiovascular disease, any neurological complications or any respiratory disease.
6. Patients in active labor.

METHOD OF ESTIMATION

After thorough history taking and clinical examination ,the procedure was explained to the subjects and informed consent was obtained. Blood pressure was measured by using manual BP meter and noted. Blood samples were collected into 3ml pro-coagulant tubes at the time of routine antenatal visits. Then the samples are sent to biochemistry department for estimation of serum CRP and to central laboratory for other required investigations.3ml of venous blood(fasting) was collected from antecubital vein under aseptic precautions in a plain test tube and was allowed to clot and then centrifuged for serum preparation . The test was done on the same day after serum preparation on ERBA XL 600 fully automated biochemistry analyzer . Estimation of CRP done by TURBIDIMETRIC IMMUNOASSAY method with the principles of Latex particles coated with specific anti- human CRP are aagglutinated,when mixed with samples containing CRP. The agglutination causes an absorbance change, dependent upon the CRP contents of the patients sample that can be quantified by comparison from a calibrator of known CRP concentration at a wave length of 340 nm.

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

RESULT

Table no 1: Distribution of mean in all parameter

		Number	Mean	SD	Minimum	Maximum	Median	p-value
POG(WKS)	**CASE**	140	36.2571	1.0274	34	39	36	0.0865
	CONTROL	140	36.4500	0.9239	35	39	36	
TLC (/mm^3)	**CASE**	140	9825.0357	477.3561	8900.0000	11050.0000	9800.0000	<0.0001
	CONTROL	140	9310.9286	321.1241	8800.0000	11000.0000	9265.0000	
PLATELET(Lakhs/mm^3)	**CASE**	140	1.7000	.3742	1.0000	2.5000	1.8000	<0.0001
	CONTROL	140	2.0521	.3533	1.1000	2.6000	2.1000	
SERUM URIC ACID (mg/dL)	**CASE**	140	6.7546	.9180	3.9800	8.9100	6.8400	<0.0001
	CONTROL	140	4.2971	1.2346	2.0400	6.9800	4.1200	
SERUM CRP(mg/L)	**CASE**	140	20.0700	8.2155	2.8000	36.4000	20.2000	<0.0001
	CONTROL	140	6.3357	3.0993	1.2000	14.9000	6.0000	
SBP(mmHg)	CASE	140	156.8286	9.2635	140.0000	180.0000	156.0000	<0.0001
	CONTROL	140	115.9286	6.2440	100.0000	128.0000	118.0000	
DBP(mmHg)	CASE	140	99.5429	7.2977	90.0000	120.0000	100.0000	<0.0001
	CONTROL	140	78.8000	4.4741	68.0000	86.0000	80.0000	

Table no 2: Pearson Correlation between CRP and clinical parameters in the PIH group

	CRP	
	R	P-value
MATERNAL AGE	-.058	0.4960
PERIOD OF GESTATION	.0058	0.9457
TOTAL LEUCOCYTE COUNT	0.107	0.208
PLATELET COUNT	0.066	0.439
SERUM SODIUM	-.035	0.684
SERUM POTASSIUM	-0.054	0.524
SERUM URIC ACID	0.065	0.448

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

SYSTOLIC BLOOD PRESSURE	0.3942	<0.00001
DIASTOLIC BLOOD PRESSURE	0.3579	0.000014

Table no 3: Validity of CRP as predictor of PIH

CUT OFF VALUE	CASE	CONTROL	TOTAL
CRP >13.8	108	2	110
CRP ≤13.8	32	138	170
TOTAL	140	140	280

From ROC curve analysis cut off value of CRP was determined as 13.8.

Table no 4: Relationship between CRP levels in the healthy group

Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
77.0	98.6	98.2	81.2	87.8

AUC (95% CI) = 0.933 (0.903_0.964); P- value <0.0001

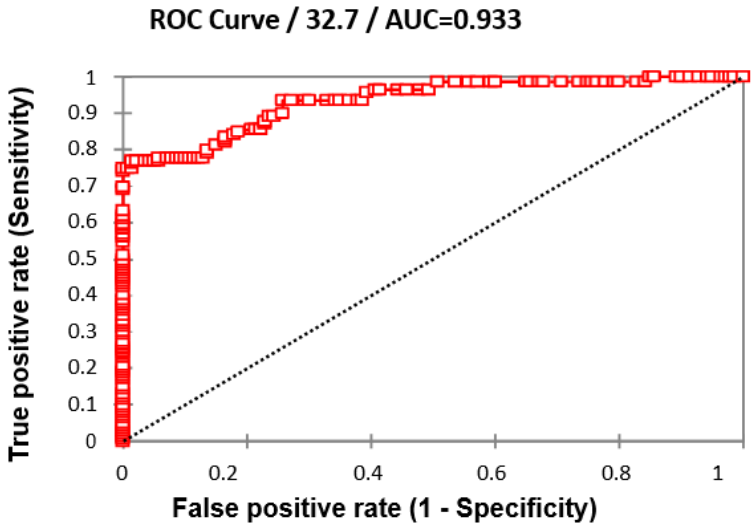
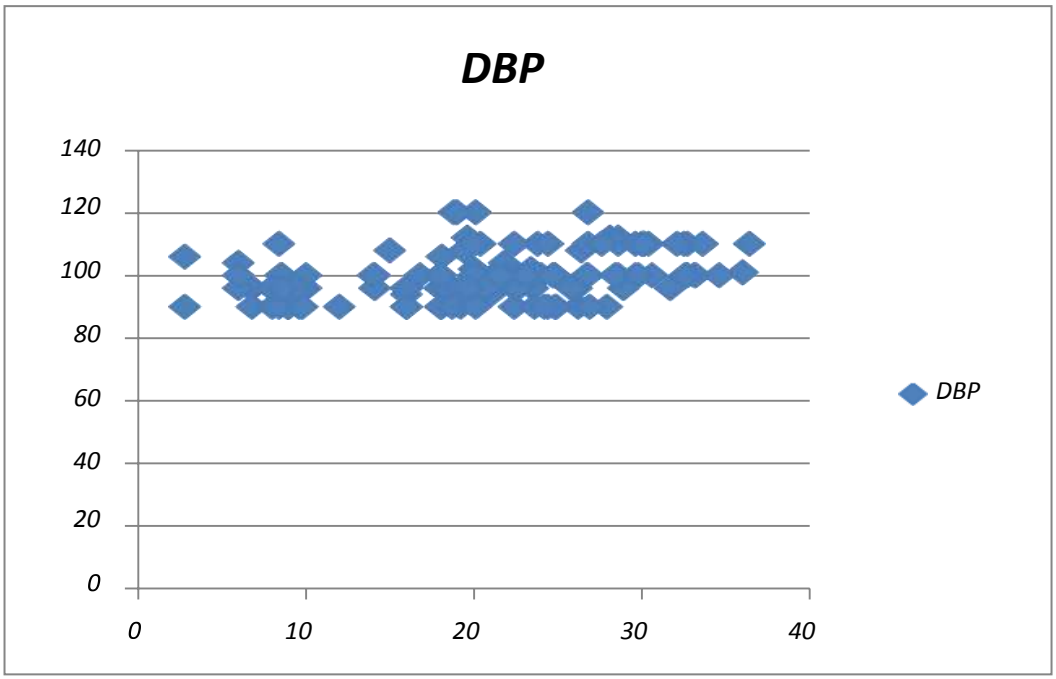


Table no 6: Pearson Correlation between CRP and clinical parameters in the PIH group

Clinical Parameters	CRP	
	R	P- value
Maternal Age	-.058	0.4960
Period of Gestation	.0058	0.9457
Total Leucocyte Count	0.107	0.208
Platelet Count	0.066	0.439
Serum Sodium	-.035	0.684
Serum Potassium	-0.054	0.524
Serum Uric Acid	0.065	0.448

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

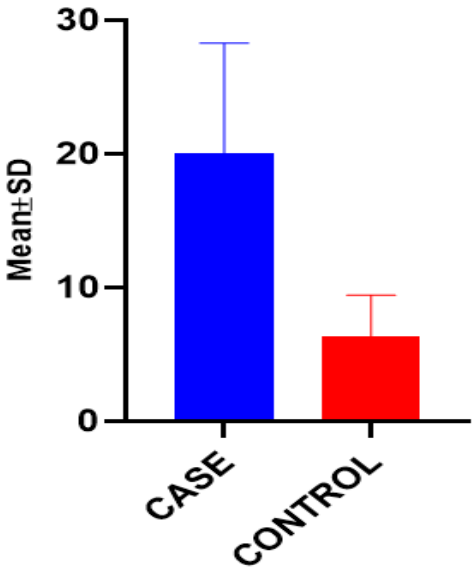
Systolic Blood Pressure	0.3942	<0.00001
Diastolic Blood Pressure	0.3579	0.000014



Correlation between serum CRP and diastolic BP

Correlation between serum CRP and systolic BP

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024



Distribution of mean CRP in Cases and Control group

The patients in the CASE Group had a mean POG (weeks) of 36.2571±1.0274, with a mean ± SD. With respect to weeks, the mean POG (mean ± SD) of the patients in the CONTROL Group was 36.4500± 0.9239. Not statistically significant (p=0.0865) was the difference in mean POG (weeks) between the two groups. The mean TLC (/mm3) (mean ± SD) of the patients in the CASE Group was 9825.0357± 477.3561. The mean TLC (/mm3) (mean ± SD) of the patients in the CONTROL Group was 9310.9286± 321.1241. The mean TLC (/mm3) differed between the two groups in a statistically significant way (p<0.0001).This indicates that the case group has more TLC than the control group. The mean PLATELET COUNT (lakhs/mm3) of the patients in the CASE Group was 1.7000±.3742. The mean PLATELET COUNT (lakhs/mm3) (mean±SD) of the patients in the CONTROL Group was 2.0521±.3533. The mean PLATELET (in lakhs/mm3) differed statistically significantly (p<0.0001) between the two groups. This indicates that the case group's platelet count is lower than that of the control group. The mean serum URIC ACID (mg/dl) (mean ± SD) of the patients in the CASE Group was 6.7546±.9180. The mean serum URIC ACID (mg/dl) (mean ± SD) of the patients in the CONTROL Group was 4.2971± 1.2346. In CASE Group, the mean SBP (mmHg) (mean ± SD) of patients was 156.8286± 9.2635. In Control Group, the mean SBP (mmHg) (mean ± SD) of patients was 115.9286± 6.2440. Difference of mean SBP (mmHg) in between both Group was statistically significant (p<0.0001). This means there is high level of systolic BP in case group as compared to control group. In CASE Group, the mean DBP (mmHg) (mean ± SD) of patients was 99.5429± 7.2977. In CONTROL Group, the mean DBP (mmHg) (mean ± SD) of patients was 78.8000± 4.4741. Difference of mean DBP (mmHg) in between both Group was statistically significant (p<0.0001).This means there is high level of diastolic BP in case group as compared to control group.

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

The mean serum URIC ACID (mg/dl) difference between the two groups was p<0.0001, indicating statistical significance. This indicates that the case group's uric acid levels are higher than those of the control group. A statistically non-significant association between CRP and maternal age, gestational age, total leucocyte count, platelet count, serum sodium, serum potassium, and serum uric acid was found by using the Pearson correlation test (p>0.05).However, CRP, SBP, and DBP have a statistically significant positive connection. (p<0.05). With a rise in CRP, there was a considerable elevation in SBP and DBP levels.

In CASE group, the mean CRP (mg/L) (mean±SD) was 20.0700±8.2155, and in control group was 6.3357±3.0993. In CASE Group, 108(77.1%) patients had CRP >13.8 and 32(22.9%) patients had CRP ≤13.8. In CONTROL Group, 2(1.4%) patients had CRP >13.8 and 138(98.6%) patients had CRP ≤13.8. Association of CRP in cases vs. control group was statistically significant (p<0.0001).Association of CRP in cases vs. control group was statistically significant (p<0.0001).

The above table shows that there is a difference in level of CRP in healthy group and group having hypertensive disorder of pregnancy which showing that the maternal CRP at 13.8 is an excellent indicator of the PIH with sensitivity of 77.0% , specificity of 98.6%, positive predictive value of 98.2%, negative predictive value of 81.2% and diagnostic accuracy of 87.8%.

By applying Pearson correlation test the result showed that there is statistical non-significant correlation regarding CRP and maternal age, period of gestation, total leucocyte count, platelet count, serum sodium, serum potassium and serum uric acid (p>0.05).But there is statistically significant positive correlation between CRP,SBP and DBP.(p<0.05). The level of SBP, DBP was significantly elevated with increase CRP level

DISCUSSION

With assistance from the Department of Biochemistry, the study was carried out at the Department of Gynecology and Obstetrics, Medical College and Hospital, Kolkata. As a case control study, the research aimed to determine if there was any correlation between the levels of serum C- reactive protein in pregnant women with hypertension (140 CASES) and normotensive women who appeared to be in good clinical condition (140 CONTROL).

Chen H et al [5] (2018) found that serum hs-CRP and mALB levels in the severe preeclampsia group were significantly higher than those in mild preeclampsia group (P<0.05). The ROC curve analysis indicated that hs-CRP was a high-risk factor. The 95% confidence range was 0.848–0.974, while the area under the curve was 0.943.

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

The above study took hs-CRP, but this study took CRP as a predictive parameter. We found that the serum level of CRP was significantly higher in case group i.e., in PIH group than those in control group ($p<0.0001$). ROC curve analysis showed that CRP was a factor of high risk.

Vecchié A et al [6] (2018) found that Serum samples were collected and compared across the study groups in order to quantify hs-CRP and PCT. 50 healthy expectant mothers and 59 pregnant PE mothers—26 (44.1%) mild and 33 (55.9% severe—were examined in this study. Pregnant women with PE had greater mean hs-CRP and PCT (7.71 ± 6.19 vs. 5.44 ± 3.94, P = 0.02 for hs-CRP and 0.05 ± 0.03 vs. 0.04 ± 0.01, P = 0.001 for PCT) than pregnant women without PE. PCT and hs-CRP had area under curves of 0.646 and 0.611, respectively.

In our investigation, we discovered that the case group's mean CRP was higher than the control groups, at 20.0700 ± 8.2155 vs 6.3357 ± 3.0993 mg/L ($p<0.0001$).Therefore, serum CRP will be useful in lowering maternal morbidity and death and may be a suitable marker for examining pregnant women with PIH.

Shruti P et al [7] (2013) found that When comparing the cases to the normal controls, there was a statistically significant rise in the levels of serum uric acid and CRP ($P < 0.001$) and a statistically significant drop in the levels of blood calcium ($P < 0.001$).

Serum uric acid and CRP levels increased statistically significantly ($p<0.0001$) in cases compared to controls. However, the serum calcium level was not taken into account in this investigation.

Onuegbu AJ et al [8] (2015) found that the mean values of the BMI in case versus control group were 29.47 ± 6.90 versus 26.14 ± 2.92, of the diastolic blood pressure 109.14 ± 15.41 versus 72.29 ± 9.42 mm Hg and of the systolic blood pressure 170.57 ± 19.55 versus 120.86 ± 17.72 mm Hg for women with and without pre-eclampsia, respectively, and the differences were statistically significant ($p = 0.012$, $p = 0.001$ and $p = 0.001$, respectively). The biochemical analysis also indicated that the women with pre-eclampsia had a significantly higher mean serum CRP (8.57 ± 2.68 vs. 6.46 ± 2.46 mg/l, $p = 0.001$), TG (2.84 ± 0.45 vs. 1.87 ± 0.38 mmol/l, $p = 0.001$) and total cholesterol (5.59 ± 0.92 vs. 4.63 ± 0.78 mmol/l, $p = 0.001$) level but a lower mean HDL-C (1.10 ± 0.12 vs. 1.26 ± 0.15 mmol/l, $p = 0.001$) level than the controls. There was no statistical difference in the mean LDL-C values between the 2 groups (1.58 ± 0.8 vs. 1.45 ±0.78 mmol/l, $p > 0.05$).

The results of our study showed that there were statistically significant differences in the mean diastolic blood pressure (99.5429 ± 7.2977 against 78.8000 ± 4.4741 mmHg) and systolic blood pressure (156.8286 ± 9.2635 compared 115.9286 ± 6.2440 mmHg) between the case and control groups. Statistically significant differences were seen in the total leucocyte count between the

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

case and control groups (9825.035, ± 477.356 against 9310.9286, ± 9310.928/m^3; p<0.0001) and platelet count (1.7000, ± 0.3742, compared 2.0521, ± 0.3533 lakhs/m^3) (p<0.0001).

The biochemical analysis also indicated statistical significant increase in serum CRP and serum uric acid in case versus control group having CRP 20.0700 ± 8.2155 versus 6.3357 ± 3.0993 mg/L(p<0.0001) ; and uric acid 6.7546 ± 0.9180 versus 4.2971 ± 1.2346 mg/dl(p<0.0001).

Bandyopadhyay R et al [9] (2019) found that Correlation between total thiol and hs-CRP with age, systolic blood pressure, diastolic blood pressure and retinopathy was done using Pearson's correlation coefficient. Results showed that serum total thiol levels were lower and serum hs-CRP was higher than the control group, with an increased level of serum total thiol and hs-CRP was found in preeclampsia and severe preeclampsia as compared to normal pregnancy that correlated with retinopathy.

We found that correlation between CRP with age, POG, SBP, DBP, parity, total leucocyte count, platelet count, serum sodium, serum potassium, and serum uric acid by using Pearson's correlation coefficient.

Kholief A et al [10] (2019) found that CRP levels showed statistically significant difference between the control and mild PE cases and between the control and severe PE cases.CRP was more sensitive and specific than PLR to predict PE in pregnant women, so it can be used in prediction of PE.

We found that serum CRP level in case group was higher than control group which was statistically significant (p<0.0001). So that CRP can be used as a good marker for prediction of PIH.

Kumru S et al [11] (2006) found that in Correlation analysis tests in the preeclampsia group revealed a negative correlation between serum hsCRP and weight ($r = -0.6$, $p = 0.02$, $n = 20$) and length ($r = -0.5$, $p = 0.05$, $n = 20$) of the newborns, and a strong positive correlation between serum hsCRP levels and diastolic blood pressures ($r = 0.9$, $p = 0.05$, $n = 20$) and urinary protein excretion ($r = 0.8$, $p = 0.05$, $n = 20$). The weights ($r = 0.5$, $p = 0.02$, $n = 20$) and lengths ($r = 0.5$, $p = 0.05$, $n = 20$) of the neonates in the control group similarly showed a negative correlation with serum hsCRP levels.

Serum hsCRP levels increase in women with PE. Elevated serum levels of hsCRP in preeclamptic women are correlated with clinical and biochemical parameters of PE. Determination of serum hsCRP levels may be used as a marker for the severity of PE.

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

According to our research, there was a statistically significant strong positive connection (r = 0.359, p = 0.000014) and systolic blood pressure (r = 0.3942, p<0.00001) between serum CRP levels and both diastolic and systolic blood pressure in the case group.

There was positive correlation between serum CRP and period of gestation (r = 0.0058, p = 0.9457); total leucocyte count (r =0.107, p = 0.208); platelet count (r = 0.066, p = 0.439); serum uric acid (r = 0.065, p = 0.448) but all were statistically not significant.

There was negative correlation between serum CRP and maternal age (r = -0.058, p = 0.4960); serum sodium (r = -0.035, p = 0.684); serum potassium (r = - 0.054, p = 0.524). We did not assess newborns in this study. From this study it can be concluded that serum CRP is a good predictive parameter for PIH.

Mishra N et al [12] (2019) found that in severe PE, hsCRP was considerably higher than in PE without severe symptoms or in normal individuals. Severe PE patients required more inductions of labor and cesarean sections, as well as more stillbirths and low birth weight newborns. In individuals with severe PE, hs CRP correlated negatively with fetal weight and stillbirths and positively with other indicators of PE severity. Nonetheless, a significant range in hs CRP concentrations was seen, despite being elevated in each case with severe PE. For women who appear late in the third trimester of pregnancy, hs CRP alone is not a reliable indicator of severity or a forecaster of result. However, it can be utilized for that purpose when combined with serum uric acid.

We discovered that the CRP value in the instance was significantly greater than the control. However, we did not monitor whether the patient opted for an induction of labor or a cesarean section, nor did we monitor the health of the newborns.

Kalva-Borato DC et al [13] (2019) found that MPO levels in the normal pregnant women were not elevated in every trimesters of pregnancy (P=0.456) or in systemic inflammation (P=0.446). The hs-CRP levels, total leukocyte, absolute neutrophil and monocyte counts are present in higher concentrations in normal pregnant women in relation to non-pregnant women. The MPO did not exhibit variations in plasma levels during the course of the three trimesters of pregnancy or in response to various inflammatory states. Given that both MPO and hs-CRP levels fluctuate in high-risk cardiovascular disorders and that MPO levels did not rise during a simple pregnancy, in contrast to hs-CRP, MPO may be a more useful biomarker for these individuals to be followed than hs-CRP.

In our study, we found that serum CRP, total leucocyte count were significantly high in case group. Our study did not take MPO into consideration.

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

CONCLUSION

Considering the flogistic pathogenesis we suppose that inflammation is the basis of pregnancy induced hypertension. From this study ,we can notice that measurement of serum CRP is a good preliminary biomarker for the detection of hypertensive disorders of pregnancy in India. These findings can be used to set expected values of CRP concentration in pregnant Indian women. We conclude that, the serum CRP levels were significantly high in PIH women thus suggesting inflammatory pathogenesis and oxidative stress as a major conflict behind the disease progression. The CRP levels in patients increased statistically significantly ($P < 0.0001$). There was a strong positive connection between CRP and both diastolic and systolic blood pressure, and the diagnosis accuracy in these patients was 87.8%. This implies the inflammatory response linked to the presence of dead placental cells in the uterine and placental bed, the immunological activation linked to endothelial dysfunction, and the inflammatory processes that cause vasospasm. Therefore, serum CRP may be used in conjunction with other traditional indicators as a complementary diagnostic tool in preeclampsia.

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ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

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