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Biochemical Markers and Uterine Artery Doppler Study for the Prediction and the Severity of the Hypertensive Disorders during Pregnancy

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Objective: Study of biochemical markers and uterine artery Doppler for the prediction of hypertensive disorders and its severity. Sensitivity and Specificity of biochemical markers and Uterine Artery Doppler and their comparison for the prediction and the severity of hypertensive disorders during pregnancy.

Material & Methods: This is a prospective study. Approximately hundred patients with hypertensive disorders during pregnancy attending the OPD (Out patients Department) and IPD (In patient Department) in Obstetrics & Gynecology department will be included.

Keywords: hypertension, hypertensive disorder in pregnancy, biochemical markers, uterine artery doppler.

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Biochemical Markers and Uterine Artery Doppler Study for the Prediction and the Severity of the Hypertensive Disorders during Pregnancy

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All the patients in this study group will be subjected to biochemical markers tests and Ultrasonographic evaluation of the pregnancy along with the Arterial Doppler of both the Uterine Artery and Umbilical Artery will be done.

Conclusion: Using biochemical markers (Inhibin-A and PAPP-A) and Uterine Artery Doppler Study in combination is significantly useful in early prediction of PIH having specificity and sensitivity of Inhibin-A as 88.89% and 83.33%, PAPP-A as 89.29% and 71.43%, Uterine artery Doppler study – Pi Index as 91.67% and 85.71 %, Ri Index as 87.5% and 71.43% and diastolic notch as 94.44% and 92.85 % respectively. The use of biochemical markers and uterine artery Doppler Study as an important tool for early prediction of PIH and has a lot of prognostic value.

Keywords: hypertension, hypertensive disorder in pregnancy, biochemical markers, uterine artery doppler.

I. Introduction

Hypertensive disorders of pregnancy are one of the major cause of maternal and perinatal mortality and morbidity worldwide particularly in developing countries. Hypertensive disorder of pregnancy is a sign of an underlying pathology which may be pre existing or appear for the first time during pregnancy. The identification of this clinical problem & effective management plays a significant role in the prevention of the adverse effects on pregnancy outcome [1].

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Hypertensive Disorders of Pregnancy is a multi-system disorder, which is characterized by new onset hypertension (systolic and diastolic blood pressure of≥ 140 and 90 mm Hg, respectively, on two occasions, at least 6 hours apart) and proteinuria (protein excretion of ≥ 300 mg in a 24 h urine collection, or a dipstick of ≥ 2+), that develop after 20 weeks of gestation in previously Normotensive women [2].

Hypertensive Disorders of Pregnancy can have an early onset (preeclampsia starting before 34 weeks of gestation) or late onset (preeclampsia starting after 34 weeks of gestation), can show mild or severe symptoms (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg, proteinuria >5 g/24 hours, oliguria, neurological symptoms, other clinical symptoms such as deranged liver function, thrombocytopenia < 100 000 mm3, HELLP syndrome), and can evolve in eclampsia in the most severe cases whereas Eclampsia is the occurrence of one or more convulsions superimposed on the syndrome of pre-eclampsia [3].

Dependent on the systemic involvement along with several other symptoms, such as edema, disturbance of hemostasis, renal or liver failure, and the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts) also complicates the clinical picture.

Most theories on the etiology of hypertensive disorders of pregnancy suggests that the disease is a cascade triggered by combination of abnormal maternal inflammatory response, endothelial cell activation/ damage with deranged hemodynamic milieu, and deranged immunity [4,5].

Numerous patho-physiological mechanisms, alone or in combination, have been suggested to be responsible for the diverse subsets of hypertensive disorders of pregnancy. They include impaired vascular remodeling of the maternal–fetal interface, excessive immune response to paternal antigens, systemic inflammatory response, and dysfunctional placental or endothelial response, all of these processes being modulated by genetic and environmental parameters. Such heterogenicity of potential processes leading to, or resulting from, hypertensive disorders of pregnancy has contributed to the lack of diagnostic means for identification of women susceptible to developing pre-

eclampsia, resulting in delayed recognition and severe complications and impeding evaluation of new preventive interventions [6].

Since there is an involvement of various organ systems, the potential markers would include inhibin A, PAPP-A, Activin A, angiotensin 11 sensitivity, urine albumin excretion, uric acid and microproteinuria, urinary inhibin-a, urinary kallikrein –calcium/kallikrein ratio, maternal serum alpha fetoprotein; coagulation and platelet activation [7].

Risk factors for preeclampsia: Include nulliparity, multifetal gestations, previous history of preeclampsia, obesity, diabetes mellitus, vascular and connective tissue disorders like systemic lupus erythematosus and antiphospholipid antibodies, age >35 years at first pregnancy, smoking, and African American race. Ultrasonography Color Doppler study may also help in the prediction of hypertensive disorder. Persistence of high impedance to blood flow in the uterine arteries of women with hypertension, which is one of the indirect evidence of abnormal placentation also helps in early identification of disease[8].The changes are increased systolic to diastolic ratio, absent diastolic flow, reverse diastolic flow depending upon severity of the disease[9]. With the help of Uterine Artery Doppler Velocity waveform analysis we can measure resistance index, pulsatility index, systolic/diastolic ratio, diastolic/systolic ratio, presence of any diastolic notch [10].

The specificity and sensitivity of the Uterine Artery Color Doppler Study for Pi Index are 91.67% and 85.71%, Ri Index 87.5% and 71.43% and for Diastolic Notch are 94.44% and 92.86% which is very useful in early detection of PIH [11]. Therefore, Ultrasonography Color Doppler study may also help in the prediction of hypertensive disorder. Persistence of high impedance to blood flow in the uterine arteries of women with hypertension, which is one of the indirect evidence of abnormal placentation also helps in early identification of disease[12].The changes are increased systolic to diastolic ratio, absent diastolic flow, reverse diastolic flow depending upon severity of the disease[13,14].

WHO, UNFPA, UNICEF, IPPFF, the population council and other national & international agencies concerned with safe motherhood concluded that it is possible to reduce maternal mortality significantly with investigation and its effective management [15].

Reducing maternal mortality by 75% between 1990 and 2015 has been considered as part of the millennium development goals of the World Health Organization (WHO) Nations [15].

II. Materials and Methods

This is a prospective study done at Mahatma Gandhi Medical College & Hospital, Sitapura, Jaipur. Approximately 100 patients, during pregnancy attending the OPD and IPD in Obst. & Gynae department will be included. Patient's detailed clinical history, personal history, significant medical history, obstetric history and menstrual history will be taken.

General examination of all the patients will be done and Pulse, Blood Pressure, Temperature and Respiratory Rate will be noted.

Systemic examination including heart, lungs and other systems will be examined in detail.

All the patients in this study group will be subjected to all the routine blood tests and special tests, including biochemical markers. A detailed Ultra-sonographic evaluation of the pregnancy along with the Arterial Doppler of both the Uterine Artery and Umbilical Artery will be done. All patients will be kept in the regular follow up and in the end, their maternal and fetal outcome will also be noted.

Special blood tests will be including:

1) Complete blood count (specially hemoglobin and platelet count),
2) Liver function tests including SGOT, SGPT, Alkaline Phosphatase Level, LDL Level and PT/INR.
3) Lipid profile – LDL, HDL, Triglyceride, Total Cholesterol, VLDL.

Biochemical Markers: Serum Uric Acid, Blood Urea, Serum Creatinine, Activin-A, Pregnancy Associated Plasma Protein-A (PAPP-A)

Urinary Tests: Urinary Micro Albumin Level, Urine Protein/Creatinine Ratio, Urinary Calcium Creatinine Ratio.

In the Doppler study following parameters will be assessed:

Pulsatility Index: A measure of the variability of the blood velocity in a vessel equal to the difference between the peak systolic and minimum diastolic velocities divided by the mean velocity during the cardiac cycle.

Calculated by = Peak Systolic Velocity - End Diastolic Velocity/Mean Velocity

Resistance Index: Is a measure of pulsatile blood flow that reflects the resistance to blood flow caused by microvascular bed distal to the site of measurement.

Calculated by = Peak Systolic Velocity - End Diastolic Velocity/Peak Systolic Velocity

Systolic to Diastolic Ratio: Determinations of blood flow velocities that reflects intrinsic resistance in an arterial blood vessel.

Presence and absence of the diastolic in both the uterine arteries.

Using Statistical test i.e. Z-test where the distribution of the test statistic under the null hypothesis can be approximated by a normal distribution, using expected value θ of T under the null hypothesis, and then obtaining an estimate S of the standard deviation of

T, the standard score Z = (T– θ) / s is calculated, will be applied wherever needed.

With the help of these statistical methods, the sensitivity and the specificity of the biological markers and the Uterine Artery Doppler study will be calculated.

III. Results

Pregnancy Induced Hypertension is the most common obstetrical disorder world-wide and on a national scale in India also. It is one of the major causes of maternal and fetal mortality.

Table 1: Distribution of the cases according to Age

Age in Years	No. of patients	Percentage
20 -24	48	48%
25 – 29	27	27%
29- 33	17	17%
34 – 38	7	7%
39 – 40	1	1%
Total	100	100%

Table 1 showed the age distribution of 100 patients of my study group that maximum patients 38% were in the age of 20 – 24 years and second most common were in the age group in between 25 – 29 years that was 27%. While only 8 patients were above 35 years.

Table 2: Distribution of the cases according to Parity

Parity	No. of patients	Percentage
Para 1	22	81 %
Para 2	32	12 %
Para 3	20	3%
Para 4	18	2%
Para 5	7	2%
Total	100	100%

In this present study of 100 patients, maximum number of patients was primigravida (81%), while multiparous women were 19%.

Table 3: Distribution of the cases according to occupation

Wife Occupation	Number	Percentage
Farmer	6	6
Housewife	84	84
Labour	1	1
Nurse	3	3
Self Employed	1	1
Sweeper	1	1
Teacher	4	4

Out of 100 patients, maximum number of patients 84% was from house wife while 16 had their own jobs (4 were teacher, 3 had nursing job, 6 were working in the field etc.)

Table 4: Distribution of the cases according to Residence

Location	Number	Percentage
Rural	56	56
Urban	44	44
Total	100	100

Out of 100 patients, 56 patients were residing in rural area while 44% in urban area.

Table 5: Distribution of the cases according to Socioeconomic Status (Kuppuswami Scale)

SE. Status	Number	Percentage
Lower Class	65	65
Middle Class	31	31
Upper Class	4	4
Total	100	100

In this study of 100 patients, 65 patients were from lower socioeconomic group, while only 4 patients belong to upper class and 34 were from middle class.

Distribution according to age group: In my study, 55% were present between 20- 35 years, 7% 34 – 38yrs and 1% 39 – 40yrs.

Same age groups were studied by MANJUSHA SAJITH, VANDANA NIMBARGI et. al. in their study had 1330 patients, out of which 104 were between the age group of 18-32 years.

Distribution according to Parity: In my study on the basis of parity showed that maximum number of patients were from the Primigravidae group comprising about 81% of the total patients.

Mary Esien Kooffreh, Mabel Ekott, Dorcas O Ekpoudom in their study on the prevalence of pre-eclampsia among pregnant women including 8524, showed that majority of the patients between the age group of 25-29 years that is about 104 patients were Primigravida.

Distribution according to Occupation: In my study out of 100 patients 84% were housewives and 16% were working women.

Swati Singh, Ekele Bissallah Ahmed, Shehu Constance Egondu and Nwobodo Emmanuel Ikechukwu in their study on Hypertensive disorders in pregnancy among pregnant women showed that maximum number of patients that is 88.13% were housewives.

Distribution according to Residence: In my study maximum numbers of patients were from rural area i.e.56%.

Shikha Saxena, Prem Chandra Srivastava, K. V. Thimmaraju et. al in their study on Socio-demographic Profile of Pregnancy Induced Hypertension in a Tertiary

Care Centre showed that maximum number of patients that is 77.14% were residing in rural area.

Distribution of the cases according to Socioeconomic Status: In my study maximum number of patients i.e. 65% were from lower socioeconomic status.

Parveen M. Aabidha, Anne G. Cherian, Emmanuel Paul and Jasmin Helan in their study on Maternal and fetal outcome in pre-eclampsia in a secondary care hospital in South India showed that maximum number of patients 61% were from lower socioecono

Uterine Artery Doppler Study specificity and sensitivity in the prediction of PIH

It showed that Doppler Study of Uterine Artery depicting 100 patients. In this table out of 100 patients, Pi Index was normal in 66 patients and elevated in 6 patients, out of 72 normotensive patients, whereas in Ri Index 63 patients were normal and 6 elevated, out of 72 normotensive patients and in diastolic notch 68 patients were having absent notch and 4 patients had notch present out of 72 patients who were normotensive on follow-up. Whereas in case of 28 PIH patients, Pi Index was elevated in 24 patients and 4 patients were in normal value, whereas in Ri Index 20 patients were having elevated Ri Index and 8 patients were having normal value and in diastolic notch 26 patients had present notch and 2 had absent. This table showed the specificity and sensitivity of Pi Index, Ri Index and Diastolic Notch as 91.67%, 87.5% and 94.44% and 85.71%, 71.43% and 92.86% respectively along with Pi Index PPV 80%, NPV 94.29% and accuracy of 90%, whereas Ri Index PPV 68.97%, NPV 88.73% and accuracy of 83% and diastolic notch PPV 86.67%, NPV 97.14% and accuracy 94% showing Pi Index is having higher specificity and sensitivity along with other parameters after diastolic notch.

IV. Conclusion

I from my study infer that using biochemical markers (Inhibin-A and PAPP-A) and Uterine Artery Doppler Study in combination is significantly useful in early prediction of PIH having specificity and sensitivity of Inhibin-A as 88.89% and 83.33%, PAPP-A as 89.29% and 71.43%, Uterine artery Doppler study – Pi Index as 91.67% and 85.71 %, Ri Index as 87.5% and 71.43% and diastolic notch as 94.44% and 92.85 % respectively.

V. Discussion

My Study on Early prediction of Hypertensive Disorders of Pregnancy using biochemical markers and uterine artery Doppler study was conducted on 100 pregnant women attending the antenatal clinic of Mahatma Gandhi Medical College, Jaipur. Out of 100 patients, 72 patients were normotensive and 28 patients were of PIH.

In my study group maximum patients were in the age group of 20-29 years comprising 75% and second most common were in the age group in between 29 – 33 years that was 17%, While only 8 patients were above 35 years with mean age 26.7 years.

Maximum number of patients were primigravida (81%), while multiparous women were 19%. Maximum number of patients was housewives 84%, while 16 had their own jobs. 56% patients were from rural area while 44% in urban area. 65% patients were from lower socioeconomic group, while only 4 patients belonged to upper class and 34 were from middle class.

9% patients were between 16-20 weeks, 26% between 20-24 weeks and 65% patients were between 25-29 weeks.

77% showed normal range of blood urea 20-24mg/dl, while 23% showed slightly high level of urea, while 93% patients had slightly raised serum bilirubin, while serum creatinine were normal in all the patients.

Out of 72 normotensive patients, 64 patients had normal level of Inhibin-A 514-890 pg/ml, while 8 patients had elevated level of Inhibin-A (891-1021 pg/ml) and out of 28 PIH patients, 3 patients had an Inhibin-A level within normal range and 25 patients had elevated Inhibin-A level showing the specificity and sensitivity of Inhibin-A as 88.89%, 83.33%, PPV 75.76%, NPV 95.52% and accuracy of 89%.

Out of 72 normotensive patients, 60 patients showed normal level of PAPP-A 0.90-0.60, while 12 patients had decreased level of PAPP-A (0.50-0.40) and out of 28 PIH patients, 8 patients had normal PAPP-A level and 20 patients had decreased PAPP-A level showing the specificity and sensitivity of Inhibin-A as 89.29% and 71.43%, PAPP-A PPV 62.5%, NPV 88.24% and accuracy of 80%.

12. Out of 72 normotensive patients, 66 patients had normal Pi Index while 6 patients had slightly elevated level. Out of 28 PIH patients 24 patients had elevated Pi Index and 4 had normal Pi Index. This result showed the specificity and sensitivity of Pi Index as 91.67% and 85.71 % and having a PPV of 80%, NPV of 94.29% and accuracy of 90%.

Out of 72 patients who remained normotensive, 63 patients had normal Ri Index, while 9 had slight elevated level and out of 28 patients who developed PIH on follow-up, 20 patients showed elevated level of Ri Index, while 8 patients had normal Ri Index, showing the specificity and sensitivity of Ri Index are respectively 87.5% and 71.43%, which is followed by 68.87% of PPV, 88.73% of NPV and accuracy of 83%.

Out of 72 normotensive patients, 57 patients had absent diastolic notch, while 15 patients had diastolic notch present and Out of 28 patients who developed PIH on follow-up, 21 patients had diastolic notch present, while 7 patients had absent diastolic notch showing the specificity and sensitivity of 94.44%

and 92.85 % respectively while PPV was 94.44%, NPV 86.67% and accuracy of 94%.

VI. Acknowledgements

I would like to acknowledge:

Abbreviations:

HDP –Hypertensive Disorder in Pregnancy,
OPD – Out Patient Department,
IPD – In Patient Department,
PAPP-A – Pregnancy Associated Plasma Protein-A.

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