

# A cross-sectional study on the incidence of retinal changes and its correlation with variables like blood pressure, liver function tests, kidney function tests, proteinuria, and pedal edema in patients of pregnancy-induced hypertension in a rural setting

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**Purpose:** Pregnancy-induced hypertension is a multisystem disorder that occurs after 20 weeks of pregnancy usually in primigravidas and is characterised by proteinuria, pedal edema, hypertension, and abnormal liver and kidney function tests. Since there exists a close relationship between retinal, cerebral, and renal vessels, funduscopy gives the opportunity of observing the changes in the vascular tree. **Methods:** We conducted a study on 203 pregnant females over a period of 1.5 years in the rural population of North India. We recorded the baseline data from the patient files, including the biochemical investigations, and conducted a fundoscopic examination of all patients included in the study, and correlation of various variables was established. **Results:** Out of 203 patients (403 eyes), 60% were primigravidas of mean age  $25.71 \pm 4.46$  years with the mean duration of pregnancy being 36 weeks. The mean systolic and diastolic blood pressure were 160 and 101 mmHg, respectively. There was no significant correlation was seen of proteinuria with eclampsia and the fundus findings. But there was a significant correlation between proteinuria and pedal edema and between the fundus findings and deranged LFT and KFT values. Relationship between the variables was calculated by using Chi-square and Fisher's exact test. A  $P$  value  $< 0.05$  was taken as significant. **Conclusion:** Hypertension in pregnancy is the major concern of public health issue worldwide. With proper understanding of the correlating factors such as fundus changes which are directly correlated with whole body vascular changes, which might affect the fetal growth, we can easily predict the outcome and can take appropriate actions as early as possible.

**Key words:** Kidney Function Test, liver function test, pedal edema, preeclampsia, proteinuria

The preeclampsia/eclampsia syndrome is a multisystem disorder that can include cardiovascular changes, hematologic abnormalities, hepatic and renal impairment, and neurologic and cerebral manifestations.<sup>[1]</sup> It can also affect the eye and visual pathways. Vasospasm is the basic to the pathophysiology of preeclampsia/eclampsia.

Vascular constriction causes resistance to blood flow and accounts for the development of arterial hypertension. The various pathological changes in different organs of the body in preeclampsia can be studied directly by visualizing the ocular fundus and may give a true index of changes in the vascular system of brain and retina.

Abnormalities of the conjunctiva like capillary tortuosity, conjunctival hemorrhage, intravascular thrombi, and localized ischemic necrosis of the conjunctiva due to severe vasospasm have also been observed along with changes in retina, retinal vasculature, choroid, optic nerve, and visual cortex.<sup>[2,3]</sup> Since there exists a close relationship between retinal, cerebral, and renal vessels, funduscopy gives the opportunity of observing the changes in the vascular tree.

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The eye serves as the window through which vessels of the brain can be studied. The retina acts as an index of the state of parenchyma of kidney. Since there exists a close relationship between retinal, cerebral, and renal vessels, funduscopy gives the opportunity of observing the changes in the vascular tree and deducing therefrom the general condition of vascular system of the body.<sup>[2,3]</sup>

## Methods

A cross-sectional, observational study was carried out jointly by the Department of Ophthalmology and Department of Obstetrics and Gynecology in our institute between January 2015 and- June 2016. All pregnant women having Pregnancy induced hypertension (PIH) during the study period, that is, 1.5 years, and who were willing to participate in the study were considered as the study sample. Results are presented in the form of percentage and proportions, and the relationship between various factors was analyzed by Chi-square test and Fisher's exact test.

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Patients who had preexisting diabetes, hypertension, renal disease, hazy ocular media, or any other ocular disease causing retinopathy were excluded from the study.

An informed consent was taken, and baseline data of all pregnant patients, including the liver function tests (LFTs) and kidney function tests (KFTs), proteinuria etc., was recorded. In all patients with elevated liver enzymes, ultrasonography of the abdomen was done by a radiologist. All patients were initially evaluated by an obstetrician. Age, para, gravida, and blood pressure (BP) were noted from the case record. Detailed history, general, physical, and systemic examination were then done by the obstetrician, followed by ocular evaluation, which included visual acuity with Snellen's chart and best-corrected visual acuity (BCVA) (in possible cases after refraction). Detailed ocular examination was done with slit lamp (whenever possible). Fundus evaluation was done after instilling 1% tropicamide eye drops with direct and indirect ophthalmoscope, and imaging of any significant finding was done using the Zeiss fundus camera, wherever possible.

Retinal changes in one or both eyes were considered as a positive finding in the patient according to the Keith Wegner and Barker classification [Fig. 1]

The PIH was graded as preeclampsia (mild and severe) and eclampsia.

All the findings were noted on a data sheet. The severity of PIH was classified into preeclampsia (mild and severe) and eclampsia, based on the following findings:

- Mild preeclampsia – BP >140/90 mmHg, proteinuria +, and/or mild edema of legs;
- Severe preeclampsia – BP >160/110 mmHg, proteinuria ++ or +++, headache, cerebral or visual disturbances, epigastric pain, impaired LFTs, and increased serum creatinine; and
- Eclampsia – severe preeclampsia + convulsions. Proteinuria was tested using dipstick method and was graded as + = 0.3 g/L, ++ = 1 g/L, and +++ = 3 g/L.

The results were analyzed using NCSS11 and Statistical Package for the Social Sciences (SPSS) program. Results are calculated in the form of percentage and proportions. Relationship between the variables was calculated by using Chi-square and Fisher's exact test. *P* value < 0.05 was taken as significant.

## Results

In the present study, we registered 403 eyes of 203 patients. Of these, two eyes were phthisical and one had posttraumatic total leucomatous corneal opacity, and so were excluded from the study.

Mean duration of pregnancy among all PIH patients was 36.30 weeks + 3.23. Most of the patients, that is, 123 (60.6%), were primigravidas; only a few, that is, 80 (39.4%), were multigravidas. Out of all patients, only 44 (21.7%) had eclampsia while the majority (159 [78.3%]) were non-eclamptic. The readings of systolic and diastolic BP and grades of proteinuria are tabulated in Tables 1 and 2.

The diagnosis of preeclampsia requires BP >140/90 mmHg on two occasions combined with urinary protein excretion >300 mg/day.

Proteinuria is an important finding consistent with PIH. Most of the PIH patients had grade 2 proteinuria (87 [42.9%]). Grade 1 proteinuria was seen in 25.6% (52) of patients, grade 3 proteinuria in 21.7% (44) of patients, and grade 4 proteinuria in 1% (2) of patients. Also, 8.9% (18) of patients had no proteinuria.

Among the various retinal findings observed in the fundus of PIH patients, the most common finding was arterial attenuation of the nasal midperipheral blood vessels, which was followed by copper wiring, flame-shaped hemorrhages, cotton wool spots, hard exudates, and papilledema with macular edema [Figs. 2 and 3].

In 87 patients with fundus changes, the mean value of systolic BP was 166 mmHg + 12.08 and the standard error was 1.31. Maximum systolic BP in these patients was 200 mmHg and minimum systolic BP was 140 mmHg. Mean value of diastolic BP in patients with fundus changes was 105.20 mmHg + 8.21 and the standard error was 0.89. Maximum diastolic BP in these patients was 130 mmHg and the minimum diastolic BP was 90 mmHg.

In 116 patients without fundus changes, the mean value of systolic BP was 154.54 mmHg + 8.49 and the standard error was 0.78. Maximum systolic BP in these patients was 180 mmHg and minimum systolic BP was 140 mmHg. Mean value of diastolic BP in patients without fundus changes was 98.06 mmHg + 7.45 and the standard error was 0.69. Maximum diastolic BP in these patients was 120 mmHg and minimum diastolic BP was 84 mmHg.

Classification	Retinopathy			Arterioles		Arteriosclerosis	
	Hemorrhage	Exudates	Disc edema	AV ratio	Focal spasm	Light reflex	AV crossing defect
Stage 0	–	–	–	3:4	1:1	Fine yellow	None
Stage 1	–	–	–	1:2	1:1	Broad yellow	Mild vein depression, AV nicking
Stage 2	–	–	–	1:3	2:3	Copper wire	Vein depression
Stage 3	+	+	–	1:4	1:3, cotton wool spots	Silver wire	Right angle disappearance of vein, distal dilatation
Stage 4	+	+	+	Fibrous fine cord	Elschnig spot's, no distal flow	Stage 3	Stage 3

Figure 1: Classification of hypertensive retinopathy by Keith and Wegner

Out of all 44 (21.7%) patients with eclampsia, grade 2 proteinuria was the most common and was found in 23 (11.3%) patients, grade 3 proteinuria was found in 17 (8.4%) patients, and grade 1 proteinuria was seen in two (1%) patients. None of the patients had grade 4 proteinuria, while only two (1%) patients had no proteinuria.

Out of 161 (78.3%) patients without eclampsia, the most common grade 2 proteinuria was seen in 64 (31.5%) patients similar to those with eclampsia, followed by grade 1 proteinuria in 50 (24.6%) patients, grade 3 proteinuria in 27 (13.3%) patients, and no proteinuria in 16 (7.9%) patients. Only two (1%) patients had grade 4 proteinuria.

But there was no significant correlation between proteinuria and eclampsia.

Edema is a classic feature of the disease; however, it is no longer considered a diagnostic feature, given its lack of sensitivity or specificity.

Majority of the patients with PIH, that is, about 187 (92.10%), had pedal edema, while only 16 (7.90%) patients did not have pedal edema. Similar to the distribution of proteinuria in eclamptic patients, in PIH patients with pedal edema, grade 2 proteinuria was the most common. Among the patients without pedal edema, grade 1 proteinuria was commonly seen. There was a significant correlation between proteinuria and pedal edema ( $P < 0.5$ ) [Table 3].

We also came across some of the patients of PIH, that is, 58 (28.60%), with deranged LFT values, while the rest of the patients had normal LFT values.

On distributing the patients with deranged LFT values according to different grades of hypertensive retinopathy, the most frequent was found to be grade 1 retinopathy in 31 (15.3%) patients, followed by grade 2 retinopathy in 13 (6.4%) patients, grade 3 retinopathy in three (1.5%) patients, and grade 4 retinopathy in two (1%) patients. Nine (4.4%) patients had no fundus changes and this result was statistically significant [Table 4].

**Table 1: Mean values of different variables of blood pressure in PIH patients**

Variables	Mean	Standard deviation	Standard error	Maximum BP	Minimum BP
Systolic BP	159.54 mmHg	11.59	0.81	200 mmHg	140 mmHg
Diastolic BP	101.16 mmHg	9.03	0.63	130 mmHg	84 mmHg

BP=blood pressure

**Table 2: Correlation of presence and absence of proteinuria with eclampsia in PIH patients**

	Proteinuria present	Proteinuria absent	Total	
Eclampsia present	42 (20.7%)	02 (1%)	44 (21.7%)	Pearson Chi square 1.298 Degree of freedom 1 $P$ 0.255 (not statistically significant)
Eclampsia absent	143 (70.4%)	16 (7.9%)	161 (78.3%)	
Total	185 (91.1%)	18 (8.9%)	203 (100%)	

**Table 3: Correlation of proteinuria with pedal edema**

	Proteinuria present	Proteinuria absent	Total	
Pedal edema present	173 (85.2%)	14 (6.9%)	185 (92.1%)	Pearson Chi square 5.594 Degree of freedom 1 $P$ 0.018 (statistically significant)
Pedal edema absent	12 (5.9%)	04 (2.0%)	18 (7.9%)	
Total	185 (91.1%)	18 (8.9%)	203 (100%)	

**Table 4: Correlation of fundus findings with LFT in PIH patients**

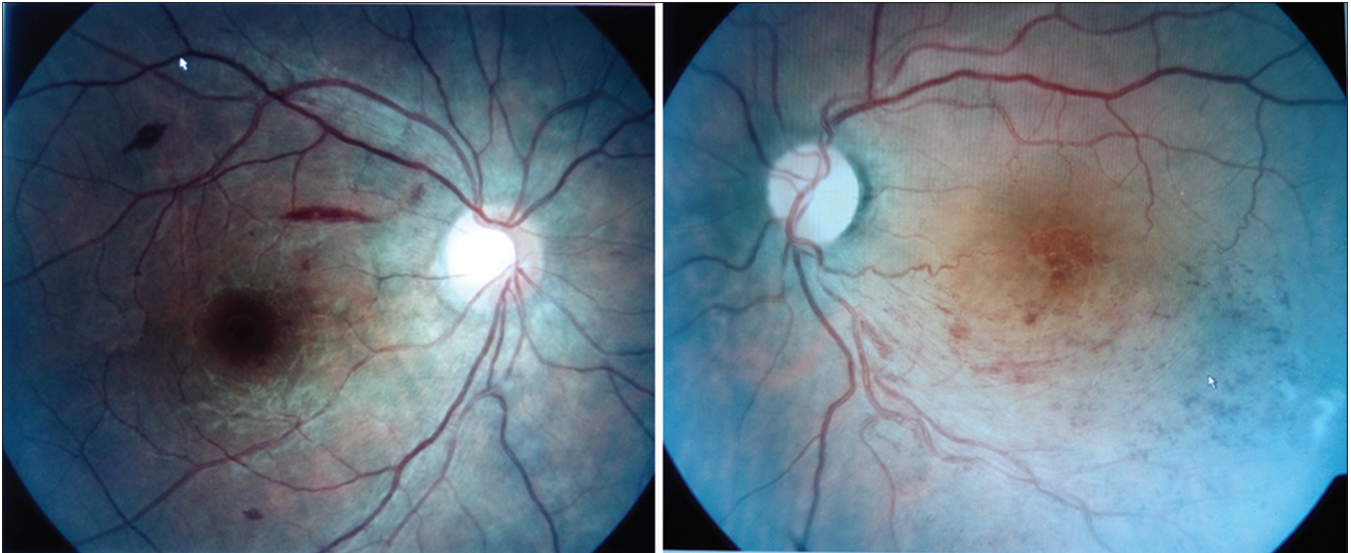
	Fundus changes present	Fundus changes absent	Total	
Normal LFT	38 (18.7%)	107 (52.7%)	145 (71.4%)	Pearson Chi square 57.45 Degree of freedom 1 $P$ 0.001 (statistically significant)
Abnormal LFT	49 (24.1%)	9 (4.4%)	58 (28.6%)	
Total	87 (42.9%)	116 (57.1%)	203 (100%)	

LFT=liver function test

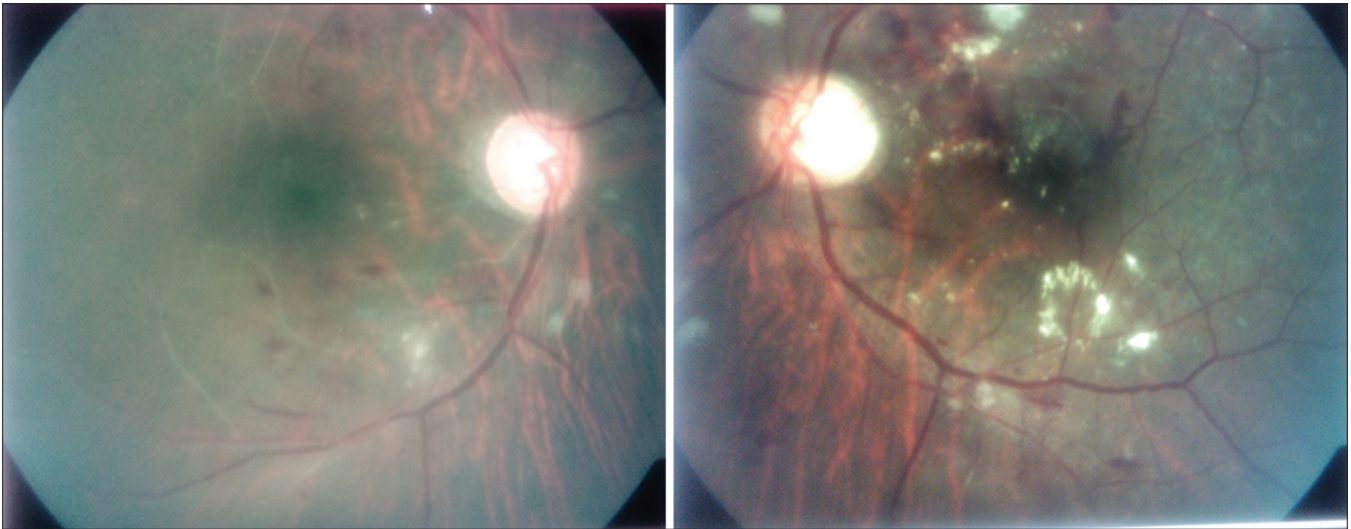
**Table 5: Correlation of fundus findings with KFT values in PIH patients**

	Fundus changes present	Fundus changes absent	Total	
Normal KFT	44 (21.7%)	108 (53.20%)	152 (74.90%)	Pearson Chi square 47.80 Degree of freedom 1 $P$ 0.001 (statistically significant)
Elevated KFT	43 (21.2%)	08 (3.90%)	51 (25.10%)	
Total	87 (42.9%)	116 (57.10%)	203 (100%)	

KFT=kidney function test



**Figure 2:** Fundus images of a patient showing generalized arteriolar attenuation and multiple flame-shaped hemorrhages



**Figure 3:** Fundus image of a patient showing generalized arteriolar attenuation, multiple flame-shaped haemorrhages, cotton wool spots around the disk and macula with few ghost vessels around the mid periphery (grade 3 hypertensive retinopathy)

PIH is also associated with pregnancy-induced cholestasis, which is a milder variant of Hemolysis, elevated liver enzymes and low platelet count syndrome (HELLP) syndrome. In our study, 2% of patients with deranged LFT values were associated with mild hepatomegaly with altered liver echotexture on ultrasonography.

Similar to LFT status, 51 (25.10%) patients had deranged KFT values. In patients with deranged KFT values, grade 1 retinopathy was observed to be the most frequent (in 26 [12.8%] patients), which was followed by grade 2 retinopathy in 13 (6.4%) patients, and grade 3 and grade 4 retinopathy in two (1%) patients. Eight (3.9%) patients had no fundus changes and this result was statistically significant [Table 5].

On distributing different ranges of systolic and diastolic BP among different grades of proteinuria, it was seen that grade 1 proteinuria was the most common with lower ranges of BP, followed by grade 2 and grade 3 proteinuria in higher ranges

of BP. None of the patients had grade 4 proteinuria. Thus, it can be said that higher grade of BP is associated with higher grade of proteinuria.

Similarly, on distributing different ranges of systolic and diastolic BP among grades of hypertension, it was seen that grade 1 hypertensive retinopathy was the most common that was found with lower ranges of BP, followed by grade 2 and grade 3 hypertensive retinopathy in higher ranges of BP. Grade 4 retinopathy was only seen in two (1%) patients when the systolic BP was or above 200 mmHg and diastolic BP was above 120 mmHg. Thus, it can be said that higher grade of BP is associated with higher grade of hypertensive retinopathy.

When grades of proteinuria were compared with hypertensive retinopathy grades in the present study, it was seen that most patients with no retinopathy also did not have proteinuria. Among the patients with grade 1 proteinuria, 49 (24.1%) had no retinopathy, only two (1%) patients and one (0.5%) patient

had grade 1 and grade 3 changes, respectively, while none of the patients had grade 2 and grade 4 retinopathy. Patients with grade 2 proteinuria, 48 (23.6%), had no retinopathy; 33 (16.3%) had grade 1 retinopathy, four (2%) had grade 2 retinopathy, and one (0.5%) had grade 3 and grade 4 retinopathy. Among patients with grade 3 proteinuria, most patients, that is, 20 (9.9%), had grade 1 retinopathy, followed by 15 (7.4%) patients with grade 2 retinopathy and six (3%) patients with no retinopathy. Only two (1%) patients and one (0.5%) patient had grade 3 and grade 4 retinopathy changes, respectively. But the results were not statistically significant.

## Discussion

Hypertensive disorder in pregnancy is the major concern of public health issue worldwide and affects 5%–10% of all pregnancies. It is a common obstetric problem contributing to maternal deaths.<sup>[4]</sup> There is a limited available data regarding hypertensive retinopathy among pregnant mothers with hypertensive disorders.<sup>[5-7]</sup>

In the present study, we tried to show the relationship between fundus changes in pregnancy-induced hypertension and certain variables like proteinuria, systolic and diastolic BP, and LFTs and KFTs. If we can establish a relationship between these variables and fundus findings, then it is possible to diagnose early and provide timely management to the pregnant females, mainly in a rural setup where resources are limited. These indicators can alert the treating doctor regarding the future plan of action in such complicated patients without compromising the lives of either the mother or the baby.

### Association of fundus changes with BP

In the present study, it was seen that higher grade of BP was associated with higher grade of hypertensive retinopathy, which is similar to the findings of Javedkar and Reddy.

In a study by Javedkar *et al.*<sup>[8]</sup> 42 patients had fundus changes where the mean systolic B.P. was 171.51mm of Hg, mean diastolic B.P. was 93.67mm of Hg. Also, 14.28% had generalized retinal edema. In these patients, the mean systolic BP was 180.66 mmHg. while the mean diastolic BP was 97 mmHg. It was also found that 9.52% had macular edema where the mean systolic BP was 190.5 mmHg and the mean diastolic BP was 99.42 mmHg. Also, 2.38% had retinal detachment. In this patient, the systolic BP was 210 mmHg, while the diastolic BP was 100 mmHg. This was also similar in a study conducted by Reddy *et al.*<sup>[9]</sup> which showed that the higher systolic as well as diastolic BP associated with fundus changes.

### Association of LFT with preeclampsia

In the present study, it was seen that deranged LFT values were associated with fundus changes, while normal LFT values were not, and this finding was statistically significant.

In a study conducted by Girling *et al.*<sup>[10]</sup> in London where they compared the LFTs in normal gestation and gestation associated with preeclampsia, it was found that aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, and gamma glutamyl transferase (GGT) were lower in uncomplicated pregnancy than the nonpregnant laboratory reference ranges. Of those cases with elevated LFTs in the preeclampsia group, 37% were abnormal only by the new reference ranges.

### Association of KFT with preeclampsia

The aftereffects of toxemia of pregnancy have been studied by many clinicians. Peckham<sup>[11]</sup> found that the frequency of chronic nephritis following eclampsia increased in proportion to systolic BP. Nephritis did not develop if the systolic pressure did not exceed 170 mmHg; however, nephritis developed in 15% of those whose pressure reached 170–200 mmHg and in 48% of those whose pressure exceeded 200 mm.

In the present study, similar to the above LFT status, it was noted that fundus changes were present in patients with deranged KFT values, and this result was statistically significant.

Similarly, Herrick and Tillman<sup>[12]</sup> reported a series of 188 cases of mild toxemia of pregnancy, one-third of whom showed hypertension 1 year or more later. Peckham and Stout<sup>[13]</sup> reported a similar series, one-half of whom showed chronic vascular or renal disease 5 years later. Stander<sup>[14]</sup> followed 800 cases, 35% of whom had chronic nephritis, and 40% of those who developed chronic nephritis died in 5–7 years.

### Association of fundus changes with proteinuria in PIH patients

Higher grades of proteinuria were associated with advanced fundus changes, which is in contrast to the study by Reddy *et al.*<sup>[7]</sup> where they observed the association between retinal changes and different parameters. There was statistically significant positive association between the presence of retinal changes and BP ( $P=0.001$ ), proteinuria ( $P=0.018$ ), and severity of PIH ( $P=0.024$ ). However, age ( $P=0.41$ ), race ( $P=0.93$ ), and *g ravidā* ( $P=0.340$ ) were not associated with occurrence of retinopathy in our study.

But no significant correlation was found between the two in the above study.

### Pedal edema and its association with proteinuria

In the present study, majority of the patients with PIH had pedal edema. There was a significant correlation between proteinuria and pedal edema. In a study by Tadin *et al.*<sup>[15]</sup> the weakest correlation was found between hypertensive retinopathy and edema, which is a finding similar to that reported by other authors.<sup>[16,17]</sup>

## Conclusion

Preeclampsia is not a rare disease in pregnant women and occurs most frequently in primigravidae, and this seems to be common in the rural population of northern India (Saifai). Both for the mother and the infant, several complications can occur due to preeclampsia, and that is why it is important and necessary to follow-up and treat these women adequately. The problem in this area is caused by lack of awareness among the population, social taboos, poverty, and illiteracy. Due to these, many women (as many as 50%) choose to give birth at home. It is difficult to follow-up those patients who do not go to the hospital or cannot afford to stay there and have to be sent home. If a preeclamptic woman gets admitted and stays in the hospital, she gets adequate health care and is followed up frequently.

Most of the previous published literatures were mainly confined only to the retinopathy observed during preeclampsia and eclampsia crisis. This study is designed to evaluate a wider spectrum of changes, both ocular as well as biochemical,

that occur in hypertensive disorders in pregnancy in a rural population, which is usually ignored.

By expanding this study, we can also formulate the guidelines of diagnosis and management in such patients and can improve our treatment outcome in the near future.

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#### Conflicts of interest

There are no conflicts of interest.

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