Optic nerve sheath diameter measurements using ultrasonography to diagnose raised intracranial pressure in preeclampsia: an observational study

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Abstract

Objective: To estimate the incidence of raised intracranial pressure (ICP) as evident by enlarged optic nerve sheath diameter (ONSD) by ocular ultrasound among patients with preeclampsia and its relationship to severity of disease.

Material and Methods: Sixty pregnant mothers with preeclampsia were compared to 30 normotensive, uncomplicated pregnant controls. For ONSD measurement, a 7-MHZ linear probe was used and three values from each optic nerve were taken and the mean of six values of both eyes was recorded. All study subjects were followed until seven days after delivery.

Results: Two cut off values (5.8 mm and 4.6 mm) were used to compare ONSD in severe and non-severe preeclampsia with that of healthy pregnant individuals. The incidence of raised ICP among severe preeclampsia above 5.8 mm and 4.6 mm cut-off were 43.3% and 90%, respectively, before delivery. ONSD was significantly elevated among preeclampsia subjects at both cut-off values at pre-delivery ($p=0.004$ for ONSD >5.8 mm and $p<0.001$ for ONSD >4.6 mm) compared to controls. There a significant association between presence of neurological manifestations and enlarged ONSD ($p<0.001$ for ONSD >5.8 mm and $p=0.04$ for ONSD >4.6 mm) before delivery.

Conclusion: Severe preeclampsia with neurological features was associated with increased ONSD, reflecting raised ICP. Further studies are needed to compare ONSD values with invasive ICP monitoring for better understanding of this relationship. (J Turk Ger Gynecol Assoc 2023; 24: 5-11)

Keywords: Preeclampsia, optic nerve sheath diameter, intracranial pressure, ultrasonography

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Introduction

Preeclampsia is a pregnancy specific syndrome and poses a reproductive disadvantage unique to humans. Preeclampsia occurs in 7-8% of pregnancies and is complicated with eclampsia in up to 0.9% of cases (1-3). It is a potentially serious disease being a common cause of maternal morbidity and mortality in low resource countries, whereas poor neonatal outcome due to iatrogenic premature delivery is its most significant consequence in resource rich countries (1). Preeclampsia is characterised by multisystem involvement and central nervous system (CNS) manifestations are well documented (4). Signs of cerebral oedema have been found in magnetic resonance images (MRI) in up to 70-100% of mothers with severe preeclampsia (5-7). Early recognition of increased intracranial pressure (ICP) and prompt treatment aimed at reduction has been found to improve clinical outcome (8). However, the exact incidence of raised ICP in preeclampsia is not known and clinical signs of increased ICP are often difficult to interpret (9).

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The gold standard method to measure ICP is by invasive procedures (10). A part of the CNS, 3 mm behind the ocular globe optic nerve, is surrounded only by fat and its dural sheath is distensible when pressure in the cerebrospinal fluid (CSF) is elevated (9). Several clinical studies confirmed the utility of non-invasive ultrasound measurement of optic nerve sheath diameter (ONSD) to diagnose raised ICP in conditions incluing head injuries, intracranial haemorrhage and hydrocephalus (11-13). However, there is little published data about ONSD in preeclampsia worldwide, and even fewer in India. This prompted the present prospective observational study that included pregnant mothers with both severe and non-severe preeclampsia to estimate the incidence of raised ICP measured by ocular ultrasound examination when compared with uncomplicated pregnancies. A further aim of this study was to study preeclampsia-related pregnancy and neonatal outcomes in relation to the magnitude of raised ICP.

Material and Methods

This was a prospective cohort study conducted over a period of one year from October 2020 to November 2021 in the department of obstetrics and gynecology in a tertiary care centre, after approval from the Calcutta National Medical College Institutional Ethics Committee (approval number: CNMC-GYN-228, date: 07.10.2019). A total of 90 subjects participated and they were divided into three groups, each having an equal number of participants with severe preeclampsia, non-severe preeclampsia and uncomplicated term pregnancy after admission. Preeclampsia was defined as an association of a blood pressure elevation (systolic pressure >140 mmHg or diastolic pressure >90 mmHg) and a proteinuria >0.3 g per day in a pregnant woman after 20 weeks of gestation (14).

Severe preeclampsia was determined by presence of one or more of the following features (15):

- Systolic BP ≥160 mm of Hg,
- Diastolic BP ≥110 mm of Hg,
- Proteinuria ≥300 mg (0.3 gm) per day or ≥1+ on dipstick test,
- Presence of headache,
- Upper abdominal pain or epigastric pain,
- Visual disturbances,
- Pulmonary edema,
- Oliguria (urinary output ≤400 mL/day),
- Thrombocytopenia (platelets count <100,000/mm^3)
- Elevated serum transaminase (alanine aminotransferase and/or aspartate aminotransferase) levels of twice the upper limit of normal,
- Elevated serum creatinine (>1.1 mg/dL or doubling of baseline),
- Intrauterine growth restriction of fetus.

Patients with preeclampsia but not meeting these criteria were classified as having non-severe preeclampsia. Women with uncomplicated singleton pregnancy at term (gestational age 37 weeks or more) served as the control group. Informed consent was obtained from study subjects.

Exclusion criteria included unwillingness to participate in the study, prior ocular injury, prior ocular surgery, prior optic nerve disease, including optic neuritis and optic atrophy.

ONSD measurements were done before delivery prenatally (day P) and on day 4 and day 7 after delivery with the HD 7 ultrasonography (USG) machine (Philips) using a high frequency (7 MHz) linear transducer. Each patient was placed in the supine position and the probe placed over closed lids after applying a USG gel on the lid. The gel serves as a coupling fluid to prevent sound wave attenuation caused by air. ONSD was measured 3 mm behind the optic globe using an electronic calliper and an axis perpendicular to the optic nerve. For each optic nerve, three ONSD measurements were taken in the vertical transverse plane at low gain settings (16). The recorded ONSD was the mean of six values taken, three from each eye.

Demographic information including age, body mass index (BMI), parity, period of gestations at study measurement was obtained for each subject. Data regarding obstetric and neonatal outcomes in terms of mode of delivery, fetal growth restriction, sick new-born care unit (SNCU) admission and neonatal deaths were recorded.

Statistical analysis

All categorical data were represented as frequency (percentage) and continuous data as median (interquartile range). Comparisons of means were done with Mann-Whitney U test (between two groups) or Kruskal-Wallis test (more than two groups) and comparison of proportions with chi-squared test or Fisher's exact test. To determine optimal cut off values for the optic sheath measurements, receiver operating characteristic (ROC) curves were drawn and analysed. All statistical tests were performed using SPSS, version 21 (IBM Corp., Armonk, NY, USA).

Results

A total of 90 patients were included, consisting of 30 patients each with severe and non-severe preeclampsia and 30 subjects with uncomplicated pregnancies. Baseline comparisons of the groups are given in Table 1. Patients in the preeclampsia group were matched in terms of age with the non-preeclampsia group. Hypertension (100% vs. 0% respectively, $p<0.001$), micro-albuminuria [49 (81.7%) vs. 0% respectively, $p<0.001$] and thrombocytopenia [29 (48.3%) vs. 1 (3.3%) respectively, $p<0.001$] were more frequent in the preeclampsia group. Patients in the preeclampsia group had higher BMI compared

to the non-preeclampsia subjects and the prevalence of obesity tended to be higher in the preeclampsia group [19 (31.7%) vs. 4 (13.3%), respectively, p=0.06] although this did not reach significance.

Optic nerve sheath diameter measurements

Descriptive data of ONSD are given in Table 2. There was a variable period between first ONSD measurement (day P) and delivery (1-5 days) among the study subjects including healthy controls. ONSD was measured again on the fourth day post-partum (day 4) and then on seventh post-partum day (day 7).

ROC curve analysis was performed to identify optimal cut-off values for ONSD to distinguish preeclampsia from controls, which were (Figure 1): ≥4.25 [sensitivity 81.7%, specificity 83.3%, area under curve (AUC): 0.89, 95% confidence interval (CI): 0.821-0.954] for day P, ≥4.05 (sensitivity 83.3%, specificity 93.3%, AUC: 0.912, 95% CI: 0.849-0.975) for day 4, and ≥3.25 (sensitivity 78.3%, specificity 83.3%, AUC: 0.827, 95% CI: 0.74-0.913) for day 7. The distribution of the newly identified cut-offs when compared between the three groups is displayed in Table 2. The number of patients with higher ONSD, in terms of either cut-off value, was greater in the severe and non-severe preeclampsia groups compared to controls (Figure 2).

Association of ONSD measurements with maternal and neonatal outcome

The newly derived ONSD cut-off was compared with two previous cut-offs, one developed internationally and another specific to India (12,17) in terms of the relationship with maternal and neonatal outcome.

Neurological symptoms were present in 22.2% (20/90) patients, all among patients with severe preeclampsia. Emergency caesarean section was needed in 47.7% (43/90), mostly among patients with severe preeclampsia (20/30 vs. 10/30 among controls, p=0.03). Neonatal SNCU admission was needed in 27.8% (25/90) and neonatal mortality was 8.9% (8/90), the

Table 1. Baseline demographics, clinical and laboratory features of the entire cohort

Characteristics	Preeclampsia group, (n=60)	Severe preeclampsia group, (n=30)	Non-severe preeclampsia group, (n=30)	Non-preeclampsia group, (n=30)	p[a]	p[b]
Age in years	26 (20.25-29.75)	26 (22-30.25)	22.5 (20-28.25)	23 (20-27.25)	0.13	0.263
POG	38 (36.45-39)	37.2 (36.15-38.2)	39 (37.275-39.7)	38.45 (38-39.4)	<0.001	0.005
BMI	28 (26-30)	28 (26-31.25)	26 (23.75-30)	24 (22-26)	<0.001	0.001
SBP	160 (150-170)	170 (167-180)	150 (141.5-154.5)	118 (109.5-126)	<0.001	<0.001
DBP	106 (92.5-117)	116 (110-118.5)	93 (90-100)	74 (68-80)	<0.001	<0.001
24-hour urine protein excretion (mg/day)	320 (300-350)	340 (317.25-385)	308 (287.5-326)	276 (264.25-286)	<0.001	<0.001
Platelet (/μL)	150000 (112000-207500)	140000 (107000-180000)	167500 (120000-275000)	276000 (228750-354250)	<0.001	<0.001
Urea (mg/dL)	27.5 (22-30)	30 (23.5-37)	25 (21.5-28.5)	26 (23.5-28)	0.07	0.56
Creatinine (mg/dL)	0.8 (0.7-0.9)	0.9 (0.775-0.9)	0.8 (0.7-0.9)	0.9 (0.775-0.9)	0.15	0.43
AST (IU/L)	49 (36-141.5)	69 (37-180)	47.5 (35.5-110.5)	39 (35.75-45)	0.036	0.023
ALT (IU/L)	48 (36-119.5)	59 (36-137.25)	48 (33.5-84.5)	36.5 (34-40)	0.013	0.010
FHR	136 (118-140)	136 (114.5-140)	137 (124.5-140)	137 (132-142)	0.085	0.073
Birth weight	2.9 (2.425-3.2)	2.7 (2.2-3.1)	3 (2.6375-3.65)	2.85 (2.6-3.2)	0.086	0.67
Past history PIH	9 (15)	5 (16.7)	4 (13.3)	0	0.071	0.025
Headache	18 (30)	18 (60)	0	0	<0.001	0.001
Visual disturbance	9 (15)	9 (30)	0	0	<0.001	0.025
Epigastric pain	11 (18.3)	11 (36.7)	0	0	<0.001	0.012
FGR	11 (18.3)	7 (23.3)	4 (13.3)	0	0.013	0.012
Pulmonary oedema	1 (1.7)	1 (3.3)	0	0	0.99	0.99

Cells indicate median (25-75 percentile) or frequency (percentage). ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BMI: Body mass index in kg/m^2, DBP: Diastolic blood pressure (mmHg), FGR: Fetal growth restriction, FHR: Fetal heart rate, PIH: Pregnancy induced hypertension, POG: Period of gestation (weeks), SBP: Systolic blood pressure (mmHg). [a]P-value derived from Kruskal-Wallis test or 2x3 chi-squared test (omnibus test result comparing severe preeclampsia, non-severe preeclampsia and non-preeclampsia). In bivariate tests between severe group versus control group, additional significant difference was in FHR (p=0.025); in comparisons between non-severe group and control group no additional significant differences were found, but differences in terms of POG (p=0.73), BMI (p=0.08), AST (p=0.15) and ALT (p=0.118) lost significance, [b]Comparison between pooled patients of preeclampsia patients versus non-preeclampsia subjects

Table 2. Comparison of different optic nerve sheath measurement cut-offs

ONSD measurements	Preeclampsia group, (n=30)	Severe preeclampsia group, (n=30)	Non-severe preeclampsia group, (n=30)	Non-preeclampsia group, (n=30)	p[a]	p[b]
ONSD day P	5.2 (4.6-5.7)	5.65 (4.875-5.9)	4.88 (3.975-5.4)	3.7 (3.175-4.2)	<0.001	<0.001
ONSD day P >5.8 mm	14 (23.3)	13 (43.3)	1 (3.3)	0	<0.001	0.004
ONSD day P >4.6 mm	48 (80)	27 (90)	21 (70)	5 (16.7)	<0.001	<0.001
ONSD day P ≥4.25 mm	49 (81.7)	28 (93.3)	21 (70)	5 (16.7)	<0.001	<0.001
ONSD day 4	4.6 (4.2-5)	4.8 (4.575-5.4)	4.25 (3.95-4.8)	3.2 (2.8-3.6)	<0.001	<0.001
ONSD day 4 >5.8 mm	2 (3.3)	2 (6.7)	0	0	0.33	0.55
ONSD day 4 >4.6 mm	37 (61.7)	23 (76.7)	14 (46.7)	1 (3.3)	<0.001	<0.001
ONSD day 4 ≥4.05 mm	50 (83.3%)	30 (100)	20 (66.7)	2 (6.7)	<0.001	<0.001
ONSD day 7	3.7 (3.4-4.075)	3.9 (3.6-4.325)	3.6 (2.975-3.825)	2.95 (2.6-3.2)	<0.001	<0.001
ONSD day 7 >5.8 mm	0	0	0	0	-	-
ONSD day 7 >4.6 mm	8 (13.3)	6 (20)	2 (6.7)	0	0.025	0.036
ONSD day 7 ≥3.25 mm	47 (78.3)	26 (86.7)	21 (70)	5 (16.7)	<0.001	<0.001

Cells indicate median (25-75 percentile) or frequency (percentage). ONSD: Optic nerve sheath diameter. [a]P-value derived from Kruskal-Wallis test or 2x3 chi-squared test. [b]Comparison between preeclampsia patients and non-preeclampsia subjects, day P: Day prenatal (first day of ONSD measurement before delivery after admission in hospital), day 4: Day 4 postpartum, day 7: Day 7 postpartum

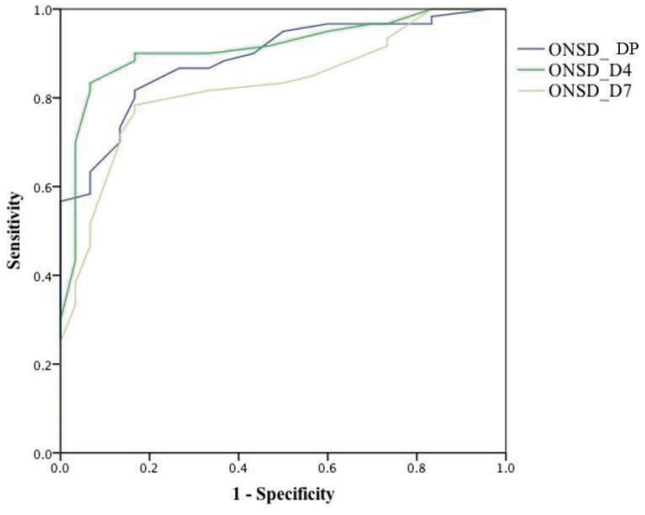

Figure 1. ROC curve analysis was performed to identify optimal cut-off values for ONSD to preeclampsia
ROC: Receiver operating characteristic, ONSD: Optic nerve sheath diameter

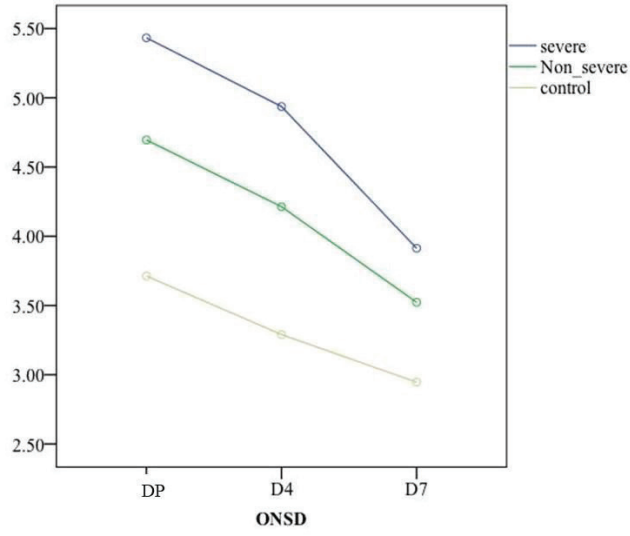

Figure 2. The number of patients with higher ONSD, in terms of either cut-off value in the severe and non-severe preeclampsia groups compared
ONSD: Optic nerve sheath diameter

latter exclusively among patients with severe preeclampsia. Association of these outcome measures with the optic nerve sheath measurements are given in Table 3. Higher ONSD were seen in patients with neurological symptoms and associated with physician's decision to perform emergency caesarean section. Among patients with severe preeclampsia, patients with neurological symptoms (n=20) had higher ONSD compared to patients without neurological symptoms (n=10) on day P [respectively 5.8 (5-5.9) vs. 5.4 (4.5-5.6), p=0.028], on day 4 [respectively 5.1 (4.7-5.5) vs. 4.6 (4.2-5), p=0.017] and on day 7 [respectively 4.05 (3.7-4.6) vs. 3.6 (3.1-3.7), p=0.008]. In this group, no significant association with other outcome measures were noted, except the need for emergency caesarean section with ONSD on day 7 [4.1 (3.7-4.6) vs. 3.6 (3.1-3.7), p=0.005]. Among patients with preeclampsia, different cut-offs for ONSD were associated with development of neurological symptoms. These are detailed in Table 4.

Discussion

In severe preeclampsia and eclampsia neurological complications may arise from co-existence of reversible

Table 3. Association of optic nerve sheath measurements with pregnancy and neonatal outcomes

	Neurological symptoms			Neonatal death			SNCU admission			Emergency caesarean section		
	Absent, (n=70) Present, (n=20)			Absent, (n=82) Present, (n=8)			Absent, (n=65) Present, (n=25)			Absent, (n=47) Present, (n=43)		
ONSD day P	4.2 (3.6-5.1)	5.8 (5-5.9)	<0.001	4.7 (3.8-5.4)	5.3 (4.7-6.1)	0.14	4.6 (3.8-5.3)	5.2 (4.6-5.8)	0.016	4.2 (3.6-5.1)	5.1 (4.2-5.8)	0.001
ONSD day 4	4 (3.2-4.6)	5.1 (4.7-5.6)	<0.001	4.2 (3.4-4.8)	4.6 (4.1-5.2)	0.23	4 (3.2-4.8)	4.6 (4.25-4.9)	0.02	3.8 (3.2-4.6)	4.6 (4-5)	<0.001
ONSD day 7	3.2 (2.8-3.6)	4.05 (3.7-4.6)	<0.001	3.45 (2.8-3.8)	3.95 (3.1-4.7)	0.09	3.4 (2.8-3.8)	3.7 (3.2-4)	0.09	3.2 (2.7-3.6)	3.8 (3.2-4.2)	<0.001

Cells indicate median (25-75 percentile). ONSD: Optic nerve sheath diameter, SNCU: Sick new-born care unit. P-values were calculated using the Mann-Whitney U test

Table 4. Comparison of different optic nerve cut offs on day P in terms of their association with pregnancy and neonatal outcomes

	Neurological symptoms			Emergency caesarean section			Neonatal death		
	Present, (n=20)	Absent, (n=40)	p	Present, (n=33)	Absent, (n=27)	p	Present, (n=7)	Absent, (n=53)	p
ONSD day P >5.8 mm	11 (55)	3 (7.5)	<0.001	12 (36.4)	2 (7.4)	0.008	2 (28.6)	12 (22.6)	0.73
ONSD day P >4.6 mm	19 (95)	29 (72.5)	0.04	29 (79.4)	19 (70.4)	0.42	6 (85.7)	42 (79.2)	0.68
ONSD day P ≥4.25 mm	20 (100)	29 (72.5)	0.009	30 (90.9)	19 (70.4)	0.041	6 (85.7)	43 (81.1)	0.77

Cells indicate frequency (percentage). ONSD: Optic nerve sheath diameter

cerebral vasoconstriction syndrome and posterior leuco-encephalopathy syndrome, giving rise to clinical features like headache, reversible blindness, confusion, and convulsions (18-21). Reversible cerebral vasoconstriction syndrome is associated with subarachnoid and intracerebral haemorrhage and posterior leukoencephalopathy syndrome results in diffuse vasogenic oedema (22,23). Such vasogenic oedema happens due to failure of cerebral autoregulation, disruption of blood brain barrier and endothelial dysfunction (23,24). The resultant cerebral oedema arising from both vasogenic oedema and vasoconstriction-induced cytotoxic oedema contributes to raised ICP (24). Invasive monitoring of ICP is expensive and associated with complications, such as bleeding and infection (17). Performing MRI scans for regular assessments and comparisons may not be cost effective in resource poor countries and transportation of critically ill pregnant mothers to radiology departments may be hazardous (25). USG is a less expensive, quick, real time, and dynamic imaging modality with an objective endpoint in this situation. It has been observed that about 25 scans are enough for an inexperienced sonographer to become proficient in its use (26). In contrast, fundoscopy for papilledema to detect raised ICP has limitations, as papilledema takes time to become evident (27). Moreover, the findings are subjective with inter-observer variability and detection of early papilledema can be a diagnostic challenge (28).

Optic nerve, being a direct extension of the CNS, and unlike other cranial nerves, is surrounded by the meninges and is subjected to the same pressure changes as occur in the intracranial compartment when CSF pressure increases. The increased CSF pressure is transmitted directly to the subarachnoid space between the nerve and its sheath, leading to distension of the intra orbital part of the sheath, particularly the retrobulbar segment (17). The resultant increase in ONSD, can be measured by USG B scan and provides strong evidence of intracranial hypertension (29). When compared with invasive monitoring of ICP, an ONSD value >5.8 is associated with 95% risk of raised ICP (>20 mmHg) (12). Average ONSD among Indian women, aged between 18 and 40 years, was 4.6 mm (17). In this study we compared ONSD measurements with the maternal and neonatal outcomes at both these cut-offs values of 5.8 mm and 4.6 mm. The two prominent studies on changes in ONSD measurements in preeclampsia by Dubost et al. (9) and Brzan Simenc et al. (30) did not a significant correlation between severity of the disease and increased ONSD values, probably due to small sample size. Incidence of raised ICP (ONSD >5.8 mm) in severe preeclampsia was found to be 19% by Dubost et al. (9) and 43% by Brzan Simenc et al. (30). In our study, it was 43.3%, similar to the study by Brzan Simenc et al. (30). We found a significant association between increased ONSD and neurological manifestations in our study at different cut off values including the newly derived optimal cut-off, particularly in the pre delivery state. A study with transcranial Doppler has shown a gradual reduction of cerebral oedema in preeclampsia and eclampsia over 5 to 6 days after delivery (31). A similar

reduction in ONSD in severe preeclampsia was found following delivery over one week in these three studies. Both Dubost et al. (9) and Brzan Simenc et al. (30) found higher ONSD values after delivery and 5 days postpartum when compared with uncomplicated normotensive pregnant controls. We too found significantly higher ONSD measurements when compared to that of uncomplicated pregnancy at the 4.6 mm cut-off and at the newly derived cut-off values over 7 days postpartum. However, the data regarding time course of persistence of enlarged ONSD once dilated is lacking. Rajajee et al. (32) postulated a delayed reversibility of ONSD in long standing increased ICP. Bala et al. (33) commented that increase in OSND occurred before manifestation of neurological features when ICP starts to increase and the reverse occurs during resolution of intracranial hypertension, with ONSD reversal lagging behind resolution of CNS manifestations. Some studies have shown persistent excess fluid accumulation in extravascular lung spaces for several days after delivery in severe preeclampsia (34,35). This information, along with the findings of increased ONSD over seven days post-delivery highlights the importance of intensive monitoring of such critical patients for several days after delivery.

Study Limitations

The limitations of our study were that we did not compare our findings with invasive ICP monitoring and we did not have MRI brain scans for correlation.

Conclusion

We were able to identify much lower new cut off values for ONSD, at which neurological manifestations became evident. Further studies involving larger sample sizes and longer duration of follow-up are needed to be undertaken. Furthermore, ONSD measurements can be compared with invasive ICP values, MRI brain studies and treatment outcomes using diuretics and/or fluid restrictions.

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Ethical Committee Approval: *The study was approved by the Calcutta National Medical College Institutional Ethics Committee (approval number: CNMC-GYN-228, date: 07.10.2019).*

Informed Consent: *Informed consent was obtained from study subjects.*

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