



Factors Associated with Perinatal Mortality in Adult Pregnant Women with Hypertensive Disorders: A Case–Control Study

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Received: 9 November 2022 / Accepted: 28 May 2023 / Published online: 30 June 2023
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Abstract

Background Hypertension complicates 5–10% of pregnancies and is a common cause of perinatal death. The perinatal mortality is estimated to be 3 to 5 times higher in hypertensive women compared to those without hypertension.

Methods A hypertensive mother either with a stillbirth or if baby died within 7 days of life was included as a case. Once a case was recognized, the next two consecutive hypertensive mothers who delivered a live baby, who survived up to 7 days of life, were taken as controls. Fetuses with congenital malformations incompatible with life and multiple pregnancies were excluded from the study. One hundred and twelve women in cases and 224 women in controls were studied.

Results Among 112 cases of perinatal death, 70% had died in utero before labor. Among the 33 fetuses alive, 50% were born still after labor and 50% died within 7 days of birth. We found that early onset hypertension (<34 weeks) ($p < 0.001$ (Chi2-23.819)), gestational age at termination of 28–32 weeks (OR 2.76), value of serum creatinine > 1.1 mg/dl (OR 10.1), abruption (OR 6.2) and birth weight < 1.5 kg was significantly associated with perinatal mortality ($p = 0.007$, OR 5.7). Abnormal Doppler findings was a predictor of perinatal deaths.

Conclusion Severely growth retarded fetuses in association with early onset severe preeclampsia are likely to die in utero and need vigilant monitoring antenatally. Abnormal umbilical artery Dopplers predict perinatal mortality. Caesarean section at the gestational age of ≥ 32 weeks and an estimated fetal weight of ≥ 1.2 kg in our hospital resulted in favorable outcome.

Keywords Hypertension · Pregnancy · Pre-eclampsia · Doppler · IUGR · Perinatal mortality

Introduction

Perinatal mortality in our country is 18 per 1000 live births ranging from 12 in urban areas to 21 in rural areas in 2020 [1].

Hypertension complicates 5–10% of pregnancies and is a common cause of perinatal death [2]. Hypertensive

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disorders are quite often associated with preterm delivery and growth restriction of the fetuses and require admission to intensive care unit [3, 4]. Spectrum of hypertensive disorders in pregnancy include preeclampsia (PE), eclampsia, chronic hypertension, PE superimposed on chronic hypertension and gestational hypertension [5].

Hypertensive disorders endanger the life of both mother and fetus during pregnancy. It can result in utero-placental insufficiency which may lead to antepartum and intrapartum hypoxia ultimately causing growth retardation and increased perinatal morbidity and fetal death [6].

Many studies have compared the perinatal outcome of women with hypertensive disorders with those without hypertension. The perinatal mortality is estimated to be 3 to 5 times higher in hypertensive women compared to those without hypertension [4].

There is paucity of case-control studies within the group of hypertensive women.

In a tertiary care setup like ours with intensive labor monitoring and prompt round-the-clock cesarean facility and highest level of nursery care, the perinatal mortality associated with hypertensive women continues to be high. There are about 120 to 140 hypertensive women delivering in our hospital every month, and among them 10–15 perinatal deaths were observed.

This case-control (1:2 ratio) study was conducted in pregnant women with hypertension to determine the factors that affect the perinatal death among the women with hypertension. Pregnancies with hypertension resulting in perinatal mortality were considered as case and without perinatal mortality as controls. This helped us to identify the modifiable factors and implement measures to reduce the perinatal deaths among women with hypertensive disorders.

Materials and Methods

Study Setup

The study was conducted in the Obstetrics and Gynecology department in collaboration with the department of Neonatology at Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India, from October 2015 to March 2017. The Institute Ethics Committee approved the study.

Study Population

All women with hypertensive disorders who delivered in JIPMER.

Study Procedure

A hypertensive mother with a perinatal death (stillbirth or those who died within 7 days of birth) was included as a case. For each case, two controls were selected and those were the next two hypertensive mothers who had delivered consecutively and whose neonates had survived beyond 7 days of life. Fetuses with congenital malformations incompatible with life and multiple pregnancies were excluded from the study. After taking informed consent, details of these women in both cases and controls, as well as the baby details, were collected as per the proforma. The status of neonates, who got discharged before 7 days, were followed up on the 8th day of life by a phone call.

Study Outcomes

Structured proforma was used to collect the data. Data included demographic details, obstetric details, details of hypertensive disorders, ultrasound details, the number of doses of steroids completed and use of magnesium sulfate. The intrapartum details and the mode of delivery were noted. We recorded the neonatal outcomes like Apgar score at one minute and five minutes, birth weight, admission to neonatal care unit, neonatal complications, cause of death and day of death. We estimated the proportion of perinatal deaths in each of the hypertensive disorders. We assessed the sociodemographic, obstetric and fetal/newborn factors associated with perinatal mortality. We followed up all the babies till 8th day of life.

Sample Size Calculation

Assuming power of 80%, 95% confidence interval and case versus control ratio as 1:2, sample size calculation was done for the possible predictors documented in the literature [7]. Highest sample size required was 112 cases and 224 controls. All consecutive hypertensive mothers with perinatal deaths during the study period were included as cases till the sample size was achieved.

Analysis

Data were entered in Epi Data entry, and Stata software was used for analysis. Categorical variables like maternal parity, age group, gravida, antenatal care, presence of any complications or risk factors in the mother, type of delivery, labor and gestational age were summarized as percentages using the unpaired t test. Continuous variables like birth weight (< 1.5 kg/1.5–2.5 kg/> 2.5 kg), SGOT levels, urine protein, blood urea, serum creatinine

and uric acid were summarized as Mean ± 2SD using the Chi-square test.

Odds ratio was calculated to assess possible association of selected sociodemographic, clinical and biochemical factors with perinatal mortality. Factors significant at *p* value of <0.1 in unadjusted analysis were included in multivariate analysis. Adjusted odds ratio using binary logistic regression analysis (perinatal mortality as dependent variable) was calculated to identify the predictors of perinatal mortality. For all analyses, *p* value of <0.05 was considered for statistical significance.

Results

Among 112 cases in the study group, there were 79 cases of antepartum intrauterine deaths and 33 cases with live fetus at the time of admission to our hospital. Among these 33 cases, there were 16 cases of intrapartum deaths and 17 early neonatal deaths. Baseline characteristics of study population

did not show significant association with perinatal mortality (Fig. 1).

Among the participants, majority of women had PE (70.2%), followed by 14.3% cases of eclampsia, 10.1% cases of gestational hypertension and 5.4% cases of chronic hypertension. The onset of hypertension was 3 weeks earlier in the case group (mean-29.4 ± 6.1 weeks) compared to controls (mean-32.5 ± 6 weeks) (Chi-square-0.057, *p*-<0.001). There was significant association of early onset of hypertension (<34 weeks) (Chi-square-23.8, *p*-<0.001) with perinatal mortality. But use of antihypertensives, presence of comorbidities, urine protein creatinine ratio and abnormal fundus findings showed no significant association with perinatal mortality. Also, maternal complications were not significantly associated with perinatal mortality except for reduced urine output (*p*-0.004). Distribution of women based on severe features of PE is given in Table 1.

The mean period of gestation at delivery among the study group was 32.5 ± 3.5 weeks compared to 35.5 ± 3 weeks among controls (Fig. 2). There were

Fig. 1 Baseline characteristics of the control and the case group

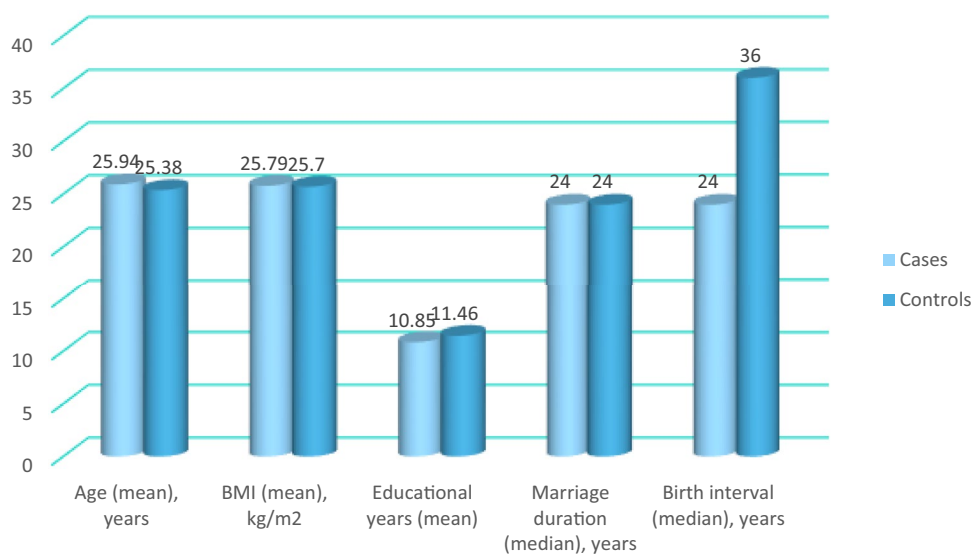


Table 1 Distribution of women based on severe features of preeclampsia

Variables	Cases <i>N</i> (%) <i>N</i> =112	Controls <i>N</i> (%) <i>N</i> =224	Total <i>N</i> (%)	<i>p</i> value
SBP ≥ 160 or DBP ≥ 110 mmHg	69 (61.6)	154 (68.8)	223(66.4)	0.191
Platelet count < 1 lakhs	13(11.6)	13 (5.8)	26 (7.7)	0.060
SGOT or SGPT > 70 U/L	7 (6.3)	20 (8.9)	27 (8)	0.394
Microangiopathic hemolytic anemia	5 (4.5)	5 (2.2)	10 (3)	0.256
Serum creatinine > 1.1 mg/dL	13 (11.6)	10 (4.5)	23 (6.8)	0.014 (χ²-5.974)
proteinuria	87 (77.7)	177 (79)	264 (78.6)	0.779
Urine protein 1+ or more	80 (71.4)	168 (75)	248 (73.8)	0.482

χ² - Chi-Square

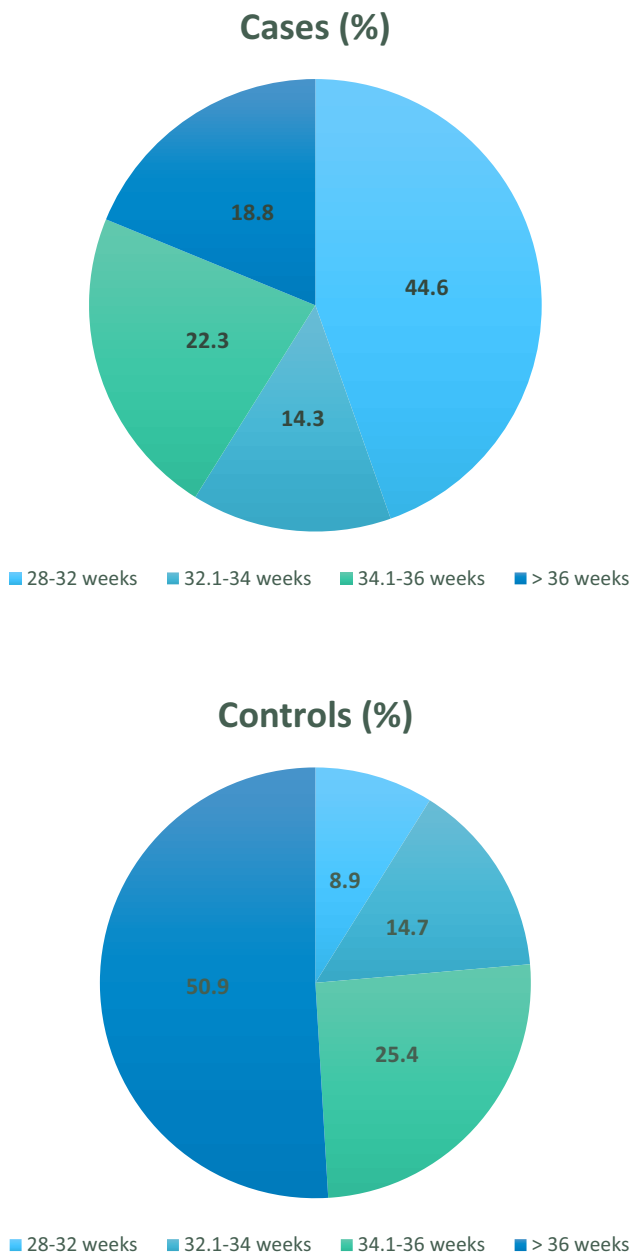


Fig. 2 Distribution of the two groups based on period of gestation at delivery

Table 2 Distribution of women with live fetus who underwent labor among study group based on gestational age, Doppler and mean birth weight

Gestational age (weeks)	Doppler					Type of perinatal death		Mean birth weight (Kg)
	Normal	AEDF	REDF	Not recorded	Reduced flow	intrapartum	Neonatal death	
28–30	1	3	4	2	2	10	2	0.815
30.1–32	1	1	3	1	0	6	0	1.08
32.1–34	1	0	2	0	0	3	0	1.17
34.1–36	0	1	2	0	0	2	1	1.26
> 36	1	0	1	3	0	3	2	2.75

more perinatal deaths in association with lower period of gestation at delivery ($p < 0.001$, Chi-square-24.23). Only 161 women out of 336 women had undergone fetal Doppler studies. Among them, 80 (49.7%) had abnormal findings. Eighty-three percentage women of study group had abnormal Doppler compared to 36% women of controls, which was statistically significant. There were 13 cases of reversed end diastolic flow (REDF) and 6 cases of absent end diastolic flow (AEDF) in study group compared to 5 REDF and 20 AEDF in controls. The mean birth weight was 1.44 ± 0.8 kg for the study group and 2.06 ± 0.7 kg for controls. Among AEDF babies, mean birth weight was 950gms for the study group and 1.2 kg for controls. Among REDF babies, mean birth weight was 1.1 kg for the study group and 1.25 kg for controls. In view of the extreme prematurity and very low birth weight, the women were counseled about the neonatal survival in consultation with the neonatologist, and after counseling, 12 women with REDF and 5 women with AEDF in the case group refused caesarean section. Four women out of the 33 with live fetus of the study group were delivered by caesarean section without labor in view of abnormal Doppler finding (AEDF and REDF). In view of the fact that very few ($n = 29$) women in the case group with live fetus underwent labor, it was difficult to analyze the association of mode of delivery with perinatal mortality.

Distribution of study group with live pregnancy at admission based on Doppler finding, period of gestation, birth weight, type of labor is given in Table 2.

The neonatal outcomes are given in Table 3. The most common cause of early neonatal death was septic shock. Nine (52.9%) out of 17 babies died due to septic shock mainly following prematurity. There were 14.3% of women from the study group who had placental calcification, whereas only 3.1% of women from controls had placental calcification. Placental calcification was significantly associated with perinatal mortality ($p < 0.001$).

Predictors of perinatal mortality in women with hypertensive disorders of pregnancy by multivariate analysis are

Table 3 Distribution of study population based on neonatal factors

Neonatal factors	Study group <i>N</i> (%)	Controls <i>N</i> (%)	Total <i>N</i> (%)	<i>p</i> value (χ^2)
Apgar score < 7 at 5 min	10 (50)	10 (4.5)	20 (7.7)	< 0.001 (270.509)
Neonatal Intensive Care Unit (NICU) admissions	17 (100)	132 (59.2)	149 (62.1)	< 0.001 (11.174)
Need of ventilation	15 (88.2)	10 (7.6)	25 (16.8)	< 0.001 (70.171)
Respiratory distress syndrome	9 (52.9)	32 (24.2)	41 (27.5)	0.012 (6.219)
Early onset sepsis	10 (58.8)	8 (6.1)	18 (12.2)	< 0.001 (39.475)
Late onset sepsis	0	2 (1.5)	2 (1.3)	0.609
Necrotizing Enterocolitis (NEC)	0	6 (4.5)	6 (4)	0.369
Hypoxic ischemic encephalopathy (HIE)	3 (17.6)	2 (1.5)	5 (3.4)	< 0.001 (12.085)
Birth asphyxia	6 (35.5)	5 (3.8)	11 (7.4)	< 0.001 (21.864)
Seizures	3 (17.6)	1 (0.8)	4 (2.7)	< 0.001 (16.444)
Persistent pulmonary hypertension (PPHN)	1 (5.9)	2 (1.5)	3 (2)	0.227

χ^2 - Chi-Square

Table 4 Predictors of perinatal mortality in women with hypertensive disorders of pregnancy

Variables	Cases	Controls	Adjusted OR (confidence interval)	<i>p</i> value
Age (mean, years)	25.9	25.3	1.0 (0.9–1.1)	0.510
Total number of visits (median, years)	8	9	0.8 (0.6–0.9)	0.018
Period of gestation at diagnosis of hypertension (<i>N</i> (%))				
< 20 weeks	7 (6.3)	11 (4.9)	3.9 (0.7–20.5)	0.100
20–34 weeks	77 (69.4)	96 (42.9)	1.3 (0.5–3.1)	0.575
> 34 weeks	27 (24.3)	117 (52.2)	1	
Type of hypertension (<i>N</i> (%))				
Chronic hypertension	7 (6.3)	11 (4.9)	1	
Gestational hypertension	12 (10.7)	22 (9.8)	4.9 (1.2–18.2)	0.019
PE	82 (73.2)	154 (68.8)	2.4 (0.9–6.3)	0.072
Period of gestation at termination (<i>N</i> (%))				
28–31.6 weeks	50 (44.6)	20 (8.9)	2.8 (0.9–7.7)	0.052
32–35.6 weeks	16 (14.3)	33 (14.7)	1.1 (0.3–3.1)	0.878
36–40 weeks	25 (22.3)	57 (25.4)	1	
> 40 weeks	21 (18.8)	114 (50.9)	1.4 (0.4–4.0)	0.524
Use of corticosteroids (<i>N</i> (%))				
Yes	33 (50)	48 (90.6)	1	
No	33 (50)	5 (9.4)	5.8 (2.8–9.4)	< 0.001
Birth weight (<i>N</i> (%))				
< 1.5 kg	73 (65.2)	61 (27.2)	5.7 (1.6–20.1)	0.007
1.5–1.999 kg	18 (16.1)	62 (27.7)	2.1 (0.6–6.8)	0.228
2–2.499 kg	11 (9.8)	33 (14.7)	2.9 (0.9–8.9)	0.073
> 2.5 kg	10 (8.9)	68 (23.2)	1	
Abruptio (<i>N</i> (%))				
No	76 (67.9)	211 (94.2)	1	
Yes	36 (32.1)	13 (5.8)	6.2 (2.6–14.5)	< 0.001

OR - Odds ratio

given in Table 4. We found that gestational age at termination of 28–32 weeks (OR 2.76), value of serum creatinine > 1.1 mg/dl (OR 10.1), abruptio (OR 6.2) and birth

weight < 1.5 kg were significantly associated with perinatal mortality (*p*-0.007, OR 5.7).

Discussion

This study was undertaken in a large tertiary care teaching hospital in south India, to determine the factors that influence perinatal mortality in pregnant women with hypertensive disorders.

We studied 336 women with hypertensive disorders and compared women with perinatal mortality and those with favorable perinatal outcome. We did not find any significant association of age, body mass index (BMI), education, occupation, marriage duration, parity and birth interval with perinatal mortality. Similar findings were observed by other authors [7–9]. But study conducted by Panda S et al. reported significantly higher perinatal deaths in young women < 25 years and elderly women > 35 years ($p=0.0001$) [10]. Also, another study conducted in Haiti observed that women with stillbirth were more likely to be parous ($p=0.047$) [11].

We observed fewer perinatal deaths in women who had more number of antenatal visits. Similar observation was made by other authors from different countries [10, 12, 13].

Barbosa et al. and Panda et al. [10, 14] found higher perinatal mortality in women with eclampsia, whereas we found the contribution of eclampsia to be low. The possible reason could be that the mean birth weight of babies of women with eclampsia in our study was 1.8 kg with a mean period of gestation of 34.4 weeks.

The mean period of onset of hypertension in our study was 29.4 ± 6.1 weeks among the case group and 32.5 ± 6 weeks among controls. We observed that early onset preeclampsia was more often seen in women with perinatal mortality compared to those with favorable perinatal outcome. Similar findings were observed in a study conducted in Netherlands. The authors reported that in comparison with non-preeclampsia women, early onset PE (24–32 weeks) women had significantly higher perinatal mortality (7% versus 13%) [15]. Similar observation was made by the authors in a study from Ethiopia [16]. We also observed that severe PE requiring termination before 32 weeks of gestational age is a predictor of perinatal mortality (OR 2.02) which is consistent with a study conducted in Ethiopia and Suriname [7, 17].

The mean birth weight in our study for perinatal deaths was 1.44 ± 0.8 kg and for live babies was 2.06 ± 0.7 kg. Very low birth weight was a significant predictor of perinatal mortality which is consistent with the findings of other authors [7, 9, 17]. Bridwell M et al. identified that low birth weight (< 2.5 kg) was seen three times more in women with stillbirths (aOR 3.51, $p < 0.0001$) [11].

There was no significant association of systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 110 mmHg with

perinatal mortality in our study. But, some studies have shown significant association of perinatal mortality with systolic blood pressure (SBP) ≥ 160 mmHg or diastolic blood pressure (DBP) ≥ 110 mmHg [7, 10, 12, 18, 19].

In our study, among laboratory findings, significant association with perinatal mortality was seen with serum creatinine > 1.1 mg/dL. Platelet count < 1 lakhs, serum creatinine > 1.1 mg/dL and serum glutamic oxaloacetic transaminase (SGOT) raised by \geq twofold were found to be predictors of perinatal mortality in a study conducted in Ethiopia [7]. Further, Tlaye et al. observed that odds of perinatal death among those with end organ involvement were 4 times higher [19].

Proteinuria was not significantly associated with perinatal mortality in our study. But the presence of urine protein was significantly associated with perinatal deaths in study by other authors [10, 12].

Among those with < 34 weeks pregnancy and live babies at admission in the study group, only 76% received steroids compared to 90.6% of controls. The reason could be the emergent maternal condition requiring urgent termination and not giving adequate time to wait for the completion of the steroids. We found that non-administration of corticosteroids had higher risk of perinatal mortality in multivariate analysis. Similar observation was made by Meuma et al. [9].

We found a significant association of abruption to perinatal mortality ($p < 0.001$). Similar observation was made by the authors who conducted a study in various hospitals in Haiti ($p=0.01$) [11]. In a review article by Katheryne et al., the authors reported that abruption was a significant risk factor for stillbirths (3.4–51.8%), neonatal deaths (1.1–19%) and total perinatal deaths (4–56.3%) [20].

Among the 112 cases with perinatal mortality, 79 were intrauterine demise before the onset of labor. Another 33 cases had live fetus. Four were delivered by prelabor caesarean section, but the babies died later. Among these, 17 had unfavorable Doppler (12 with REDF and 5 with AEDF). Abnormal Doppler was predictive of mortality. Similar observation has been made by other authors [21–24].

Twenty six of the 33 with live fetus in the study group were delivered vaginally. These 26 cases were not taken for caesarean in view of extreme prematurity, growth restriction and guarded prognosis, and on informed counseling the patients and relatives refused caesarean section. Three women out of 29 with gestational age > 36 weeks were delivered by caesarean for fetal distress in labor. There were 16 intrapartum stillbirths, and the others expired in the neonatal period. Due to small numbers of 29 with live pregnancy undergoing labor in the study group, the association of mode of delivery with perinatal mortality could not be analyzed. But significant association of vaginal delivery to perinatal mortality was shown in a study conducted by Endeshaw et al. (OR 5.3) and Bridwell M et al. (p value 0.0005) [7, 11].

Among the 17 babies born alive in the study group, half of them had low Apgar score and all had NICU admission; 15 out of these 17 (88.2%) needing ventilation. This reflects that severe IUGR baby with period of gestation < 32 weeks cannot withstand labor and labor worsens the hypoxia and asphyxia at birth. Such babies also cannot withstand any infection and can die of sepsis. Apgar score was found to be a significant predictor of unfavorable fetal outcome in our study. Similar observation was made by other authors [12, 17, 19, 25].

We observed that respiratory distress, early onset neonatal sepsis and birth asphyxia were significantly increased in the study group. This might be because the mean gestational age and birth weight were significantly lower in the study group. Similar observations have been made by Van Esch et al. [15, 25].

We recommend future studies on influence of mode of deliveries in these pregnant women of hypertensive disorders with extreme prematurity of less than 32 weeks and extremely low birth weight of 1 to 1.4 kg weight who require termination of pregnancy.

Conclusion

The factors associated with perinatal mortality are early onset of hypertension (< 34 weeks), gestational age at termination 28–32 weeks, value of serum creatinine > 1.1 mg/dL, abruption, low birth weight and abnormal Doppler to perinatal mortality. To improve the neonatal outcome in women with fetal REDF, the best way is to deliver the baby by caesarean section if the gestational age is \geq 32 weeks and an estimated fetal weight is \geq 1.2 kg. Fetuses with AEDF can withstand labor, but it increases the chances of neonatal morbidity and mortality by being more susceptible to sepsis and asphyxia specially if they are less than 1 kg and less than 32 weeks.

Acknowledgements We acknowledge the authorities of JIPMER for allowing us to use the infrastructure of JIPMER for carrying out the study.

Author Contributions All authors contributed to the study conception and design. Material preparation and data collection were performed by Blessy John. Analysis was performed by Blessy John, Gowri Dorairajan and Palanivel Chinnakali. The first draft of the manuscript was written by Blessy John and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This research did not receive any specific grant from funding agencies in the public commercial, or not-for-profit sectors.

Declarations

Conflict of Interests All the authors declare that there is no conflict of interest.

Ethical Approval The study was approved by the Institute Ethics Committee (Human Studies) Reg. No: ECR/342/Inst/PY/2013 in JIPMER, India.

Informed Consent Individual consent was obtained from all the individual participants included in this study and for publication of results of the study.

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