



# Perinatal Survival in Women with Low Resources with Early Onset, Late Onset Hypertensive Disorders

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## Abstract

**Background:** Perinatal outcome is affected in Hypertensive disorders during pregnancy (HDsP). Due to many reasons, including gestation, interventions done. It seems etiology, pathogenesis of Early Onset (EO), Late Onset (LO) HDsP, effects on mother, baby too are different.

**Objectives:** To know perinatal survival in EO, LO HDsP cases.

**Material Methods:** Study subjects according to inclusion criteria, 1076 cases of HDsP (11.73% of 8920 births during study) with singleton pregnancy, beyond twenty weeks, without any pre-existing disorders, were divided into, EO (category A  $\geq 20$  to  $<28$  weeks, B ( $\geq 28$  to  $<34$  weeks), LO (category C  $\geq 34$  to  $<37$  weeks, D  $\geq 37$  weeks), as per onset of HDsP.

**Results:** Mean gestation at birth in category A was 30+1 weeks, B 32+6, C 35+4 weeks, D 38+4 weeks. In category A there were 97.5% preterm births 42.5% caesarean sections, 100% perinatal deaths in births before 28 weeks, 2 babies who reached term survived. Critical gestation was 32 weeks plus. In category B, 84.29% were preterm births, 15.71% term births, CSR 53.93%. In category C, 31.37% were preterm births, 68.63% term 40.63% CSR, category D, 54% vaginal births, CBs 46%. Mean birth weight in category A was 1741.54 gms, B 1936.31 gms, C 2633.38 gms, D 2677.30 gms. Perinatal deaths in category A were 45%, B 25.13%, C 14.32%, D 14.00%.

**Conclusion:** EO HDsP have more adverse perinatal outcome than LO HDsP. For pregnancy which could go to around 34 weeks survival was similar to term cases. More research is needed.

**Keywords:** Early onset; Late onset; Hypertensive disorders of pregnancy; Fetal neonatal outcome

## Background

Hypertensive Disorders of Pregnancy (HDsP) are multi-system disorders that significantly contribute to fetal/neonatal morbidity and mortality [1,2,3,4,5,6]. For better understanding of the etiopathogenesis, course and outcome, these disorders are being divided into Early Onset (EO) and Late Onset (LO) disorders, depending upon the gestation at which they occur. Care of critically ill mothers and very low birth weight babies is affected in low resource settings which affects perinatal survival. There are not many studies from low resources settings.

## Objectives

Present study was done, to know the differences in foetal/neonatal outcome in EO and LO cases of HDsP with singleton pregnancy, beyond 20 weeks.

## Material Methods

Study was carried out in Obstetrics Gynaecology of referral hospital with the help of Biochemistry after approval of the institute's ethics committee. Consent was taken from all the study subjects of singleton pregnancy beyond twenty weeks gestation, diagnosed as gestational hypertension, preeclampsia or eclampsia. Women with pre-pregnancy hypertension, renal, liver, cardiac disease, known diabetes or other medical disorders, past or current smokers, not willing to deliver at the place of study were excluded. Study subjects were divided in two major groups  $\geq 20$  to less than 34 wks (EO) and 34 wks onwards (LO). For further analysis cases were categorized into 4 subgroups, EO A  $\geq 20$  to  $<28$ , B  $\geq 28$  to  $<34$  and LO into, C  $\geq 34$  to  $<37$  and D  $\geq 37$ . Information including demography, day to day investigations of all the cases was recorded on the predesigned tool. Cases were followed up to 7 days postpartum or discharge. Fetal/neonatal outcome of the four groups were compared using unpaired student's t test and ANOVA test and P values of less than 0.05 were considered significant.

## OPEN ACCESS

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Received Date: 12 Apr 2018

Accepted Date: 18 May 2018

Published Date: 25 May 2018

### Citation:

Chhabra S, Singh A. Perinatal Survival  
in Women with Low Resources with  
Early Onset, Late Onset Hypertensive  
Disorders. Ann Pregnancy Birth. 2018;  
1(1): 1003.

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**Table 1:** Gestation at delivery in study subjects and birth weight.

Category	Weeks at delivery	Birth Weight (grams)																		Total		
		<1000				1000-1499				1500-1999				2000-2499				≥ 2500				
		M	N	L	F	M	N	L	F	M	N	L	F	M	N	L	F	M	N			
A n=80	<28	4	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15
	≥ 28-34	0	0	15	1	3	11	2	0	3	1	0	0	0	0	0	0	0	0	0	0	36
	≥ 34-37	0	0	0	0	0	0	17	0	0	0	8	0	2	0	0	0	0	0	0	0	27
	≥ 37	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	2
		4	11	15	1	3	11	19	0	3	1	10	0	2	0	0	0	0	0	0	0	80
B n=191	≥ 28-32	5	15	36	2	6	6	61	0	4	1	0	0	0	0	0	0	0	0	0	0	136
	≥ 34-37	0	0	0	1	0	0	0	0	0	0	40	2	2	4	0	0	0	0	0	0	49
	≥ 37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	6
		5	15	36	3	6	6	61	0	4	1	40	2	2	4	6	0	0	0	0	0	191
C n=475	≥ 34-37	0	0	3	0	0	0	54	2	3	10	50	1	9	17	0	0	0	0	0	0	149
	≥ 37	0	0	0	0	0	0	0	0	0	0	100	4	0	10	200	1	0	11			326
		0	0	3	0	0	0	54	2	3	10	60	5	9	27	20	1	0	11			475
D 300	≥ 37	0	0	0	0	0	0	19	0	5	0	55	10	6	10	184	3	1	7			300
TOTAL		9	26	54	3	9	15	153	0	16	14	255	16	22	41	390	4	1	18			1046
		35				81				183				334				413				

M: Macerated Still Birth, N: Neonatal Death, L: Live Birth, F: Fresh Still Birth

**Table 2:** Perinatal loss in different categories.

Category	Mode of labour Onset	Gestational Delivery(weeks)																			
		<28				≥ 28-32				≥ 32-34				≥ 34-37				≥ 37			
		LB		SB		LB		SB		LB		SB		LB		SB		LB		SB	
		L	N	M	F	L	N	M	F	L	N	M	F	L	N	M	F	L	N	M	F
A 80	S	2	2	1	0	2	1	1	0	2	0	0	0	6	0	0	0	0	0	0	0
	I	9	9	3	0	12	8	2	1	13	2	3	0	19	0	2	0	2	0	0	0
B 191	S	0	0	-	-	16	8	0	2	14	0	1	0	17	0	0	1	4	0	0	0
	I	0	0	-	-	19	12	6	0	20	2	8	0	52	4	2	2	27	0	0	0
C 475	S	0	0	-	-	0	0	-	-	0	0	-	-	60	7	2	1	73	0	0	2
	I	0	0	-	-	0	0	-	-	0	0	-	-	74	20	10	2	228	1	4	19
D 300	S	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	106	1	4	2
	I	0	0	-	-	0	0	-	-	0	0	-	-	0	0	-	-	165	12	8	15
Total		11	11	4	0	49	29	9	3	49	4	12	0	228	31	16	6	605	14	16	38
		26				90				65				281				673			

LB: Live Births, SB: Still Births, L: Live Birth, F: Fresh Still Birth, M: Macerated Still Birth, N: Neonatal Death, S: Spontaneous, I: Induced.

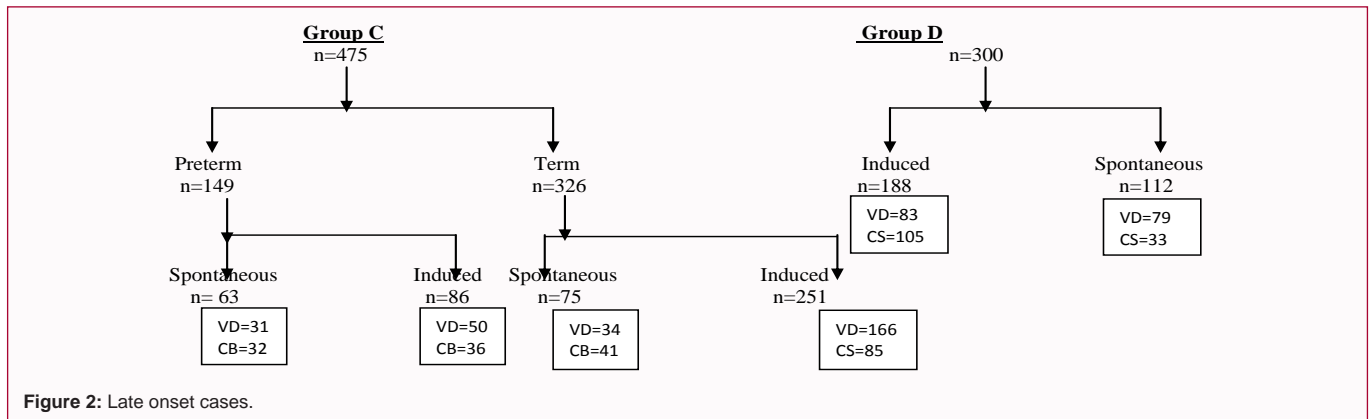
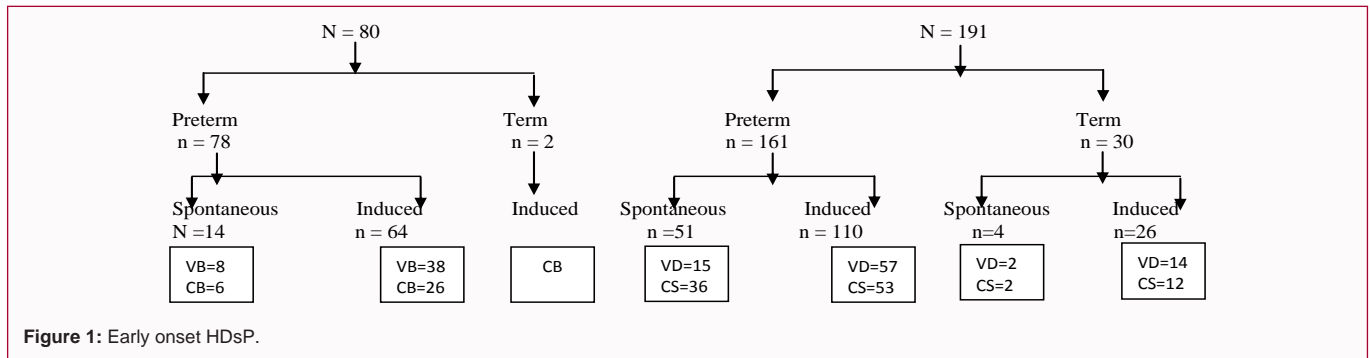
## Results

As per the study criteria, there were 1046 study subjects, 11.73% of 8920 births during the study period. In category A, there were 80 patients, 0.89% of all births, 2.31% of births at the gestation similar to category A patients and 7.65% of all cases with HDsP. There were 191 cases in category B, 2.14% of all births, 2.88% of births at gestation similar to category B and 18.26% of all births with HDsP. In category C, there were 475 patients, 5.33% of all births, 15.25% of births at gestation similar to category C and 45.41% of births with HDsP. In category D, there were 300 cases, 3.37% of births, 6.42% of births at gestation similar to category D and 28.68% of births with HDsP. Over all 26% cases of HDsP were of less than 34 weeks gestation (EO).

Significantly more (p=0.001) cases of EO disorders had severe gestational hypertension, compared to LO cases [43.75% (35 of 80) A, 41.9% (80 of 191) of B, 17.5% (83 of 475) of C and 12% (36 of 300)

of D] and also severe preeclampsia [25% (20 of 80) of A, 25.1% (48 of 191) of B, 9.6% (46 of 475) of category C and 11.3% (34 of 300) of D].

Of 80 patients of category A, 18.75% (15 of 80) delivered before 28 weeks, 5 babies were Still Born (SB) after induced or spontaneous labour and 10 neonatal deaths, no survival (100% perinatal loss). In 18 women (22.5%) pregnancy could be taken up to 32 weeks, 55.5% (10 of 18) had labour induced for maternal / foetal concern, 10 had vaginal births, all SB or NND and 8 had Caesarean Births (CB) with 4 NNDs, total, 14 perinatal deaths out of 18(77.7% perinatal loss). Further, 18 mothers reached 34 weeks (22.5%) gestation. There were 3 still births, 4 NND and 11 survived, perinatal loss 38.8%. In 29 (36.25%) women pregnancy could be prolonged to ≥ 34-37 weeks with 14 VB, 15 CB, and all babies survived. Only 2 women reached term in category A and had labour was induced for materno-fetal concern and both babies survived. Overall in category A, 77.5% (62 of 80) babies were SGA, 100 % (15 of 15 births) with birth at <28 weeks,



69.44% (25 of 36 births)  $\geq$  28-34 weeks, 74.07% (20 of 27 births) of  $\geq$ 34-37 weeks and 100, 0% (both births at  $\geq$  37 weeks).

Of 191 patients of category B, 43 (22.5%) delivered between  $\geq$  28-32 weeks 35 VB (81.40%) and 8 had CBs (18.60%) and perinatal loss was 51.16%. Overall 44 (23.04%) of 191, delivered between 32-34 weeks, 25 (56.82%) VB and 19 (43.18%) CBs, CSR (43.18%), with 9 SBs and 3 NNDs, perinatal loss 27.27%. Of 74 (38.74%) women who delivered between  $\geq$  34-37 weeks, 26 (35.14%) had VBs, 48 CBs (64.86%) with perinatal loss of 9.46%. Of 191 women of category B, 19 (9.95%) reached term, with, 11 CBs (57.89%) and all babies survived (Figure 1).

Of 475 women of category C, 149(31.37%) delivered between  $\geq$  34-37 weeks, 82 (55.03%) VBs, 67 CBs. (44.97%) and 326 reached term. Of the 326 term cases 200 had VBs and 126 CS. (38.65%). In preterm perinatal loss was 28.18%. Overall 326 (68.63%) of 475 category C, had term births, 200 VB (61.35%) and 126 CB (38.65%) and perinatal loss 7.97%, total perinatal loss in category C 14.32%.

In category D of 300 patients, 162 (64%) had VBs and 138 (46%) CBs with 42 (14%) perinatal deaths occurred (Figure 2).

The mean gestation at delivery in category A was (30 weeks +1 day), significantly less compared to category B (32 weeks + 6 days) and LO, category C (35 weeks +4 days) and in D (38 weeks +4 days) (p value <0.001). Similarly the mean gestation at delivery in category B (32 weeks +6 days) was significantly less compared to Category C (35 weeks +4 days) and D (38 weeks +4 days) (p value <0.001). Among LO cases the mean gestation at delivery in category C was 35 weeks +4 days significantly lower than gestation at delivery in Category D (38 weeks +4 days) (p value <0.001). In A and B with increase in gestation the perinatal survival improved. In category A, the mean birth weight was 1741.54 grams, in category B was 1936.31 grams, significantly lower compared to late onset cases (2633.38 grams in Category C

and 2677.30 grams in Category D) (p<0.0001) (Table 1). Overall 78 of 80 (97.5%) of second trimester hypertensive disorders delivered preterm, highly significantly more compared with category B 84.29%, and category C 31.37%.

In category A, 77.5% (62 of 80) babies were small for gestational age (SGA), (100 % of 15 who delivered at <28 weeks gestation, 69.44% (25 of 36 births between  $\geq$  28-34 weeks, 74.07% (20 of 27 births) at  $\geq$  34-37 weeks and 100% (2 of 2) at  $\geq$  37 weeks). In category B 35.08% (67 of 191) babies were SGA, 76.74% (33 of 43) with births between  $\geq$  28-32 weeks, 50.0% (22 of 44) between  $\geq$  32-34 weeks, 16.22%(12 of 74) between  $\geq$  34-37 weeks and 63.33% (19 of 30) term births. In LO cases, in category C 42.28% babies (63 of 149) born between  $\geq$  34-37 weeks were SGA and 30.98% (101 of 326) babies born at term were SGA, 32.76% (57 of 174) delivered at 37 weeks, 34.69%(34 of 98) at 38 weeks, 20.59%(7 of 34) at 39 weeks and 15%( 3 of 20) at >39 weeks. CBs did not change the neonatal survival (some CB still born at birth). Perinatal mortality was significantly higher in EO cases 45% in category A, 25.13% in B than LO 14.32% in category C and 14% in category D (p<0.001) because of SGA and prematurity and associated complications in EO cases (Table 2). There was no maternal death though mothers had more morbidity in EO cases, analysed separately.

**Discussion**

The concept of EO and LO HDsP is modern and it is being widely accepted that these two entities have different etiologies and need to be regarded as different forms of HDsP [7,8,9,10]. Worldwide the EO HDsP comprises a small subset of all cases (5 to 20%), but the most severe cases for immediate and late effects. LO comprise more than 80% of cases of HDsP [9]. In the present analysis 26% cases were of EO and 74% LO. Ebeigbe et al. [11] in their study of second trimester HDsP reported good obstetric outcome for the majority of fetuses with conservative approach to the management of EO HDsP.

However researchers suggested that balance was essential against the significant risk of morbidity to the mother. EO HDsP contributed to 6.3% of all cases of HDsP with an incidence of 1:141 deliveries. Their most cases presented between 28-32 weeks gestation (78.3%). The disease was severe at presentation or rapidly progressive in 39 cases (84.8%), leading to delivery within 72 hours of presentation. Banhidly et al. [12] reported 19.4% preterm births in cases that had hypertension at 4th month of pregnancy which dropped to 4% in 9th month. However hypertension is categorised as essential hypertension, prior to 20 weeks and is not considered gestational hypertension. In the present study 22.50% women in category A and 12.04% in category B had severe HDsP at presentation leading to delivery within 48 hours. While in LO cases, in category C, only 3.79% cases and in category D 2.67% cases were severe at presentation, leading to delivery within 48 hours. Most of the cases with EO preeclampsia were associated with Fetal Growth Restriction (FGR) in various studies [8,9,11,13,14,15,16,17,18,19]. The reason seems to be vascular pathogenesis, which might be responsible for severity of disorder and growth restriction of baby. Hall et al. [14] reported that EO disease had a larger impact on the fetus and neonate than LO HDsP due to more severe prematurity as well as dysmaturity. The expectant management of EO severe pre-eclampsia and careful neonatal care led to better perinatal and neonatal survival. Onah et al. [20] have reported  $8.8 \pm 1.5$  (range: 0-19) weeks mean gain in gestational age in the EO cases. The Perinatal Mortality Rate (PMR) was fourfold in the EO cases compared to the LO due principally to prematurity and FGR. The study revealed that conservative management improved perinatal outcome. Ganzevoort et al. [17] also reported that adverse neonatal outcome was predominantly influenced by gestational age.

In the present study the average gestation at delivery in category A was 30+1 weeks, in category B 32+6 weeks, in category C 35+4 weeks and 38+4 weeks in category D. Even in patients with HDsP at term in some cases, pregnancy was extended to an average of 14 days on individualized basis. Recent research revealed that fetal brain is the last major organ to develop. The baby's brain at 35 weeks weighed only 2/3 rd of what it weighed at 40 weeks. The last weeks of pregnancy seemed very crucial for fetal brain development. It is essential that baby gets the maximum possible intrauterine environment, keeping balance with maternal health and danger of intrauterine death.

In a study by Yang et al. [7], of 255 patients with severe preeclampsia from  $\geq 20$  weeks to term, 24 of  $<28$  weeks, 50 of 28-31 weeks, 34 of 32-33 weeks and 147  $\geq 34$  weeks, the average pregnancy prolongation was  $9 \pm 3$  days (range 1 to 40). Murphy et al. [21] reported CSR of 80% in second trimester HDsP. Researchers reported that 84.8% patients of EO HDsP had preterm births. In the present study in category A 98.5% births were preterm with 77.5% (62 of 80) babies SGA, (100 % SGA (all 15) with births at  $<28$  weeks, 69.44% (25 of 36 births between  $\geq 28-34$  weeks, 74.07% (20 of 27 births) between  $\geq 34-37$  weeks and 100% (both births) at  $\geq 37$  weeks). In category B 35.08% (67 of 191) babies were SGA, 76.74% (33 of 43) in births between  $\geq 28-32$  weeks, 50.0% (22 of 44) births between  $\geq 32-34$  weeks and 16.22% (12 of 74) between  $\geq 34-37$  weeks and 63.33% (19 of 30) at birth at term. While in LO cases, in category C 42.28% (63 of 149) births between  $\geq 34-37$  weeks and 30.98% (101 of 326) babies born at term were SGA, 32.76% (57 of 174) delivered at 37 weeks, 34.69% (34 of 98) at 38 weeks, 20.59% (7 of 34) at 39 weeks and 15% (3 of 20) at  $>39$  weeks. CB did not change the neonatal survival with some fresh still births in c-section cases. Patients with second trimester HDsP had significantly more SGA newborns, compared to

LO cases. Rasmussen et al. [22] in their population-based study of records of 672,130 pregnancies from the Medical Birth Registry of Norway during 1967-1988, reported that in cases of preeclampsia in preterm births, mean difference in birth weight ranged between 11-23% against near-equal birth weights in term births.

Perinatal mortality was significantly higher in EO cases (45% in category A, 25.13% in B) than LO (14.32% in category C and 14% in category D) ( $p < 0.001$ ) because of SGA and prematurity and associated complications in EO cases. Perinatal survival improved in cases who delivered beyond 32 weeks, around 34 weeks. However beyond 34 weeks there was not much difference. Perinatal survival in category C and D was almost similar C (85.68%) and D (86.0%) respectively. Conservative management in EO disorders improved perinatal survival in second trimester HDsP. There was no maternal death, though mothers did have more morbidity in EO cases, analysed separately.

Hall et al. [14] in their prospective study reported that a mean of 11 days were gained by expectant management in EO HDsP. The PMR was 24 with a neonatal survival rate of 94%. In a larger retrospective study of 49,812 women, Murphy et al. [21] reported that of 71 patients with second trimester HDsP, 12 had intrauterine deaths (16%), 9 neonatal deaths (12%) occurred and 50 survived (72%). The combination of (HDsP and FGR) may be because EO disorder is caused by, changes in the blood flow of the uterine as well as the umbilical arteries described to be causative for FGR also. Placental and fetal growths are promoted by the presence of Pregnancy-Associated Plasma Protein A (PAPPA) in the placenta [23]. Placental glycoprotein cleaving insulin-like growth factor binding protein-4 (IGFBP4) positively regulated Insulin-Like Growth Factors (IGFs) [24]. Lisonkova [25] reported that the most significant maternal and fetal complications were related to EO.

Irgens [26] also reported unfavorable neonatal outcome in women with EO HDsP. The researchers reported risk of preterm delivery, 2.71-fold higher risk in EO than term HDPs. Ganzevoort et al. [17] reported that the adverse neonatal outcome in EO HDsP was predominantly influenced by gestational age. In the study by Sezik et al. [27] the mean prolongation of gestation in second trimester HDsP was only  $4.8 \pm 4.1$  days (range: 1-13 days). Conservative management was associated with 94.5% (52/55) intrauterine fetal loss. Crispi et al [28] in their study reported the mean gestational age at delivery in EO HDsP 29 weeks and in LO, 37 weeks. Ebeigbe et al. [11] reported most cases presented between 28-32 weeks gestation (78.3%). 84.8% had delivery within 72 hours of presentation and most of the cases delivered by CS (58.7%) and the perinatal survival was 34.0%. Researchers concluded that most EO cases presenting with severe and rapidly progressive disease were associated with significantly higher risk of obstetric interventions and poorer perinatal outcome than LO disease. Vasculopathy does explain poor perinatal outcome in EO HDsP but not in LO. In the study by Ebighe et al. [11] the rate of CS in EO and LO HDsP was not significantly different (43.75% in group A, 47.64% in group B and 42.71% in LO HDsP).

Abdel-Hady el-s et al. [29] reported the median prolongation of gestation  $12 \pm 6$  days. The rate of neonatal survival significantly increased from 12/61 (19.7%) between 24 and 28 weeks to 30/66 (45.5%) between 28 to  $<32$  weeks and 67/84 (79.8%) between 32-34 weeks. Researchers concluded that in low-resource settings, expectant management of EO severe PE was associated with relatively higher rates of perinatal mortality and should be limited to gestational ages



between 28 and 34 weeks of gestation. Crispi et al. [28] in their study reported the mean birth weight in EO HDsP  $998 \pm 323$ gms and in LO disorders  $2345 \pm 479$  gms. In the present study, in category A, the mean birth weight was 1741.54 grams and in category B was 1936.31 grams, significantly less compared to LO cases (2633.38 grams in Category C and 2677.30 grams in Category D). Bombrys et al. [30] in their retrospective analysis of outcome in patients with severe preeclampsia, at 27 to 33 weeks of gestation reported that the birth weights of 19 (27%) were 10% < for gestational age, and 6 (8%) were 5%. Kovo et al. [31] reported pathological placental differences between EO and LO disorders, in relation to FGR. Esch et al. [32] reported that perinatal outcome was significantly worse in neonates born to mothers with EO PE. However whether these differences were due to uteroplacental factors or intrinsic neonatal factors remained to be elucidated.

In the present study also it was evident that EO disorders adversely affected perinatal survival research needed to be done to improve survival in low resource settings. Overall the perinatal deaths in second trimester HDsP were 45% significantly high compared to category B (25.13%), in category C of late onset disorder (14.32%) and in category D (14%). Gestational age around 34 weeks was very important for neonatal survival especially with limited resources. Conservative management in EO disorders improved perinatal survival especially in second trimester HDsP cases. Expectant management should be carried out in well-selected patients with severe preeclampsia remote from term, with critical vigilance. In the present study it was revealed that EO disorders adversely affected perinatal survival but perinatal mortality in the late onset was also 14.00%, which too is a matter of concern and more research needs to be done.

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