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Original Research Article

Pregnancy outcome in women with previous preeclampsia versus women normotensive in previous pregnancy

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ABSTRACT

Background: Women with history of preeclampsia have reportedly higher risk of development of preeclampsia in subsequent pregnancies, along with other adverse pregnancy outcomes. Authors aimed to study the incidence of recurrent preeclampsia and compare the pregnancy outcome in women with history of preeclampsia in previous pregnancy with those who were normotensive in previous pregnancy and further compare outcomes in women with recurrent preeclampsia between their previous and index pregnancy.

Methods: Pregnancy outcome was studied in women with preeclampsia in previous pregnancy (cases) and compared with women normotensive in previous pregnancy (controls). Further analysis of cases was done by dividing them into subgroups: those with recurrent preeclampsia in index pregnancy (A1) and those normotensive in index pregnancy despite being pre-eclamptic in previous pregnancy (A2). Total 100 cases and 100 controls were enrolled in the study, which was conducted at present tertiary care centre from January 2012 to June 2013.

Results: Out of total 200 participants (100 cases, 100 controls) enrolled in the study; 58 out of 100 cases had recurrent preeclampsia and remaining 42 remained normo-tensive in index pregnancy. Among 100 controls, 93 were normotensive in index pregnancy.

Conclusions: Women with history of preeclampsia in previous pregnancy had adverse maternal and perinatal outcome in subsequent pregnancy when compared to the women who were normotensive in the previous pregnancy. But when compared with their own previous preeclamptic pregnancy, they had better pregnancy outcome with good perinatal outcome in their index pregnancy.

Keywords: Perinatal outcome, Preeclampsia, Recurrent preeclampsia

INTRODUCTION

Hypertensive disorders of pregnancy, including preeclampsia and HELLP syndrome (Haemolysis, elevated liver enzymes and low platelet count) affect 2-7% of pregnancies.¹ Preeclampsia is one of the top three causes of maternal mortality and is the leading cause of maternal and fetal morbidity.² Women with history of preeclampsia have a higher risk of development of preeclampsia in subsequent pregnancies, along with other adverse pregnancy outcomes like higher rates of LSCS,

preterm delivery, delivery of small-for-gestational-age (SGA) babies, hypoglycaemia, sepsis and necrotising enterocolitis.^{3,4} Similarly, perinatal mortality rates were also reported to be higher in them.⁵

Very few studies from central India are available which show the trend in the incidence of recurrent preeclampsia and the pregnancy outcome. This led to conceptualisation of the present study. The aim of this research therefore was to study the incidence of recurrent preeclampsia in all pregnant patients admitted in the obstetric wards of

present tertiary care centre during the study period and to compare the pregnancy outcome in women with history of preeclampsia in previous pregnancy with those who were normotensive in previous pregnancy. Comparison of pregnancy outcomes in women with recurrent preeclampsia between their previous and index pregnancy was also undertaken.

METHODS

It was a hospital based observational study carried out in a tertiary care teaching hospital from January 2012 to June 2013. All second gravida patients admitted in labour ward and delivered in during the study period at present institute were studied. Based on a previous similar study, the sample size was estimated on the assumption that fetal loss was higher in women with recurrent preeclampsia (19%) than in women with preeclampsia with normotensive obstetric history (4.7%), with adjusted odd's ratio of 5.77 (95% confidence interval- 0.84-39.54), the sample size required and finally collected in each group was calculated to be 100 (Total- 200).

Operational definitions

- Cases (Group A)-All second gravida women who delivered in present hospital during the study period with history of preeclampsia/eclampsia in their previous pregnancy.
- Controls (Group B)-All second gravida women who delivered in present hospital during the study period who have been normotensive in their previous pregnancy.

Inclusion criteria

- Both booked and emergency admissions were included.

Exclusion criteria

- Women with pregnancy induced hypertension, chronic hypertension, renal disease, diabetes mellitus, multiple pregnancy, autoimmune disorder or any other medical disorder were excluded.

Discharge cards or inpatient case records of previous pregnancy, which contained all the relevant mother and infant hospitalization details, were examined for analysis. Details of index pregnancy w. r. t. immunization history, past/personal/family history and obstetric history were noted. Gestational age was calculated in each patient from the last LMP and/or by ultrasound scan.

Maternal variables included gestational age at onset of preeclampsia, gestational age at termination of pregnancy, severity of preeclampsia in index pregnancy (if there), interval from the time of onset of preeclampsia to time and mode of delivery, symptoms, complications

and lab values. Neonatal outcome was assessed in terms of live birth, still birth, birth weight, APGAR score at 1 and 5 minutes, neonatal complications, perinatal mortality and its causes. Neonatal complications, number of NICU admissions, duration of NICU stay and reason for NICU admission were also analysed in detail.

All the patients in both the groups were provided with the standard medical/ obstetric care as per predefined protocols.

Statistical analysis

The data was analysed using SPSS (version 20); by applying chi-square test and ANOVA wherever applicable. Multiple comparisons were made using Bonferroni test. Fischer exact test was applied in small numbers, wherever applicable.

Approval from Institutional Ethics Committee was obtained before start of the study. Informed written consent was obtained from each patient before participation in the study.

RESULTS

In this hospital based observational study, the incidence of recurrent preeclampsia was studied along with comparison of the pregnancy outcomes in women with history of preeclampsia in previous pregnancy with those who were normotensive in previous pregnancy.

The pregnancy outcome was studied in women with history of preeclampsia in previous pregnancy (cases) and comparisons drawn with women normotensive in previous pregnancy (controls). Further analysis of cases was done by dividing them into subgroups: those who had recurrent preeclampsia in index pregnancy (A1) and those who were normotensive in index pregnancy despite being pre-eclamptic in previous pregnancy (A2). Similarly, the controls were divided into two groups as those who developed preeclampsia in index pregnancy despite being normotensive in previous pregnancy (B1) and those who remained normotensive in the index pregnancy (B2).

Total 100 cases and 100 controls were enrolled in the study. Among 100 cases, 58 had recurrent preeclampsia (A1) and 42 remained normo-tensive in index pregnancy (A2). Among 100 controls, 93 were normotensive in index pregnancy (B2). The pregnancy outcome analysis was restricted to these 58 (A1), 42 (A2) and 93 (B2) groups of women.

Majority of women were belonging to age group 25-30 years in both subgroups of cases: A1 (50%) (mean age-24.7 years) and A2 (45.2%) (mean age-25.88 years); while controls (B2) fell in the 18-24 years age group (mean age-24.62).

Most of the patients in case group were booked for ANC care (77.6% in A1 and 95.2% in A2) as well in control group (64.5% in B2); but the difference in booking status was highly significant ($p < 0.001$).

While comparing the severity of preeclampsia between their two pregnancies within the case group, 23% had mild eclampsia and 77% had severe preeclampsia in their previous pregnancy. The incidence of severe preeclampsia was reduced to 50% in index pregnancy. Of the women who had severe preeclampsia, the incidence of eclampsia was significantly higher in women in their previous pregnancy (43%) than in index pregnancy (10.35%). In previous pregnancy, 52% of cases had early-onset preeclampsia whereas in index pregnancy it was noted in 31.03% cases, the difference being significant. Of the 100 cases, majority (41%) had onset of preeclampsia between 28-34 weeks of gestational age in their previous pregnancy (mean-33.48 weeks), similar to incidence in the recurrent pre-eclamptic group (46.6%) (mean-34.34 weeks). Majority of cases required termination at 28-34 weeks in their previous pregnancy (37%), while most of the cases were terminated at >37 weeks in the index pregnancy (58.6%); the difference was statistically highly significant ($p < 0.001$). The mean gestational age of termination of pregnancy in cases during previous pregnancy was 34.01 weeks,

significantly lesser than the 36.05 weeks reported in index pregnancy.

Of the 100 cases, 99 required antihypertensive drugs in varied forms during previous pregnancy, while only 46 (79.3%) of the 58 women in recurrent group required it in index pregnancy ($p < 0.001$). Magnesium Sulphate was used as anticonvulsant in 59% cases in previous pregnancy and in 24.1% cases in index pregnancy ($p < 0.001$).

In previous pregnancy, majority of cases (57%) had undergone caesarean section; while only 35% controls had it, with rest (65%) having vaginal delivery. The difference between the groups for mode of delivery in previous pregnancy was highly significant ($p < 0.001$). As for mode of delivery in the index pregnancy, majority of cases (A1-75.9%, A2-71.4%) as well as controls (62.4%) underwent caesarean section ($p = 0.082$).

Table 1 summarizes the clinical and laboratory parameters across all the three comparison groups. Except for comparable serum creatinine values, the difference two case subgroups (A1 vs A2) was statistically significant; while the clinical and laboratory findings of the cases and controls were comparable throughout.

Table 1: Clinical and laboratory findings in cases and controls.

Parameter	Cases		P-value (A1 vs A2)	Control B2	P-value (A2 vs B2)
	A1	A2			
Maximum systolic BP (mmHg)	155.61±11.34	123.72±7.24	<0.001	123.93±16.58	0.94
Maximum diastolic BP (mmHg)	99.64±7.55	80.23±1.54	<0.001	78.48±10.43	0.28
Platelet count (lakh/mm ³)	2.07±0.89	2.42±0.71	0.04	2.12±0.98	0.08
SGOT (U/UL)	39.98±2.06	30.62 ±7.10	0.02	27.55±11.18	0.10
Proteinuria	1.9	Nil	<0.001	Nil	-
Serum uric acid (mg/dl)	5.10±1.06	4.71±0.97	0.02	4.60 ±0.62	0.43
Serum creatinine (mg/dl)	1.03±0.65	0.93±0.3	0.35	0.95 ±0.27	0.65

Table 2: Incidence of maternal complications across groups.

Parameter	Cases		P-value (A1 vs A2)	Control B2 (n=93)	P-value (A2 vs B2)
	A1 (n=58)	A2 (n=42)			
Retinopathy	34 (58.62%)	0	<0.001	0	<0.001
SGA	25 (43.1%)	8 (19.04%)	0.012	16 (17.2%)	0.012
Oligohydraminos	22 (37.93%)	9 (21.43)	0.78	12 (12.9%)	0.003
Preterm delivery	21 (36.2%)	0	<0.001	2 (2.15%)	<0.001
Ascites	20 (34.48%)	1 (2.38%)	<0.001	0	<0.001
PPH	16 (27.59%)	1 (2.38%)	<0.001	3 (3.23%)	0.002
APH	10 (17.24%)	0	<0.001	0	<0.001
ARF	7 (12.07%)	0	<0.001	0	<0.001
PROM	7 (12.07%)	6 (14.29%)	0.745	18 (19.36%)	0.23
Eclampsia	6 (10.35%)	0	0.038	0	0.029
Impending eclampsia	6 (10.35%)	0	0.038	0	0.029

As for the occurrence of maternal complications, retinopathy (34, 58.6%) was the commonest complication in A1 group, with no cases reported in A2 and B1 groups. Incidence of SGA babies was the second commonest complication, with it being reported in 43.1% in A1, 19.04% in A2 and in 17.2% in B2 groups ($p < 0.001$). PROM (18, 19.36%) and oligohydramnios (12, 19.36%) were the two commonest maternal complications observed in the control group. Oligohydramnios (37.93% in A1 vs 21.43% in B1), PROM (12.07% in A1 vs 14.29% in A2) and cerebral edema (6.9% in A1 vs 0 cases in A2) were the only complications not differing significantly between the two case sub-groups; apart from the solitary case of pulmonary edema in A1, which required ICCU admission and eventually leading to the only maternal death in the study. PROM (14.29% in A2 vs 19.36% in B2) and cerebral edema (no cases in both

A2 and B2 groups) were the only maternal complications not differing significantly between the cases and control groups (Table 2).

Table 3 compares the various maternal and neonatal outcomes in women with recurrent preeclampsia (A1) as observed in the previous and index pregnancy. All the outcome variables, except gestational age at onset (21.82 weeks in previous pregnancy vs. 24.7 weeks in index pregnancy, $p = 0.18$), were significantly different in the index pregnancy as compared to back in the previous pregnancy.

Table 4 compares the neonatal outcomes among the three predefined subgroups (A1, A2 and B2). The incidence of live borne was 100% in B2 and A2 and 96.6% in A1, the difference being statistically insignificant.

Table 3: Outcomes in women with recurrent preeclampsia (A1) in previous and index pregnancy.

Characteristics	A1 during previous pregnancy (n= 58)	A1 during index pregnancy (n= 58)	P-value
Maternal Age (years)	21.82±2.43	24.7±2.7	<0.001
Gestational age at onset (weeks)	33.48±4.08	34.34±3.57	0.184
Gestational age at termination (weeks)	34.01±4.04	36.05±3.14	0.0012
Maximum systolic blood pressure (mmHg)	168.27±10.28	155.61±11.34	<0.001
Maximum diastolic blood pressure (mmHg)	108.27±8.81	99.64 ±7.55	<0.001
Proteinuria (dipstick+)	58 (100%)	49 (84.5%)	0.003
Birthweight (kg)	1.55±0.6	2.08±0.48	<0.001
SGA (%)	11 (18.9%)	25 (43.1%)	0.018
IUGR (%)	14 (24.1%)	2 (3.4%)	0.001
Perinatal mortality (%)	34 (58.6%)	11 (18.9%)	<0.001
Rate of LSCS/ Hysterectomy (%)	30 (51.7%)	44 (75.8%)	0.007
Duration of hospital stay (>10 days)	14 (24.1%)	41 (70.7%)	<0.001

Table 4: Neonatal outcome comparison.

Parameter	Cases		P-value (A1 vs A2)	Control B2 (n=93)	P-value (A2 vs B2)
	A1 (n=58)	A2 (n=42)			
Live birth	56 (96.6%)	42 (100%)	0.51	93 (100%)	0.5
Fresh still birth	2 (3.45%)	0	0.51	0	0.5
Neonatal death	9 (16.07%)	0	0.009	2 (2.2%)	0.06

Table 5: Incidence of neonatal complications across groups.

Parameter	Cases		P-value (A1 vs A2)	Control B2 (n=93)	P-value (A2 vs B2)
	A1 (n=58)	A2 (n=42)			
SGA	25 (43.1%)	8 (19.04%)	0.012	16 (17.2%)	0.012
NICU admission	25 (43.1%)	3 (7.14%)	<0.001	16 (17.2%)	0.072
Prematurity	21 (36.2%)	0	0.003	2 (2.16%)	0.008
RDS	17 (29.31%)	1 (2.38%)	0.001	10 (10.75%)	0.153
Birth asphyxia	12 (20.69%)	0	0.001	6 (6.5%)	0.97
Perinatal mortality	11 (18.97%)	0	0.009	2 (2.2%)	0.332
Septicemia	6 (10.35%)	3 (7.14%)	0.581	1 (1.08%)	0.872
Jaundice	4 (6.9%)	3 (7.14%)	0.962	11 (11.8%)	0.5

The mean birth weight in A1 subgroup was 2.08kgs, in A2 was 2.72kgs and in B2 was 2.78kgs, the respective intergroup differences being highly significant ($p < 0.001$). In the A1 category, majority of women (41.4%) had newborn babies weighing between 2-2.5kgs, while only 19.04% women in A2 subgroup and 15.1% women in B2 group had birth weight between 2-2.5kgs, the difference being significant.

Table 5 details the neonatal complications observed in the present study across cases and control groups. The two cases subgroups were significantly different from each other in most of the parameters, except occurrence of jaundice (6.9% in A1 vs 7.14% in A2) and septicaemia (10.35% in A1 vs 7.14% in A2); while cases and controls had similar neonatal outcomes across variables, except significant differences in incidence of prematurity (no case in A2 vs 2.15% in B2, $p = 0.008$) and SGA (19.04% in A2 vs 17.2% in B2, $p = 0.012$).

Out of the total 9 neonatal deaths reported in A1 subgroup of cases, 2 were still birth and 7 had overlapping causes of death. As for the causes of perinatal mortality, preterm and RDS (15.5% each) were the commonest causes in subgroup A1 of cases, being held responsible in all the 9 deaths.

DISCUSSION

Preeclampsia, whether a first or a recurrent episode, is a major cause of maternal and fetal morbidity and mortality.^{1,6} In present study, the overall incidence of recurrence of preeclampsia in subsequent pregnancy was found to be 58%, which is higher than 13-18% reported previously.⁷ Even though several studies have quoted recurrence risk to be high as well, it doesn't recur in about 80% of women with a history of preeclampsia.⁸ In present study too, 42% of women with history of preeclampsia in previous pregnancy remained normotensive in their index pregnancy. The odds of recurrent preeclampsia have been shown to increase with earlier gestational age at prior delivery, among other factors like inter-birth interval, birth weight etc. Authors report majority (52%) to be having had early-onset preeclampsia resulting in delivery before 34 weeks of gestation in their previous pregnancy, with 77% of women having severe preeclampsia; both factors being reported to be important risk factors for the disease recurrence.

The higher rate of recurrence in index pregnancy with early-onset preeclampsia in previous pregnancy justifies the plausible mechanism of abnormal plantation and invasion of the trophoblastic tissue, leading to structure and occlusive changes in the spiral arteries and under-perfusion of the placenta. These fundamental disturbances in the development of the uteroplacental and umbilicoplacental circulations occur early in the first trimester of pregnancy. Because in preeclampsia this system may be compromised by genetically determined

disturbances, it is postulated that genetic susceptibility to preeclampsia might be a risk factor for recurrence of disease in pregnancy. As against it, late-onset preeclampsia is sporadic in nature and milder form of presentation with normal placentation.

Researchers have observed that women who develop severe preeclampsia in first pregnancy and have preeclampsia in subsequent pregnancy have higher incidence of abruptio placentae, premature delivery, perinatal mortality and IUGR, as compared to women remaining normotensive; while others did not find significant difference in maternal-fetal outcomes such as gestational age at delivery and maternal serum biochemical levels.^{4,9} Present study, similar to the study by Yi-Yu Chen et al and Van Rijn et al, found that recurrent preeclampsia appeared to be less severe and had a better overall perinatal outcome than preeclampsia in previous pregnancy.^{4,9}

In the present study, the mean birth weight of babies was significantly lower in the recurrent preeclamptic group (A1) (2.08kg) when compared with those who were normotensive in index pregnancy despite preeclampsia in previous pregnancy (A2) (2.72kg) and also when compared with the normotensive obstetric subset (B2) (2.78kg). Bramham et al also found significantly lower mean birth weight in recurrent preeclamptic group when compared to normotensive group (2.32kg versus 3.22kg).¹¹ With respect to preterm delivery, authors observed significantly higher rate in the recurrent preeclamptic group as against the women normotensive despite preeclampsia in previous pregnancy. This is in line with observations by Bramham et al (57% vs 43%) and Makkonen et al (28.3% vs 3.3%).^{11,12} Small for gestational age (SGA) babies were seen in significantly higher proportion of women in A1 when compared to A2 (43.1% vs 19.04%) and also when compared to controls (B2) (43.1% vs 17.2%); which sits well with the available evidence.^{11,12} Mendicioglu et al found fetal loss to be higher in women with recurrent preeclampsia (19%) than women with preeclampsia in previous pregnancy and are normotensive in index pregnancy (4.7%).¹³

All these findings lead us to infer in totality that perinatal outcome was better in index pregnancy in the recurrent preeclampsia cases when compared to outcome in previous pregnancy, but when compared to other normotensive subgroups, adverse perinatal outcome was seen in index pregnancy in the recurrent preeclampsia cases. This could be explained in part by the fact that women who have had severe or early-onset preeclampsia in previous pregnancy received good antenatal care with early detection of preeclampsia and thorough supervision in their index pregnancy, which resulted in lowered severity of disease with better perinatal outcome in index pregnancy. However, the raised incidence of SGA in present study can be explained on the basis of the continuing placental morphological changes and dysfunction owing to disease process even if women

were normotensive or had mild preeclampsia in index pregnancy with history of early-onset or severe disease in previous pregnancy.

CONCLUSION

Authors conclude by summarizing that women with history of preeclampsia in previous pregnancy had adverse maternal and perinatal outcome in subsequent pregnancy when compared to the women who were normotensive in the previous pregnancy. But when compared with their own previous preeclamptic pregnancy, these women had better pregnancy outcome with good perinatal outcome in their index pregnancy.

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