DOI: 10.7860/JCDR/2013/7681.3785

Original Article

Obstetrics and Gynaecology Section

Risk for Recurrence of Pre-eclampsia in the Subsequent Pregnancy

TARAKESWARI SURAPANENI[1], VIDYAVATI PATIL BADA[2], C. PRAVEEN KUMAR NIRMALAN[3]

ABSTRACT

Background: Pre-eclampsia (PE) is the commonest type of pregnancy induced hypertension and it affects nearly 5% of pregnant women. Besides short term morbidity and mortality that are associated with pregnancy, PE is associated with long term morbidity in women. There is a lack of information on the risk of recurrence of PE in pregnant Asian Indian women.

Aim: To determine the rates and risk factors which were associated with recurrence of PE in the subsequent pregnancies of women with PE in index pregnancies.

Settings and Design: A retrospective, observational study done at a single tertiary care centre in southern India.

Material and Methods: The study included pregnant women with PE, who delivered at the study institute in 2008 and received care for their subsequent pregnancies at the study institute. Hypertension in pregnancy was categorized, based on the criteria of the International Society for the Study of Hypertension in Pregnancy. Point estimates and the 95% confidence intervals around point estimates of rates of recurrence of PE and associations of potential clinical and laboratory parameters with recurrence were determined by using bivariate analysis, logistic regression models and area under Receiver Operator Characteristic (ROC) curves.

Results: The study included 82 pregnant women with PE in their index pregnancies. Twenty two (26.83%, 95% CI: 17.03, 36.62) of these 82 women developed recurrence of PE in their subsequent pregnancies. Recurrence of PE was significantly higher (OR 3.94, 95% CI: 1.05, 14.80, p=0.04) among women who were nulliparous in their index pregnancies. Recurrence of PE was not significantly associated with clinical factors or laboratory parameters in the index pregnancies.

Conclusion: Nearly one in four of pregnant women with PE developed recurrences in their subsequent pregnancies, although a large proportion of pregnant women with PE (63.38% to 82.97%) in their index pregnancies were normotensive in their subsequent pregnancies.

Keywords: Pre-eclapmsia, Pregnancy, Hypertension, Recurrence

INTRODUCTION

Approximately 7-9% of women develop hypertension during the course of their pregnancies [1-4]. Hypertension in pregnancy produces several short and long term health consequences in the mother and the foetus, including perinatal mortality [5,6]. Pre-eclampsia (PE), which is one of the pregnancy induced hypertension disorders, affects approximately 5% of pregnant women [7,8]. PE is associated with foetal growth restrictions, preterm deliveries and an increased risk for foetal mortality [6]. In the long term, PE is associated with cardiovascular diseases and a consequent increased risk for mortality [5]. In the short term, however, pregnant women with PE have to be counselled about the risk for developing PE in their subsequent pregnancies and associated maternal and foetal health risks. PE is considered as a disease of nulliparity or the first pregnancy, [9] however, is not uncommon in multiparous women. To the best of our knowledge, information on the recurrence of PE and on the factors which are associated with recurrence was lacking in a population of pregnant Asian Indian women. This study aimed to determine the rates of recurrence of PE in women who had PE in their index pregnancies, the risk factors which were associated with recurrences and outcomes of pregnancies with recurrent PE at a single centre in south India.

MATERIAL AND METHODS

The retrospective study design and the study protocol were approved by the Institutional Review Board. The study institute maintains a database of women who seek care for pregnancies and deliver at the study institute. Details of pregnant women, including maternal age, number of foetuses, parity, prior obstetric history, co-existing medical or surgical co-morbidities, family history, current obstetric history, clinical exams including ultrasound imaging and laboratory exams, details of delivery including labour, and neonatal outcomes are entered in the database. This database was explored to identify women who had delivered at the study institute in the year 2008, had PE during the course of their pregnancies in the year 2008, and had subsequent deliveries at the study institute during the period from 2009-2012. The year 2008 was chosen for the index deliveries, to cover details of subsequent pregnancies, over a four year period from 2009 to 2012.

Hypertension in pregnancy was categorized as chronic hypertension, gestational hypertension, PE (mild and severe or PE superimposed on chronic hypertension), eclampsia and HELLP syndrome. Hypertension was defined as a repeated measure (at least 2 measures) of systolic blood pressure of ≥140mm Hg and/or a diastolic blood pressure of ≥90mm Hg, by using a sphygmomanometer. Chronic hypertension was defined as primary or secondary hypertension that was present at the booking visit or at <20 weeks or if the woman was already taking anti-hypertension medications when she was referred to obstetric services. Gestational hypertension was defined as hypertension which had presented for the first time after 20 weeks of gestation and without significant proteinuria. Pre-eclampsia was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy and it included proteinuria as a criteria [10]. Evidences of multisystem involvement which were associated with pregnancy induced hypertensive disorders were also extracted from the database. These included evidences of renal insufficiency, elevated liver enzymes, and haematological abnormalities including haemolysis and thrombocytopaenia.

At the study institute, women with PE or pregnancy induced hyper-

tensive disorders were routinely offered care, jointly by a team that included an obstetric medicine specialist, internists and critical care physicians. The number of episodes of severe hypertension in the mother, maternal use of anti-hypertensive medications, foetal growth during pregnancy, neonatal growth classification at birth, birth weights, admission to a neonatal intensive care unit and perinatal mortality were also explored from the database.

The extracted data was initially entered into a Microsoft Excel spread sheet and it was then exported into STATA statistical software, version 9.0 for analysis. Maternal characteristics were explored by using descriptive statistics- frequency distributions for categorical variables and measures of dispersion for continuous variables. 95% Confidence Intervals (CI) were estimated for point estimates of interest. Potential associations were initially explored by using a bivariate analysis and they were then further analyzed by using logistic regression models. Adjusted Odds Ratios (OR) and the 95% CIs around point estimates of OR were estimated. A p-value of <0.05 was considered as statistically significant for this study.

RESULTS

Eighty two women who had pregnancies with PE, had delivered at the study institute in 2008 and had received care at the study institute for their subsequent pregnancies were included in the study. The maternal and foetal characteristics of these 82 women have been presented in [Table/Fig-1].

Twenty two (26.83%, 95% CI: 17.03, 36.62) of these 82 women developed recurrences of PE in their subsequent pregnancies. Nineteen (33.93%, 95% CI: 21.13, 46.72%) of the 56 nulliparous women with PE in their index pregnancies developed recurrences of PE in their subsequent pregnancies, as compared to 3 (11.54%, 95% CI: 1.62, 24.70) of the 26 multiparous women with PE in their index pregnancies. Recurrence of PE was significantly higher (OR 3.94, 95% CI: 1.05, 14.80, p=0.04) among women who were nulliparous in their index pregnancies.

Recurrence of PE was not significantly associated with clinical factors in the index pregnancies, which included maternal age, gestational diabetes, renal disorders, severity of PE, gestational age at diagnosis of PE, gestational age at delivery, small for gestational age babies, low birth weight and intrauterine foetal demise [Table/Fig-2]. Laboratory parameters in the index pregnancies were also not discriminatory or predictive of recurrences of PE [Table/Fig-3]. Fifty seven (70.37%) women did not have any episodes of severe hypertension. Forty three (52.44%) women received methyl-dopa, 53 women received Nifedipine (64.63%) and 8 (9.76%) women received Labetalol as a part of the management of hypertension. Thirty women (36.59%) women received a combination of any two antihypertensive medications, while 5 (6.10%) women received a combination of three antihypertensive medications during the courses of their pregnancies. Recurrence of PE was not associated with the number of antihypertensive medications which was used (Fishers exact p-value=0.94) or number of episodes of severe hypertension (Fishers exact p-value=0.84)

Recurrence of PE was not associated with an increased risk of preterm deliveries (Fishers exact p-value =0.99), small for gestational age babies (Fishers exact p=0.99), intrauterine foetal demises (Fishers exact p-value=0.44), or neonatal intensive care admissions (Fishers exact p=0.89).

Characteristic	
Mean maternal age (SD)	25.16 (3.63)
Primigravid	48 (58.54%)
Nulliparous	56 (68.29%)
Spontaneous Conception	76 (92.68%)
Gestational Diabetes	7 (8.54%)
Renal disorders	4 (4.88%)
Mean gestational age at diagnosis (SD)	33.39 (4.40)
Mean SGPT at booking (SD)	60.42 (73.63)
Mean SGOT at booking (SD)	43.83 (62.59)
Mean Platelet count at booking (SD)	2.09 (0.62) lakhs
Mean Serum Uric Acid (SD)	5.38 (1.46)
Mean Serum Creatinine	0.86 (0.18)
Mean Lactate Dehydrogenase	227.30 (163.58)
Proteinuria ≥2+	28 (34.15%)
Induction of Labour	36 (43.90%)
Normal Vaginal Delivery	26 (31.71%)
Elective Cesarean Section	12 (14.63%)
Emergency Cesarean Section	38 (46.34%)
Mean gestation age at delivery (SD)	35.21 (3.24)
Preterm delivery < 37 weeks	45 (58.44%)
Preterm delivery < 34 weeks	20 (25.97%)
Small for gestational age baby	12 (14.63%)
Birthweight <1500 gms	12 (14.63%)
Neonatal Intensive Care Admission	30 (36.59%)
Intra-Uterine Fetal demise	10 (12.20%)
Neonatal Mortality	2 (2.44%)

[Table/Fig-1]: Maternal and Fetal Characteristics of the 82 women included in the study

	Parity adjusted OR, (95% CI, P-value)
Maternal age	1.00 (0.87- 1.16, 0.99)
Gestational Diabetes	0.89 (0.15- 5.12, 0.90)
Renal disorders	4.35 (0.47- 39.86, 0.19)
Severe PE	0.84 (0.30-2.29, 0.72)
Gestational age at diagnosis	0.95 (0.84-1.07, 0.41)
Preterm delivery < 37 weeks	3.02 (0.94-9.70, 0.06)
Preterm delivery < 34 weeks	1.24 (0.36-4.29, 0.73)
Intra-uterine fetal demise	1.77 (0.43-7.27, 0.43)
Small for gestational age baby	0.23 (0.03-1.93, 0.18)
Low birth weight (<1500 grams)	1.25 (0.28-5.57, 0.77)

[Table/Fig-2]: Parity adjusted Odds Ratios, 95% Confidence Intervals and P-values for clinical factors in index pregnancy potentially associated with recurrence of PE

	Area under Receiver Operator Characteristic Curve (95% CI)
SGOT	0.44 (0.28- 0.60)
SGPT	0.45 (0.28- 0.61)
Platelet count	0.30 (0.16- 0.44)
Serum Uric Acid	0.49 (0.34- 0.65)
Serum Creatinine	0.61 (0.46-0.76)
Lactate Dehydrogenase	0.46 (0.30-0.62)
Proteinuria >2+	0.52 (0.38-0.65)

[Table/Fig-3]: Effectiveness of lab parameters in the index pregnancy to predict recurrence of PE

DISCUSSION

In this study, a large proportion of pregnant women with PE (63.38% to 82.97%) were normotensive in theiies subsequent pregnancy. Nearly one in four of pregnant women with PE developed recurrences in their subsequent pregnancies. Recurrence of PE was not associated with any specific clinical or laboratory parameter in the index pregnancies. This information is very useful for clinicians for counseling pregnant women with PE, on the risk for PE in their subsequent pregnancies.

Several studies worldwide, have reported a recurrence rate which ranged from 13% to 55% [11-21]. A prospective cohort study done in Sweden reported a risk of 14.7% for recurrences in women who had PE in their first pregnancies. The risk for recurrence of PE in this cohort increased to 31.9% if the woman had PE in her previous two pregnancies [8]. The pre-eclampsia community guideline study

reported a relative risk of 7.19 (5.85-8.83) for recurrent PE [22]. Sibai et al., in their landmark study, [11] reported a recurrence of PE in nearly two thirds of pregnant women. The population in the study done by Sibai was much younger, with a mean age of 18 years, being predominantly African American, primigravid and with a mean gestational age at diagnosis of 25 weeks. In comparison, the women in this study had a mean age of 25 years, they were of Asian Indian ethnicity, and they had a mean gestational age of 33 weeks at diagnosis. Differences in population characteristics may explain the differences in rates which have been reported in several studies and emphasize the need to have data which is generated from local populations.

Relatively fewer studies have evaluated risk factors for recurrence of PE. Associations of recurrences with gestational diabetes in the index pregnancies, [13] earlier gestational ages at diagnosis, [16] and small for gestational age babies [16] have been reported as potential risk factors. A higher diastolic blood pressure in the subsequent pregnancies has also been reported as a potential risk factor for recurrence [16]. The risk of recurrent PE has also been found to be associated with gestational ages at delivery in the index pregnancies [23]. After adjusting for parity, preterm deliveries at <37 weeks and renal disorders in the index pregnancies were associated with an increased risk for recurrent PE, although these associations were not statistically significant.

The results of this study have several implications for obstetricians whose patient profiles include women of Asian Indian ethnicity. This study provides additional evidence from an Asian Indian population, that PE is not necessarily a disease which is limited to nulliparous or primigravid women and that the obstetrician has to consider the possibility of PE in a multi-parous woman. It provided some evidence on the risk of recurrence in a woman who had PE in her index pregnancy. This information is useful for counseling women with PE in their index pregnancies, who are considering the possibility of another pregnancy or in the management of subsequent pregnancies in such women. The estimates of risk can be used to advise early booking for antenatal care for such women and to monitor such women more intensely.

The strengths of the current study include paying careful attention to the diagnosis of hypertensive disorders, based on international classifications, the use of laboratory parameters for supporting clinical findings, and the confirmation of the diagnosis by a multi-disciplinary clinical team. The single centre nature of this study was a possible limitation, as the population characteristics of women who sought care at this centre would not be representative of the larger population of pregnant women in India. However, this study raises several possibilities for additional research in PE, that can be translated into clinical practice. Much of the current research being done on PE focuses on early diagnosis of PE in index pregnancies, including the use of biomarkers for screening and predicting onset of PE. The results of this study indicate the need for further research on recurrence of PE in the subsequent pregnancies and potential factors which are associated with recurrence. The lack of significant associations with recurrent PE may be a true lack of association or it may be related to the lack of power or an adequate sample size, for accurately identifying associations. This may be addressed by doing a larger multi-centric study on a more heterogenous population. Further research in this area is essential, if we consider the long term risks for hypertension, cerebrovascular and cardiovascular diseases in such women at a later (possibly younger) stage in their lives, as well as the obstetric risks for maternal mortality which are associated with pregnancy induced hypertension.

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PARTICULARS OF CONTRIBUTORS:
1. Head, Obstetric Medicine, Fernandez Hospital, Hyderabad, India
2. Research Associate, Obstetric Medicine, Fernandez Hospital, Hyderabad, India
3. Head, Woman and Child Health Research Unit, Fernandez Hospital, Hyderabad, India

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Praveen Nirmalan,
Woman and Child Health Research Unit, Fernandez Hospital, Hyderabad-500001, India.
E-mail: echasapt@gmail.com; drpraveen.n@fernandezhospital.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Sep 18, 2013**
Date of Peer Review: **Oct 11, 2013**
Date of Acceptance: **Oct 13, 2013**
Date of Publishing: **Dec 15, 2013**