Incidence and risk factors for preeclampsia in a cohort of high-risk pregnant women: a nested case-control study from South India

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Abstract

Objective: To explore the incidence and risk factors of preeclampsia (PE) among high- risk pregnant women in South India. Design: Nested case-control study Setting: Tertiary referral hospital Population or Sample: Pregnant women with risk for PE. Methods: Maternal characteristics were prospectively collected, and risk factors were assessed comparatively between women with risk for developing PE and normotensive pregnant women using risk ratio (RR) (95% CI) plus multivariate analysis. One hundred and seventy-four risk group pregnant women were followed-up once in each trimester till delivery and noted for the development of PE. Main Outcome Measures: Incidence and risk factors of PE among high-risk pregnant women. Results: 67/174 women developed PE, corresponding to an incidence of 38.51% among pregnant women with risk for PE. Women in the age group of 30 and older reported a higher incidence. Maternal factors like absence of a family history of chronic hypertension, history of abortion, non-consanguineous marriage, and AB blood group were significant protective factor and sex of the newborn being female was a significant risk factor for developing PE. Conclusion: This is the first Indian study that explored the incidence and risk factors for PE among high-risk pregnant women. Incidence of PE was higher among South Indian risk population. Female infants significantly contributed to the PE risk. Funding: JIPMER Intramural Research fund. Keywords: Preeclampsia; Incidence; South India; High-risk women; Follow-up; Risk factors Tweetable abstract: The incidence of PE is 38.51% and the significant risk factor is female foetus among high-risk pregnant women.

Title: Incidence and risk factors for preeclampsia in a cohort of high-risk pregnant women: a nested case-control study from South India

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Objective : To explore the incidence and risk factors of preeclampsia (PE) among high- risk pregnant women in South India.

Design : Nested case- control study

Setting: Tertiary referral hospital

Population or Sample : Pregnant women with risk for PE.

Methods : Maternal characteristics were prospectively collected, and risk factors were assessed comparatively between women with risk for developing PE and normotensive pregnant women using risk ratio (RR) (95% CI) plus multivariate analysis. One hundred and seventy-four risk group pregnant women were followed-up once in each trimester till delivery and noted for the development of PE.

Main Outcome Measures : Incidence and risk factors of PE among high-risk pregnant women.

Results: 67/174 women developed PE, corresponding to an incidence of 38.51% among pregnant women with risk for PE. Women in the age group of 30 and older reported a higher incidence. Maternal factors like absence of family history of chronic hypertension, history of abortion, non-consanguineous marriage, and AB blood group were significant protective factor and sex of the new-born being female was a significant risk factor for developing PE.

Conclusion : This is the first Indian study that explored the incidence and risk factors for PE among high-risk pregnant women. Incidence of PE was higher among South Indian risk population. Female infants significantly contributed to the PE risk.

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Introduction

Hypertensive disorders of pregnancy (HDP) encompass a heterogeneous group of conditions including pre-existing hypertension, gestational hypertension, preeclampsia/eclampsia, and superimposed hypertension. HDPs are the leading cause of severe morbidity, mortality, and long-term sequelae for mother and baby[1,2]. A majority of maternal and perinatal deaths due to preeclampsia (PE) are preventable if appropriate treatment is prescribed[2,3]. Most of the morbidity occurs among pregnancies complicated by PE or eclampsia and for every woman who dies, approximately 20 others suffer severe morbidity[4].In Asia, nearly about $1/10^{th}$ of all maternal deaths are associated with HDPs[3]. The burden and the magnitude of PE are not fully known in some of the places in the world, especially in low- and middle-income countries. The crude incidence of PE was 2.3%, ranging from 1.2% to 4.2% across the world regions. Incidence estimates of PE in the SEARO region varied from 1.9% in Thailand to 8.6% in Indonesia[4]. The incidence of PE in developing countries is about five to seven times higher than that in developed countries[5]. A population-based multi-country study reported the incidence of pre-eclampsia to be 3.8%among pregnant women in India[6]. The major risk factors for PE reported are the previous history of PE, chronic hypertension, pre-gestational diabetes mellitus, multiple gestations, pre-pregnancy body mass index (BMI) >30, and few others[7].

Most of the available studies evaluated the incidence and risk factors for PE in healthy pregnant women. Only a few studies evaluated the incidence among high-risk pregnant women globally. To the best of our

knowledge, this is the first study to evaluate the risk factor and incidence of PE in a South Indian cohort of high-risk pregnant womenin a longitudinal follow-up manner. Determining the incidence of PE among risk group pregnant women isa key to guiding and funding public health policies aiming towards screening, prophylaxis, early diagnosis, and treatment, as well as supporting prospective studies related to this serious maternal disorder. The objective of this study is to assess the incidence and actual risk factor for PE among the South Indian pregnant women with risk for developing PE.

Methodology

This prospective cohort study was conducted at the Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Pondicherry, India. JIPMER is a super-specialty tertiary care hospital catering to all populations in the Pondicherry state and the adjacent districts of Tamil Nadu.

The study protocol approval was obtained from the JIPMER Scientific AdvisoryCommittee and the InstituteEthics Committee (Human studies). This study was conducted according to theDeclaration ofHelsinki guidelines. All individuals provided written informed consent.

Participants were recruited from May 2012 to June 2016. A total of 1,931 pregnant women were screened for participation in the outpatient department of Obstetrics and Gynaecology, ofwhich 1,512 were enrolled and consented to participate. Among the consented population, 369 were women with risk for developing PE.Flowchart of the number of patients recruited and analysed is reported in Figure 1.The inclusion criteria of the risk group include any or all of the following characteristics like family h/o PE, PE in a previous pregnancy, body mass index (BMI) >35 Kg/m^2, diastolic blood pressure>80 mmHg at the first visit, extremes of reproductive age (18 to 20 years and more than 35 years), Pre-existing medical conditions such as renal disease and chronic hypertension, and multiple gestations (more than two).

We performed a nested case-control study to determine the risk factors for developing PE among high-risk pregnant women. We also included patient characteristics at the time of their first visit during the first trimester. Patient characteristics that were included are demographic characteristics (age, socioeconomic status), medical history (family history of high blood pressure, PE, history of abortion, multiple gestations), and clinical risk factors (maternal blood group, sex of the new-born). There were no missing data on covariates. Study participants were followed till delivery and noted for the development of PE.

Statistical Analysis: To determine the age-specific incidence of PE in the high-risk group we report the number of PE cases to the total number of persons at risk in each age group for the period of study. In the comparison of cases and controls, we first compared patient characteristics before the event using the x^2statistic for categorical variables and the Student *t*- test for continuous variables. We then sought to identify risk factors associated with PE using conditional logistical regression. All the tests for statistical significance were 2-tailed tests and a p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 18.

Results

We recruited 369 pregnant women with the risk for PE, of which 174 high-risk pregnant women were followed-up till delivery after dropouts in each trimester. The mean [SD] age of the study participants was 28.05[6.05] years. Of the identified 174 high-risk pregnant women, 67 pregnant women reported a diagnosis of PE. This represents an incidence of PE as 38.51 per 100 high-risk pregnant women during this period. The age-specific incidence rate (per 100 persons) of PE among high-risk pregnant women is described in Table 1. The highest rate of PE incidence was observed in the age group of above 30 years.

Table 2 displays the patient characteristics and risk factors associated with the development of PE. The women who had a history of multiple gestations were more likely to have PE in comparison to those who did not have such a history. The women who married consanguineously were at very high risk for the onset of PE than the one whose marriage was not consanguineous. A previous history of abortion seemed to pose a moderate risk for the onset of PE while a family history of diabetes, PE as well as a previous history

of hypertension, gestational diabetes, or a conception history through IVF seemed to have no significant influence on the development of PE.

On multivariate analysis, a family history of chronic high blood pressure, history of abortion, consanguineous marriage, the sex of the new-born and the maternal blood group were independently associated with the occurrence of PE and were found to be statistically significant (Table 3). Risk factors such as the absence ofa family history of chronic hypertension, history of abortion, non-consanguineous marriage, and maternal blood group of AB-type are protective factors of PE development. While the sex of the new-born being female was found to be a risk factor for developing PE in the study population.

Discussion

Main findings

Our study revealed that the incidence of PE in South India was 38.51% among pregnant women with a risk for developing PE. Women in the age group of 30 and older reported a higher incidence. Maternal factors like absence of family history of chronic hypertension, history of abortion, non-consanguineous marriage, and AB blood group were significant protective factor and sex of the new-born being female was a significant risk factor for developing PE.

Strengths and limitations

The study was conducted in one single tertiary hospital with smaller sample size. We did not record the pregnancy outcomes like preterm deliveries and the subtypes of PE among those who developed PE. So, the values observed here may not be comparable with the one observed in primary and secondary level settings. Also, the dropout is high in each trimester because most of the pregnant women got registered during the first trimester later moved out of the city to their mother's home for delivery. Despite the limitations, this is the first longitudinal study of its kind in Indian settings with regular follow-up of once in each trimester till delivery to measure the incidence of PE in the high-risk population. Selection bias was minimized by using the nested case-control study design compared to the traditional case-control study.

Interpretation

Compared to studies reported globally our incidence was a little higher. This is probably due to the inclusion of only high-risk pregnant women in our study, whereas in other studies the comparison was made with normotensive pregnant women. Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) Project, a study conducted among 972 pregnant women in the Finnish population with risk factors for PE reported the incidence of PE among women with previous preeclamptic pregnancy and BMI of $>30 kg/m^2$was 28.6%, and among the pregnant women with chronic hypertension and one or more risk factors, the incidence was 24.6%[8]. A US-based study conducted among the high-risk cohort of pregnant women who received skilled home nursing, reported an incidence of 26.9%[9]. Out of various factors we studied, the absence of a family history of chronic hypertension, history of abortion, non-consanguineous marriage and maternal blood group being AB-type were reported as significant protective factor and sex of the new-born being female was found to be the risk factor for PE. The possible reason for the development of PE in 67/174 high-risk pregnant women is mainly due to five major factors like a family history of chronic high blood pressure, absence ofa history of abortion, consanguineous marriage, maternal blood group other than 'AB' and sex of the new-born.

History of abortion was found to be a protective factor in this study. No studies reported among the high-risk group, but within the pregnant women, various studies reported that prior abortion as a protective factor from developing PE[10,11]. Analogous to our findings, previous studies have reported the protective effect of both induced[10–14] and spontaneous abortions[12,15,16]. The reason is unclear. But the decreased risk of PE in women with a history of abortion might be due to the longer periods of sexual cohabitation[17], thereby the protective factors like transforming growth factor β (TGF-β) present in the seminal plasma might have caused the immune-deviating effects that enhanced the foetal/placental development which further decreased the risk of PE[18–22]. In contrast to our findings, Trogstad et al. reported an increased risk of PE in women

with a history of spontaneous abortions[13]. This might be due to the association of spontaneous abortions with infertility, which is the potential independent risk factor for PE[23].Our finding of the absence ofa family history of chronic hypertension as a protective factor from developing PE is supported by a Brazilian study[24]. Another study proved that the frequency of PE is greater in women who had hypertension for at least four years and also in those with PE during a previous pregnancy[25].

The culture of marrying within the blood relations is more prevalent in south India[26]and women in consanguineous unions are more likely to have adverse pregnancy outcomes including stillbirth and abortion[27,28].Consanguineous marriages continue to be a critical predictor of adverse pregnancy outcomes in India[29]. Out of many studies attempted to find the association between PE and consanguinity[30–32], only a few studies reported an increased risk of PE in marriages with biological relatives[33].Though the exact reason is not clear, consanguinity could allow more chance for homozygosity for the same single recessive gene for mother and foetus and consequently more chance for PE.

An important finding of the current study is the protective relation between blood group AB (non-O) and PE. Our finding contradicts a population-based nested case-control study that demonstrated AB blood group as a risk factor forPE[34] and a large Swedish cohort study that showed blood group O as a protective factor against PE[35]. Similar to our findings, Amin et al reported blood group O as a risk factor[36] and a contradictory finding by Francine et al., reported non-O blood groups as risk factors while blood group O is protective against PE[37].

Female foetus was reported as a potential risk factor, which is supported by the population-based Norwegian study among 1,691,053 singleton pregnancies[38] and a nested case-control study of 216 preeclamptic women[39]. A systematic review and meta-analysis reported that male foetal sex was associated with increased maternal risk of PE in the non-Asian population[40]. Also, foetal sex might influence maternal immunological function which could be the likely mediator between foetal sex and PE. A recent finding proved the presence of a higher concentration of spermine metabolite N1,N12-diacetylspermine (DiAcSpm) in placenta, and serum of women pregnant with a female foetus, which eventually increased the risk of PE[41].

Twin pregnancy (referred to multiple gestations in the current study) is a risk factor for PE with a reported incidence of 2-3 times higher than singleton pregnancy[42].Likewise, nulliparity, increased maternal BMI and chronic hypertension were risk factors for PE in twin pregnancies, while monochorionicity, ethnicity, and assisted reproductive techniques are not. In common with singleton pregnancies, twin pregnancies complicated by PE are at greater risk of an adverse pregnancy outcome[43].In contrast with our findings, some studies suggest that IVF is significantly associated with a higher incidence of PE. Also,severe PE was more prevalent in the singleton IVF-PE group than in the singleton SC-PE group[44–46].

The prediction of PE is challenging and predicting the same among high-risk pregnant women has not been attempted so far given the complexity associated with its aetiology. Due to the multifactorial aetiology of PE, the value of maternal characteristics and maternal clinical factors can remain as one of the best ways to screen the high-risk pregnant women susceptible to PE.

Conclusion

In conclusion, this study indicates that the incidence rate of PE increases in high-risk pregnant women aged 30 years and older. Several factors including female infants significantly contributed to the risk of development of PE. The development of PE with the high-risk population can also be due to other factors like parenting experience or parental stress. Further research should explore parenting experience and parental stress as individual risk factors for PE within the high-risk population. Early identification and timely intervention are essential to minimize the risk of PE.

Author contribution

SM was responsible for the concept, protocol design, data collection, patient follow up, data interpretation, writing and revision of the manuscript. PP oversaw the work including the data interpretation and helped

write and amend the manuscript. GKP gave advice on data interpretation and amended the manuscript.SH gave advice on manuscript writing.

Details of ethics approval

The study was approved by Institute Ethics Committee for Human studies of JIPMER on 22 May 2012 with reference number JIP/IEC/SC/3/2012/2

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Disclosure of interests

Nil

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