Obstetrics and Gynaecology Section

Pre-eclampsia (PE) and Chorionicity in Women with Twin Gestations

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ABSTRACT

Background: Pre-Eclampsia (PE) affects 6-31% of pregnant women with multiple gestations. There are conflicting reports on the association of PE with Chorionicity and zygosity; however, there is a lack of information on this potential association in a population of pregnant Asian Indian women.

Aim: To determine as to whether chorionicity and zygosity were associated with PE in a population of Asian Indian women with twin gestations.

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

Material and Methods: The study included pregnant women with twin gestations, who was delivered at the study institute in 2012. Hypertension in pregnancy was categorized, based on the criteria of the International Society for the Study of Hypertension in Pregnancy. Chorionicity was determined by using ultrasonography and zygosity was determined, based on clinical criteria. Point estimates and the 95% Confidence Intervals (CI) around point estimates of PE and associations of chorionicity and zygosity with PE were determined by using bivariate analysis, logistic regression models and area under Receiver Operator Characteristic (ROC) curves.

Results: This study included 208 women with twin gestations. The incidence of PE in dichorionic twin gestations was 13.17% (n=22, 95% CI: 8.66, 18.96), it was 4.87% (n=2, 95% CI: 0.83, 15.19) in monochorionic twin gestations, it was 16.36% (n=9, 95% CI: 8.29, 27.91) in dizygous twin gestations and it was 4.88% (n=2, 95% CI: 0.83, 15.19) in monozygous twin gestations. Neither chorionicity (adjusted OR: 2.59, 95% CI: 0.55, 12.19) nor zygosity (adjusted OR 2.72, 95% CI: 0.49, 15.13) were associated with PE In a multivariate logistic regression model.

Conclusion: Although it was not statistically significant, the clinical incidence of PE was higher in dichorionic and dizygous twin gestations.

INTRODUCTION

Multiple gestations contribute nearly 20% of the overall perinatal mortality and morbidity rates [1,2]. The incidence of perinatal complications is reportedly higher in pregnant women with monochorionic twins [3-7]. Chorionicity can be reliably determined in the first trimester of pregnancy by using non-invasive ultrasonography [8]. PE is an important co-morbidity which is seen in women with multiple gestations, with an incidence that ranges from 6 to 31% [9-13]. This study was aimed at determining as to whether chorionicity was associated with PE in multiple gestations and whether the determination of chorionicity could be used as a predictor for PE in multiple gestations, in a population of Asian south Indian women.

MATERIAL AND METHODS

This study was conducted at a single, tertiary care maternal and new born centre in Southern India. A retrospective, observational study design and a data collection protocol that adhered to the tenets of the Declaration of Helsinki was used to collect information on women with twin gestations, who sought antenatal care in the first trimester and delivered at the study institute in the year 2012. Details of each pregnant woman, including maternal age, prior obstetric and medical history, current obstetric and medical history, height, weight and BMI, clinical exams, laboratory investigations and ultrasound exams were routinely transcribed from the medical records into a database. Gestational age was determined on the basis of the last menstrual period and/or ultrasound dating of gestation. Chorionicity was routinely estimated for multiple gestations with ultrasonography by using the lambda or T sign and it was based on the presence or absence of an extension of placental tissue into the base of the intertwine membrane [8]. Details of delivery, including mode of delivery, associated antenatal and intra-natal complications, gestational ages at delivery, neonatal statuses and postpartum complications were documented and they were entered into the database. PE was defined, based on the classification of the International Society for the Study of Hypertension in Pregnancy and it included the measurement of proteinuria as a criteria [14]. Gestational diabetes (GDM) was defined, based on the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) guidelines for the classification of GDM [15]. We explored the database to identify and retrieve information on pregnant women with twin gestations, who delivered at the study institute in the year 2012. The retrieved information was stored in a de-identified format in an MS Excel spreadsheet and it was exported to a statistical software package (SPSS version 14.0, SPSS Inc) for further analysis.

Associations of PE with chorionicity were initially explored by using a bivariate analysis and also by using a multivariate logistic regression model that was adjusted for maternal factors, including maternal age, parity and gestational age at delivery. Odds ratios and 95% CI around the point estimate were reported. The performance of chorionicity as a test, for identifying PE, was further explored by using measures to test effectiveness of diagnostic tests, including sensitivity, specificity, likelihood ratios and Area Under Receiver Operator Characteristic (AUROC) curves. Zygosity can be accurately identified only by prenatal invasive testing for examining DNA markers [16], but such tests are not possible in a majority of women with multiple gestations in this population. However, we categorized zygosity in this population, considering existing knowledge that dichorionic twin gestations resulting in different sex live borns were

definitely dizygotic and that all monochorionic twin gestations were definitely monozygotic, to explore any potential association of zygosity and PE [16].

RESULTS

This study included data from 208 pregnant women with twin gestations, who delivered at the study institute in the year 2012. The mean maternal age (SD) was 28.17 (4.44) years and the age of the women ranged from 18 to 41 years. Twelve (5.77%) women were aged ≥35 years at booking. One hundred and sixty one (77.78%) of these 208 women were nulliparous and 40 (19.23%) women had a BMI of ≥ 30at booking. One hundred and sixty seven (80.29%) of these 208 women had dichorionic gestations and 41 (19.71%) had monochorionic gestations. Twenty four (11.54%, 95% CI: 7.16, 15.92) of these 208 women developed PE during the courses of their pregnancies [Table/Fig-1]. Presents a comparison of maternal characteristics which were stratified by PE in this population of women with twin gestations.

The incidence of PE in dichorionic twin gestations was 13.17% (n=22, 95% CI: 8.66, 18.96) and it was 4.87% (n=2, 95% CI: 0.83, 15.19) in monochorionic twin gestations. Details of zygosity could be ascertained for 96 (46.15%) of these 208 women; 41 (42.71%) of these 96 women were monozygous. The incidence of PE was 16.36% (n=9, 95% CI: 8.29, 27.91) in women with dizygous twin gestations and it was 4.88% (n=2, 95% CI: 0.83, 15.19) in women with monozygous twin gestations.

In an unadjusted logistic regression model, neither chorionicity (reference category-monochorionic, OR 2.96, 95% CI: 0.67, 13.13) nor zygosity (reference category-monozygosity, OR 3.82, 95% CI: 0.78, 18.72) were associated with PE. After adjusting for maternal age, parity, BMI, and gestational diabetes in a multivariate logistic regression model (with all variables examined simultaneously), neither chorionicity (reference category-monochorionic, adjusted OR: 2.59, 95% CI: 0.55, 12.19) nor zygosity (reference category-monozygosity, adjusted OR 2.72, 95% CI: 0.49, 15.13) were found to be associated with PE. Chorionicity and zygosity were not effective diagnostic tests for predicting PE see [Table/Fig-2].

DISCUSSION

Out of over 1 in 10 pregnant women with twin gestations in this study population developed PE during the courses of their pregnancies. Several studies which were done worldwide, that had explored associations between zygosity and PE, have reported conflicting results on an association of PE with zygosity in twin gestations [17-21]. These conflicting results may be attributed to the changing or evolving definitions of PE over time, as well as to the determination of zygosity. Zygosity can be accurately established only by DNA marker studies and it needs invasive prenatal testing- amniocentesis, chorionic villous biopsy or foetal blood samples which are obtained through cordocentesis [16]. Zygosity may also be determined post natally by studying placental histology and placental enzymes, HLA typing of like sex twin pairs, blood groups and red cells of the neonates. However, from a clinical perspective, the determination of zygosity is not easily available, accessible and affordable in this population and hence, it does not offer the potential for its application to a larger population.

Ultrasound examination is now a recognized and a routine part of antenatal care and it offers advantages as a relatively low cost. It is a non-invasive tool that can be used to determine chorionicity. The presence or absence of the lambda sign has been proven to be reliable in the determination of chorionicity and it can be determined by a trained obstetric sonologist. In terms of clinical application, the determination of chorionicity has the potential for application to a larger population, without the need for much additional resources. However, studies done on potential associations of chorionicity with PE have also shown conflicting results [22-25].

Characteristic	With PE (n=24)	Without PE (n=184)	p–value (Test)
Mean Maternal Age (SD)	28.00 (4.56)	28.19 (4.44)	0.84 (ANOVA F test)
Nulliparous	19 (79.17%)	142 (77.17%)	0.98 (Fishers Exact test)
Body Mass Index ≥ 30	10 (41.67%)	30 (16.30%)	0.01 (Fishers Exact test)
Gestational Diabetes	2 (8.33%)	29 (16.20%)	0.54 (Fishers Exact test)
Median gestational age at delivery (25th, 75th centile) in weeks	34 (32.5, 35)	35 (33, 36)	p=0.09 (K-sample equality of medians test)
Preterm delivery <34 weeks	9 (37.50%)	56 (30.43%)	0.48 (Chi-square test)

[Table/Fig-1]: Maternal characteristics of the 208 women with twin gestations stratified by pre-eclamspia (PE)

	Di-Chorionicity	Di-Zygosity
Sensitivity (95% CI)	91.70 (73.00, 99.00%)	81.80 (48.20, 97.70)
Specificity (95% CI)	21.20 (15.50, 27.80)	45.90 (35.00, 57.00)
Area under ROC curve (95% CI)	0.56 (0,50, 0.63)	0.64 (0.51, 0.77)
Positive likelihood ratio (95% CI)	1.16 (1.01, 1.34)	1.51 (1.08, 2.13)
Negative likelihood ratio (95% CI)	0.39 (0.10, 1.53)	0.40 (0.11, 1.42)

[Table/Fig-2]: Diagnostic effectiveness of chorionicity and zygosity as predictors of pre-eclampsia

Immunological incompatibility between the mother and the foetus(es) has been hypothesized to contribute to the pathogenesis of PE [17]. A higher incidence of PE is expected in dizygous and dichorionic gestations if maternal and foetal immuno-incompatibilities influence the development of PE. The clinical incidence of PE was higher in women with dichorionic or dizygous states in this study; however, the difference was not statistically significant, even after adjusting for maternal variables. This study does not offer conclusive evidence on presence or absence of associations of chorionicity with PE, however, it does provide information that can be adapted to counsel women with twin gestations on the probability for PE, based on chorionicity. A post-test odds can be derived, based on the prevalence of PE in this population and the positive likelihood ratio for di-chorionicity. The post-test odds which are thus derived can be converted into a post-test probability for clinical application. Based on the results of this study, we found that the probability for PE increased from 11.54% to 13.14% if a woman was determined to have a dichorionic twin gestation on ultrasound examination.

It is possible that the lack of a significant difference for the incidence of PE by chorionicity or zygosity is a true lack of difference; however, this study did not have enough power (post–hoc power estimation: 53.66%) to establish that assumption. A study which was done on a larger sample of twin gestations is necessary, to further explore this lack of difference. Such a study may have to be multi-centric, considering the relative lower incidence of twin gestations.

CONCLUSION

the clinical incidence of PE was higher in mothers with dichorionic and dizygous twins, although the difference in incidence was not statistically significant. However, the difference in clinical rates is useful for counseling pregnant women with dichorionic and dizygous twins about a potential higher risk for PE as compared to pregnant women with monochorionic or monozygous twins. Chorionicity can be assessed by using routine ultrasound examination in the first trimester and it can thus help in identifying a "more-at-risk" group for PE among pregnant women with twin gestations.

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