SCREENING FOR PREECLAMPSIA IN TWIN PREGNANCIES

PhD Thesis

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INTRODUCTION

Preeclampsia, which is one of the leading causes of maternal and perinatal morbidity and mortality, is a global health problem and great efforts have been made worldwide to develop methods for prediction and prevention of PE. In singleton pregnancies, the incidence of PE is 2–3%.

In the last few years there is an increasing number of twin pregnancies due to the increase in maternal age and the improvement in assisted reproductive technology. Overall, twin gestations constitute 2-5% of all pregnancies, and they have an increased risk of almost every pregnancy complication, including GH and PE, gestational diabetes and thromboembolism. In twin pregnancy, the incidence of PE is about 9%. Consequently, the relative risk of PE for twin compared to singleton pregnancies is about 3. However, twins are delivered at an earlier gestational age than singletons and consequently comparison of the overall rates of PE between twin and singleton pregnancies underestimates the relative risk of preterm-PE in twins which is 9-times higher.

OBJECTIVES

1. To examine the predictive performance of the competing risks model in screening for PE in twins in the training dataset for development of the model and an independent validation dataset.

2. To modify the previously proposed competing risk model using the original training dataset and to examine the predictive performance of the new model in screening for PE with delivery <34 weeks (early-PE), <37 weeks (preterm-PE) and delivery at any gestation (all-PE) in twins in an independent validation dataset.

3. To demonstrate the application of the new model in screening in a mixed population of singleton and twin pregnancies.

METHODS

Three datasets were used for this study. The first study of 2,219 women, which was previously reported, was used to develop the competing risks model for prediction of PE in twins and is therefore considered to be the training set. The validation study comprised of 2,999 women.

The data for these studies were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit at 11^{+0} - 13^{+6} weeks' gestation. In this visit we recorded maternal demographic characteristics and medical history, measurement of maternal weight and height.

Patient-specific risks of delivery with PE at <34, <37 and $<41^{+3}$ weeks' gestation were calculated using the competing risks model and the performance of screening for PE in the training and validation datasets was assessed. We examined the predictive performance of the model by first, the ability of the model to discriminate between the PE and no PE groups using the area under the receiver operating characteristic (AUROC) curve and second, calibration which

assesses agreement between predicted risks and observed incidence of PE.

The training dataset was used to fit the model whereby the effect of twins in shifting the distribution of gestational age of delivery with PE in singletons to the left should not be the same for all gestational ages but the shift should depend on the singleton prior mean; the effect increases with increasing prior mean. Data obtained from the SPREE study were included to examine the performance of screening in a mixed population of singleton and twin pregnancies.

The study was approved by the NHS Research Ethics Committee in England and the Hospital Ethics Committees of the participating hospitals in Bulgaria and Spain.

RESULTS

In the first study we found that in both the training and validation datasets the incidence of early-PE and preterm-PE in twin pregnancies was substantially higher than in our previous studies in singleton pregnancies. The findings on predictive performance of the competing risks model for PE in twin pregnancies demonstrated that the results from the validation dataset, derived from prospectively collected data from multicenter studies, are consistent with those of the training set used for development of the model.

We examined the predictive performance of the proposed model through calibration plots. The results of the study demonstrate that in both the training and validation datasets the observed incidence of PE was lower than the predicted one and such overestimation of risk was particularly marked for early-PE. It was therefore concluded that the model needs to be adjusted to correct the observed overestimation of risk for early-PE.

In the second study we developed a new model for the prediction of PE in twin pregnancies and demonstrated relatively good calibration in an independent validation

dataset. The basis of the new model is that in twin pregnancies the shift to the left of the distribution of gestational age at delivery with PE in singleton pregnancies is not uniform, as in our original model, but the effect increases with increasing singleton prior mean.

In the prediction of PE in a mixed population of singleton and twin pregnancies the same risk cut-off should be used in identifying the high-risk group in need of prophylactic pharmacological interventions to prevent the development of PE and closer monitoring for early identification of the clinical signs of the disease in those that will develop PE. In this study we have demonstrated that at a risk cut-off that would classify 10% of a mixed population as being at high-risk for preterm-PE all twins will be classified as screen positive.

CONCLUSIONS

In the initial development of the competing risks model of PE in twin pregnancies we adopted the simple approach of adjusting the model for singletons; in DC and MC twin pregnancies with the same characteristics as singleton pregnancies the distribution of gestational age of delivery with PE was shifted to the left by 8 and 10 weeks, respectively.

1. We demonstrated that such approach did not adequately address the effect of twins on risk of PE and this was particularly so for early-PE. It was therefore concluded that a new model needs to be fitted whereby the effect of twins in shifting the distribution of risks in singletons to the left should not be the same for all gestational ages but such shift should be less for lower than higher gestations.

2. A new competing risks model in screening for PE by maternal risk factors in twin pregnancies was developed and using this model the predicted risks for

early-PE, preterm-PE and all-PE were in good agreement with the observed incidence of the disease.

3. In the prediction of PE in a mixed population of singleton and twin pregnancies the new model has good performance, however with risk cut-off that would classify 10% of a mixed population as being at high-risk for preterm-PE all twins will be classified as screen positive.

PUBLICATIONS OF THE THESIS

Benkő Z, Chaveeva P, de Paco Matallana C, Zingler E, Wright A, Wright D, Nicolaides KH. Validation of competing risks model in screening for pre-eclampsia in twin pregnancy by maternal factors. Ultrasound Obstet Gynecol 2019; 53:649-654.

IMPACT FACTOR: 5.595

Benkő Z, Chaveeva P, de Paco Matallana C, Zingler E, Wright D, Nicolaides KH. Revised competing-risks model in screening for pre-eclampsia in twin pregnancy by maternal characteristics and medical history. Ultrasound Obstet Gynecol 2019; 54:617-624.

IMPACT FACTOR: 5.595

OTHER PUBLICATIONS

Francisco C, Wright D, **Benkő Z,** Syngelaki A, Nicolaides KH. Hidden high rate of preeclampsia in twin compared to singleton pregnancies. Ultrasound Obstet Gynecol 2017; 50:88-92.

IMPACT FACTOR: 5.564

Francisco C, Wright D, **Benkő Z**, Syngelaki A, Nicolaides KH. Competing-risks model in screening for pre-eclampsia in twin pregnancy by maternal characteristics and medical history. Ultrasound Obstet Gynecol 2017; 50:501-506.

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Francisco C, Wright D, **Benkő Z**, Syngelaki A, Nicolaides KH. Competing-risks model in screening for pre-eclampsia in twin pregnancy according to maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol. 2017 50:589-595

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