Biological Interaction as a Useful Tool to Understand Complicated Relationship among Multiple Risk Factors

Akihide Ohkuchi*

Department of Obstetrics and Gynecology, Jichi Medical University School of Medicine, Japan

INTRODUCTION

Preeclampsia

Preeclampsia (PE) is a multifactorial disease [1]. A systematic review elucidated that there are several risk factors for PE [2]. In 52 selected studies, antiphospholipid antibodies, pre-existing diabetes, previous PE, family history of PE, nulliparity, multiple pregnancies, raised body mass index (BMI) at booking or before pregnancy, systolic blood pressure (SBP) ≥130 mmHg at booking, diastolic blood pressure (DBP) ≥80 mmHg at booking, and age ≥40 were significant risks for PE [2]. Recent multivariate analysis of a prospective multicenter cohort of nulliparous women revealed that clinical risk factors at 14-16 weeks of gestation were age, mean arterial blood pressure (MAP), BMI, family history of PE, family history of coronary heart disease, maternal body weight, and vaginal bleeding for at least five days; and factors associated with reduced risk were a previous single miscarriage with the same partner, taking at least 12 months to conceive, high intake of fruit, cigarette smoking, and alcohol use in the first trimester; however, the area under the receiver operation characteristics curve (AUC) was only 0.71; moreover, the addition of uterine artery Doppler (UAD) indices did not improve performance [3]. Thus, a multivariate model for predicting all PE using maternal factors and UAD may not be promising for clinical use.

Biological interaction

High BP and abnormal UAD findings in the second trimester are well-known risk factors for the subsequent occurrence of PE, [4,5] especially earlier onset of PE [6-8]. We recently found that high BP and abnormal UAD had a strong biological interaction for the occurrence of early-onset PE (EO-PE) with onset at <34 weeks of gestation [9]. In 2410 pregnant women, the adjusted odds ratio (95% CI) in women with abnormal UAD alone, high BP alone, and both high BP and abnormal UAD for predicting EO-PE was 4.3 (0.37-49), 12 (2.6-55) and 85 (17-422), respectively; and that for predicting late-onset PE (LO-PE) was 6.3 (1.5-27), 6.1 (2.1-17) and 15 (3.6-61), respectively. The relative excess risk due to biological interaction (RERI) between the two risk factors for EO-PE in the logistic regression model was calculated as 70; therefore, we judged that there was a very strong synergistic interaction between high BP and abnormal UAD for EO-PE risk; and the RERI between the two risk factors for LO-PE in the logistic regression model was calculated as 3.3; therefore, there was a weak synergistic interaction for LO-PE risk. These results suggested that high BP and abnormal UAD synergistically interact for the genesis of EO-PE.

Biological interaction is a relatively unfamiliar, but clinically important phenomenon. The degree of biological interaction is measured between risk factors as the deviation from additivity by the corresponding disease rates, not as deviation from multiplicity [10]. In order to specify the models, let i = 1 when the first risk factor is present and 0 otherwise, and let j = 1 when the second risk factor is present and 0 otherwise; furthermore, let RRij be relative risk in exposure category i, j. Thus, RR11, RR10, RR01, and RR00 are the relative risks for each of the four categories. We also define those unexposed to both the first and second risk factors as the reference category, i.e., RR00 = 1. The three relative risk estimates other than RR11 could obtained from a logistic regression model or Cox regression model [10].

The relative excess risk due to biological interaction (RERI) is defined as follows: [10]

$$RERI = RR_{11} - RR_{10} - RR_{01} + 1$$

If there is no biological interaction, RERI is equal to 0; if there is positive biological interaction, RERI is >0; and if there is negative biological interaction, RERI is <0 [10]. In our recent study, weak, moderate, and strong biological interactions were defined when the absolute values of RERI were 2.0-4.9, 5.0-9.9, and ≥10 [9].

To calculate biological interaction using multivariate analyses, we should perform one invention to enter variables into the models. RR11, RR10, RR01, and RR00 are created by the combination of two dichotomous variables as a series of dummy variables. For example, using SPSS, dummy variables can be easily generated using a built-in function.

Perspective

We recently elucidated that high BP levels and abnormal UAD were additively implicated in circulating abnormalities of angiogenesis-related factors in not only the second trimester but also early third trimester [11]. Thus, combination analysis of two variables sometimes identifies a hidden synergistic effect of risk factors on the subsequent phenomenon. Statistics using biological interaction is a useful tool to understand the complicated relationship between multiple risk factors in medicine.

REFERENCES


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