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CORRESPONDENCE

Response to Dr Sabour: 'Prediction and prevention of hypertensive disorders of pregnancy: a methodological mistake'

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We welcome the opportunity to respond to Dr Sabour,[1] whose most important concern was the 'lack in validation model' in our previous studies. In this review article, we summarized other researchers' study results, and we also described our own data regarding an onset threshold or a serial approach to predict the imminent onset of preeclampsia (PE), with onset at <4 weeks after blood sampling in the second and early-third trimesters, yielding a positive likelihood ratio of >10 and positive predictive value of $>20\%$.[2–4]

In these studies, we did not check the internal validity,[3–4] which Dr Sabour[1] was concerned about. However, the methodologies of our cohort studies, even without validation, were not erroneous; they were just exploratory cohort studies for the generation of hypotheses.[5] This is an established methodology, especially when the preceding data are relatively limited. Using diagnostic research studies as an example, a validation cohort study with good reference standards is classified as evidence level 1b, whereas an exploratory cohort study with good reference standards is classified as evidence level 2b.[5] This means that although a validation cohort study is of higher evidence level than an exploratory cohort study, the latter is by no means a methodological mistake if it has a good reference standard, and ours have a good reference standard.

However, bear in mind that we have actually started to collect a second cohort of pregnant women (2009–2014) to validate our initial results from the prospective study of a preliminary cohort of pregnant women (2004–2008). However, since it is expensive to measure sFlt-1 and PlGF levels, the validation study will be performed only in a high risk for PE group of women; this is reasonable because a high-risk, not low-risk, population should be the focus of this type of study.

I agree with Dr Sabour's[1] opinion that a validation study is mandatory for prediction studies.[1] The first conclusion from the mathematical likelihood model might be overestimated compared with the results using another cohort. Therefore, it is best to use data sets from two different cohorts or to split one cohort data set, in a prospective cohort study.[1] However, this validation cohort study may have several weaknesses. First, the number of patients required for the validating cohort will be large, which will elongate the study period. Second, the cost to measure molecules will be doubled for a validation cohort study. Third and most importantly, in most studies for predicting PE, there must be multivariate models for several risk factors, including high blood pressure, abnormal uterine artery flow velocity waveforms, and so on.[6] Therefore, in the first prospective study, it may be more important to evaluate potential risk or confounding factors rather than to perform a validation cohort study. The number of subjects required for multivariate analysis is several times larger than that required for univariate analysis.

We understand the importance of a validation study, and as stated, our future study will be a cohort study with validation, which is the gold standard methodology for a prospective cohort study. However, at an immature and initial stage when preceding studies are limited, we decided to focus on generating sound hypotheses rather than focus on theoretical soundness. We, together with other research teams, initiated a new era of PE prediction, but there is still a long way to go.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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