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Tiered Prediction System for Preeclampsia: an integrative application of multiple models

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Abstract: For years, it has been a challenge to identify women at risk of Preeclampsia (PE), one of the leading causes of maternal and perinatal morbidity and mortality. This would be especially useful in early pregnancy when modifiable factors can be addressed to reduce the risk or severity of outcome. Despite an increasing number of clinical and statistical prediction models being developed, which have been shown to outperform traditional maternal history or Doppler ultrasound approaches, it is still difficult to make accurate predictions based on a single model at a single time-point. Hence, here we investigate the use of multiple models integrated by Bayes' theorem.

Methods: Prediction models based on three stages of pregnancy, pre-pregnancy, 15 weeks and 20 weeks of gestation, were developed with varying levels of sensitivity and specificity specific to each stage. Post-test probabilities at each stage are then calculated based on the Likelihood of each test using Bayes' theorem. The accuracy measures and predictive values are evaluated for both pre-test and post-test probabilities.

Results: The overall proportion of truly identified cases have improved in the integrated model, with 81% correctly identified at 20 weeks of gestation, compared to 75% by the individual model. A relatively balanced accuracy can be achieved even when individual tests have been specified for higher sensitivity or specificity.

Conclusion: Through an integrated prediction system, the accuracy of prediction is further enhanced and tailored for individual women, as the risk is assessed and updated throughout pregnancy based on predictors at different stages, the likelihood of PE from prediction at earlier stages, and clinicians' knowledge or hypotheses.

Keywords: *Preeclampsia, prediction, Bayes' theorem*

1. INTRODUCTION

Preeclampsia (PE), a hypertensive disorder in pregnancy, is one of the major causes of maternal and perinatal morbidity and mortality that affects around 3-5% pregnancies worldwide (Pfeifer, 2007; Hanretty, 2009). With an increased risk of severe complications due to delays in diagnosis, screening or prediction tools prior to symptoms are valuable for assessment of interventions and tailored antenatal care.

The complexity in developing methods of prediction for Preeclampsia is largely due to its low prevalence, unknown aetiology and absence of a 'gold standard' (Briceno-Perez et al., 2009). Current approaches based on maternal history have an estimated sensitivity of only 40% and 60% for Uterine artery Doppler ultrasound studies during 2nd trimester (Papageorghiou et al., 2005; Jacquemyn and Zemtsova, 2010). Despite an increasing number of recent clinical and statistical prediction models, which have been shown to outperform traditional approaches, the majority of models only provide risk estimation during late second trimester, and treatment is often delayed.

Since an early prediction of risk is desired but a single model may not be satisfactory, a multi-model or tiered approach is considered with individual models tailored for each stage in pregnancy. This paper will focus on the effectiveness of a tiered approach integrated by Bayes' theorem based on models developed for PE.

2. METHODS

The models are developed based on the Screening fOr Pregnancy Endpoints (SCOPE) project database (Australian and New Zealand Clinical Trials Registry ACTRN126007000551493), which contains comprehensive records of maternal history, dietary practices and clinical measurements at 3 stages of pregnancy (pre-pregnancy, 15 weeks and 20 weeks of gestation). For every model, the observed and predicted cases of PE are tabulated into a 2x2 table (Table 1), showing the true positives (TP) and true negatives (TP), false positives (FP) and false negatives (FN).

Table 1. Observed Frequencies table.

	Preeclampsia				
Test result	**Yes (D)**		**No ($\overline{D}$)**		**Total**
Yes (+)	a	TP	b	FP	a+b
No (-)	c	FN	d	TN	c+d
Total	a+c		b+d		n(=a+b+c+d)

The sensitivity (r) is the proportion of truly predicted cases of PE, and specificity (s) is the proportion of truly predicted cases of uncomplicated pregnancy. The positive predictive value (PPV) is the proportion of true positives in predicted cases of PE, whereas negative predictive value (NPV) is the proportion of true negatives in predicted cases of uncomplicated pregnancy.

$$r = P(+ \mid D) = \frac{P(+ \cap D)}{P(D)} = \frac{a}{a+c} \tag{1}$$

$$s = P(- \mid \overline{D}) = \frac{P(- \cap \overline{D})}{P(\overline{D})} = \frac{d}{b+d} \tag{2}$$

$$PPV = P(D \mid +) = \frac{P(D \cap +)}{P(+)} = \frac{a}{a+b} \tag{3}$$

$$NPV = P(\overline{D} \mid -) = \frac{P(\overline{D} \cap -)}{P(-)} = \frac{d}{c+d} \tag{4}$$

A test with high sensitivity is likely to have a higher NPV, and similarly, a test with high specificity is likely to have a higher PPV. However, since PPV depends on the prevalence of disease $P(+)$, rare complications such as PE will have low PPVs even when high specificity is achieved.

An overall ratio of true vs. false classification is also obtained by:

$$\text{Overall} = \frac{P(+ \cap D) + P(- \cap \overline{D})}{P(D \cup \overline{D})} = \frac{a+d}{n} \tag{5}$$

2.1. Individual Models

Individual models are developed based on predictors collected at pre-pregnancy, 15 weeks and 20 weeks of gestation (Figure 1). The pre-pregnancy model serves as an initial 'guess' for a pre-test probability, and hence, a balanced sensitivity and specificity is preferred. This, of course, can be a probability of PE based on the clinician's hypothesis.

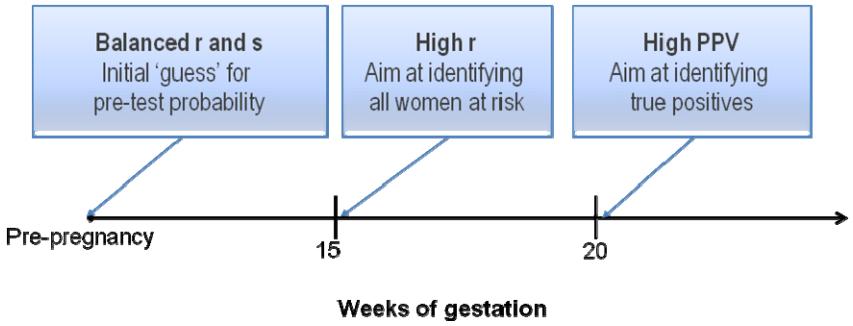

Figure 1. Individual model specifications.

For the first screening, a high sensitivity is preferred, as the aim is to identify all patients with possible risk, and those who are predicted at risk (i.e. with positive test result) may benefit from more frequent monitoring. At the later stage of pregnancy, a high positive predictive value is preferred to minimize the chance of unnecessary, and possibly hazardous, interventions.

2.2. Model Integration

For model integration, obtaining an estimated probability that integrates prior 'guess' or known knowledge may be useful. This can be done by applying the Bayes' theorem to obtain a post-test odds at each stage of pregnancy based on the odds of prior 'guess' and the likelihood of current test. An overview of the model integration process is shown in Figure 2.

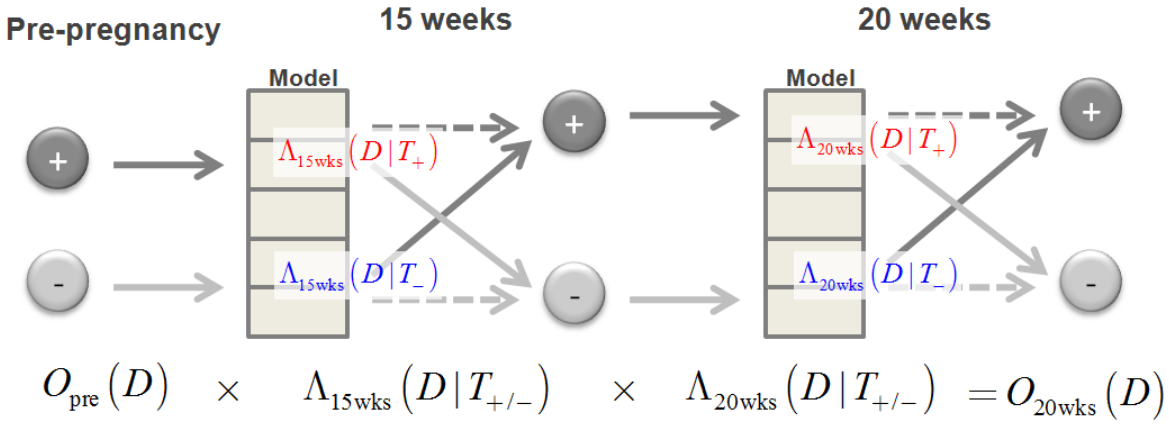

Figure 2. Overview of model integration.

The theory and application used in the initial step, where test results obtained at 15 weeks of gestation is integrated with a pre-test probability, have been widely applied in areas of evidence-based medicine, and is also used in clinical decision support systems (Hall, 1967; Round, 2001; Lindgaard et al., 2009).

After all individual models are obtained, the post-test probability can be calculated following Bayes' theorem:

$$P(D \mid T_{+/-}) = \frac{P(D)P(T_{+/-} \mid D)}{P(T_{+/-} \mid D)P(D) + P(T_{+/-} \mid \overline{D})P(\overline{D})} \tag{6}$$

This can be written in terms of the odds (Aitken and Stoney, 1991):

$$O(D \mid T_{+/-}) = \frac{O(D)P(T_{+/-} \mid D)}{P(T_{+/-} \mid \overline{D})} \tag{7}$$

Therefore, the integrated post-test odds of PE at 15 weeks of gestation, with pre-test odds obtained using the pre-pregnancy model or based on clinician's hypothesis, is given by:

$$O_{15\text{wks}}(D \mid T_{+/-}) = O_{\text{pre}}(D) \times L_{15\text{wks}}(D \mid T_{+/-}) \tag{8}$$

where $L(D \mid T_{+/-}) = \frac{P(T_{+/-} \mid D)}{P(T_{+/-} \mid \overline{D})}$ is the likelihood of PE given a positive or negative test result for the current stage in pregnancy. This can be calculated from sensitivity and specificity of each test, where $L(D \mid T_{+}) = r/(1-s)$ and $L(D \mid T_{-}) = (1-r)/s$.

For further prediction at 20 weeks of gestation, sequential odds ratios are calculated based on the pre-pregnancy odds and the likelihood of tests at 15 weeks and 20 weeks of gestation. The final post-test odds ratio is given by:

$$O_{20\text{wks}}(D \mid T_{+/-\,15\text{wks}}, T_{+/-\,20\text{wks}}) = O_{\text{pre}}(D) \times L(D \mid T_{+/-\,15\text{wks}} \cap T_{+/-\,20\text{wks}}) \times L_{20\text{wks}}(D \mid T_{+/-}) \tag{9}$$

3. RESULTS

The accuracy and predictive values at each stage are shown in Table 2. The individual measures show the accuracy and predictive values obtained from separate testing, while the integrated measures are results from post-test odds using integrated models.

Table 2. Pre-test and post-test accuracy measures (best values shown in bold italics).

		15 weeks		*20 weeks*	
	Pre-preg	**Individual**	**Integrated**	**Individual**	**Integrated**
r	0.75	***0.81***	0.78	0.59	0.60
s	0.60	0.45	0.63	0.76	***0.82***
PPV	0.10	0.08	0.11	0.13	***0.17***
NPV	0.97	0.97	***0.98***	0.97	0.97
Overall	0.61	0.47	0.64	0.75	***0.81***

As expected, the accuracy of tests increase with time as more predictors are available, with the best individual test obtained from predictors at 20 weeks of gestation (r=59%, s=76%, overall=75%). These tests outperform the traditional approach based solely on maternal history (r=40%), and achieved a sensitivity level higher than the 20 weeks Doppler ultrasound approach (r=60%) at an earlier stage in pregnancy.

Results from both integrated models have an overall increase in the proportion of truly predicted patients, where 81% of patients are truly classified as either PE or uncomplicated pregnancy at 20 weeks of gestation. By integrating the models, a prediction with a relatively balanced accuracy can be achieved even when individual tests have been specified for higher sensitivity or specificity. This, of course, is dependent on whether the pre-test model has a balanced sensitivity and specificity. For this reason, a pre-pregnancy model is provided as a reference for pre-test odds.

Interestingly, for this tiered prediction system, a NPV of at least 97% is achieved for all models, and the integrated models obtained a higher PPV while keeping the NPVs constant.

4. DISCUSSION

The results show that the overall true prediction rate of the integrated models is enhanced, and integration by Bayes' theorem may be a potential approach in combining multiple probabilistic prediction models.

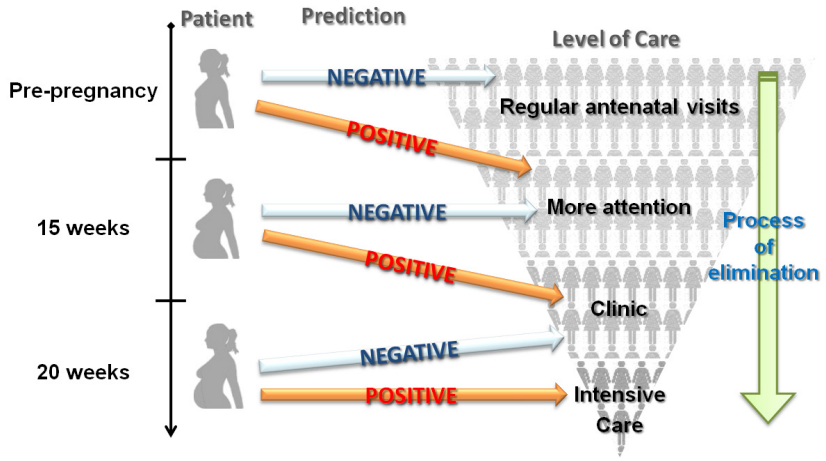

Figure 3. Process of elimination using integrated model.

A major advantage of the integrated model is that risk estimate or prediction can be obtained throughout pregnancy. This will allow constant monitoring and update of predicted risk for individuals when new predictors are available or when conditions change, and hence, the level of care may be tailored for individual women (Figure 3).

By obtaining risk estimates at each stage, the tiered prediction system can be used as a process of elimination for patients with PE. As the initial 15 week model has a high sensitivity, women with a risk of PE are likely to be identified at this stage, and with the integrated odds at 15 weeks, patients identified at risk may receive more monitoring for symptoms or intervention for modifiable risk factors. By 20 weeks, an odds of PE integrated with pre-pregnancy odds and test results from current and previous tests can be obtained, and patients identified at risk may benefit from increased levels of care.

However, a major limitation of this method is that prediction is affected by the pre-test odds and the accuracy of individual prediction models developed. The accuracy and predictive value of the whole tiered prediction system will improve if individual models are predictive. Nevertheless, this method may still be used to obtain probability estimates for tiered prediction systems.

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