Prediction of Early-Onset Preeclampsia Using Uterine Artery Doppler

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Abstract

Aim: To perform a systematic review of screening for early-onset preeclampsia (EO-PE) by uterine artery Doppler (UAD) alone or combination use of UAD and other risk factors.

Methods: We searched for eligible articles in PubMed from 2000–2012, and previously published review articles. The positive likelihood ratio (LR+) ≥10 was considered clinically useful for screening.

Results: Forty articles with sensitivity and a false-positive rate (FPR) were used for calculating LR+ and post-test probability for predicting EO-PE. In unselected or low-risk women, the average LR+ at the cut-off level of 5% FPR, using UAD alone in the 1st and 2nd trimesters, and the combination use of UAD in the 1st and 2nd trimesters, was 11.2, 11.0, 14.3, and 15.9, respectively. In three studies of high-risk women, the combination of UAD and other risk factors in the 2nd trimester yielded a post-test probability of >0.20.

Conclusion: The prediction of EO-PE using UAD indices at a cut-off level of 5% FPR in unselected or low-risk women appears to be clinically useful. In addition, the prediction of EO-PE using the combination of UAD and other risk factors in the 2nd trimester in high-risk women is promising.

INTRODUCTION

Early-onset preeclampsia (EO-PE) occurs in one-fourth to one-third of all PE [1,2], and is related to serious morbidity and increased mortality of newborn infants due to very preterm birth, severe fetal growth restriction (FGR) and intrauterine fetal distress [3-5]. Papageorghiou et al. [6], for the first time, pointed out that the sensitivity (SE) of the uterine artery mean pulsatility index (mPI) in the prediction of PE, for a given false-positive rate (FPR), increases with the severity of the disease as defined by earlier gestational age at delivery. Subsequently, studies for predicting EO-PE using uterine artery Doppler (UAD) in the 1st and 2nd trimesters have accumulated.

Cnossen et al. [7] systematically reviewed the use of UAD to predict PE in 2008, and summarized the screening properties of various Doppler indices in the 1st and 2nd trimesters; however, UAD alone in the 1st and 2nd trimesters for predicting all PE in patients at low-risk or unspecified risk did not show a positive likelihood ratio (LR+) of ≥10, which has been thought to be clinically useful as a predictive marker [8,9]. To improve screening performance, the combination of UAD and other risk factors has been continued using trial and error [10]. To the best of our knowledge, the first attempt to combine UAD with maternal factors for predicting EO-PE was performed by Yu et al. [11] in 2005. Subsequently, studies for predicting EO-PE with the combination use of UAD and other risk factors have been accumulated.

In this systematic review, we attempted to summarize the prediction of EO-PE using UAD alone and the combination use of UAD and other risk factors. We calculated LR+ and negative likelihood ratios (LR−) using a given SE and FPR, and also calculated post-test probability using a given pre-test probability (incidence rate of EO-PE) and LR+.

METHODS

We attempted to collect articles in two ways: by searching for articles using key words in PubMed to find relatively recent articles from 2000 to 2012, and by checking references in previously published systematic reviews for the prediction of PE using UAD. We searched for articles in PubMed using the following key words: (“uterine artery” OR “uterine arteries” OR...
**Utroperacental artery** OR “uteropercental arteries” OR Doppler OR ultrasound OR ultrasonography OR “resistance index” OR “pulsatility index” OR notch OR notches) AND (preeclampsia OR “pregnancy induced hypertension” OR “hypertension in pregnancy” OR “gestational hypertension” OR “EPH gestosis” OR “toxemia of pregnancy” OR eclampsia) AND (predict* OR predicting OR prediction OR ((cohort OR prospective OR retrospective OR “nested case-control”) AND study) OR “risk factor” OR “meta-analysis”OR “systemic review” OR combination OR multivariate OR “logistic regression” OR threshold) NOT (2013 [dp] OR 2014 [dp]). A). read titles and abstracts to judge their eligibility. A total of 117 possible articles on the prediction of PE using UAD were roughly selected from 705 articles extracted by this simple search (Figure 1). Next, another 31 eligible articles were found in the references previously published systematic reviews on the prediction of PE using UAD [7,10,12-14], resulting in 148 possible articles on the prediction of PE using UAD. Finally, we attempted to extract relevant articles on the prediction of EO-PE or preterm PE using UAD by filtering them using the following exclusion criteria: i) very small cohort (<200) or outcome (<10) (n = 22); ii) outcome reported pregnancy-induced hypertension, gestational hypertension or mixture of hypertensive disorders and/or fetal growth restriction (n = 3); iii) insufficient report of screening performance (n = 6); iv) no report of EO-PE or preterm PE (n = 56); and v) other reasons such as a very low incidence of abnormal UAD, only twins, very late recruitment of subjects (>30 weeks of gestation), difficulty of obtaining PDF files, writing in a language other than English, duplicated publication using the same cohort, etc. (n = 14). However, we collected a series of studies by the same authors if different combinations of UAD and other risk factors for predicting PE were used in these studies. Finally, 47 articles with outcomes of EO-PE or preterm PE were selected for the current analyses [11,15-60].

In the 47 articles, 43 articles had outcomes of EO-PE, which were roughly divided into two categories: the first category is the definition of EO-PE according to the delivery period after the onset of PE, and the second category is the definition of EO-PE according to the onset of PE. Four kinds of EO-PE were defined by the time of delivery: i) EO-PE with delivery at <32 weeks of gestation (n = 3), ii) EO-PE with delivery at <34 weeks of gestation (n = 29), iii) EO-PE with delivery at <35 weeks of gestation (n = 3), and iv) EO-PE with delivery at <36 weeks of gestation (n = 2). Three kinds of EO-PE were defined by the onset of PE: i) EO-PE with onset at <32 weeks of gestation (n = 2), ii) EO-PE with onset at <34 weeks of gestation (n = 4), and iii) EO-PE with onset at <35 weeks of gestation (n = 1). In (Table 1 (included as supplementary files), we indicated which definition of EO-PE was used in each article.

The 47 articles were assembled by the period of examination (1st trimester, 2nd trimester, both 1st and 2nd trimesters, 1st–2nd trimesters) and risk of PE in subjects (unselected or low-risk women, high-risk women): i) 1st trimester, unselected or low-risk (n = 22), ii) 1st trimester, high-risk (n = 2), iii) 1st and 2nd trimester, unselected or low-risk (n = 3), iv) 1st and 2nd trimester, high-risk (n = 1), v) 1st–2nd trimester, unselected or low-risk (n = 1), vi) 2nd trimester, unselected or low-risk (n = 14), and vii) 2nd trimester, high-risk (n = 4). Next, the values of SE and FPR were further arranged in the articles according to the 2 categories: i) individual or combination use of UAD, ii) outcomes (all PE, preterm PE, late PE or early PE). When several UAD indices were used in an article, we listed them all. When several pairs of SE and FPR per prediction were described, we chose both SE at a cut-off level of FPR of <10 (mainly around 5%) and SE at a cut-off level of FPR of ≥10 (mainly approximately 10%). When various combinations were described in an article, we selected one or two combinations showing the highest SE and/or highest LR+.

We plotted SE and FPR on receiver-operating characteristics (ROC) curves, while dividing data into 4 categories: A) UAD alone, 1st trimester, B) UAD alone, 2nd trimester, C) combination use of UAD and other risk factors, 1st trimester, and D) combination use of UAD and other risk factors, 2nd trimester (Figure 2). If two pairs of SE and FPR per prediction were reported, we plotted them simultaneously. When there were two or more SE at an FPR<0.10 on ROC graph, we attempted to construct a regression line of SE on FPR (between 0-10), while hypothesizing that the SE should have been 0% when the FPR was 0% in each study; and when there were two or more SE at an FPR ≥0.10 on ROC graph, we also attempted to construct a regression line of SE on FPR (between 10-100), while hypothesizing that the SE should have been 100% when the FPR was 100% in each study.

We constructed graphs showing the change from the pre-test probability to post-test probability according to the LR+; while dividing data into 8 categories: A) UAD alone, 1st trimester, unselected or low-risk women, B) UAD alone, 1st trimester, high-risk women, C) UAD alone, 2nd trimester, unselected or...
Ohkuchi et al. (2013)
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Figure 2 Receiver operating characteristics curves showing a false-positive rare (FPR) and sensitivity (SE) to predict early-onset PE (EO-PE), by uterine artery Doppler (UAD) alone in the 1st trimester (A), UAD alone in the 2nd trimester (B), the combination use of UAD and other risk factors in the 1st trimester (C), and the combination use of UAD and other risk factors in the 2nd trimester (D). Closed circles (●) indicate unselected or low-risk women, and closed triangles (▲) indicate high-risk women. When the FPR was <10, the regression line between FPR and SE including 0% FPR and 0% SE was plotted; and when the FPR was ≥10, the regression line between FPR and SE including 100% FPR and 100% SE was plotted.

In the current review, LR+ ≥10 was considered clinically useful for screening [8,9].

RESULTS

We included 47 articles in our review (Figure 1, Table 1 (included as supplementary files)); however, outcomes in 4 articles were only PE with preterm delivery (preterm PE) and three articles reported only area under the ROC curves (AUC); therefore, the remaining 40 articles were used for the following assessments (Table 1 (included as supplementary files)). As for assessments of SE and FPR for predicting EO-PE, 15, 13, 11 and 5 articles were included in group A (individual, 1st trimester), B (individual, 2nd trimester), C (comb., 1st trimester) and D (comb., 2nd trimester) in (Figure 2), respectively. As for assessments of LR+, pre-test probability and post-test probability for predicting EO-PE, 10, 2, 9, 3, 15, 2, 4 and 2 articles were used in group A (individual, 1st trimester, low-risk), B (individual, 1st trimester, low-risk), C (individual, 2nd trimester, low-risk), D (individual, 2nd trimester, high-risk), E (comb., 1st trimester, low-risk), F (comb., 1st trimester, high-risk), G (comb., 2nd trimester, low-risk) and H (comb., 2nd trimester, high-risk) in (Figure 3).

FPR and SE for predicting EO-PE in unselected or low-risk women

We assessed LR+ for predicting EO-PE in ROC curves (Figure 2). For UAD alone in the 1st trimester in unselected or low-risk women (Figure 2A), the regression line of SE on FPR in 10 pairs when the FPR was <10 was as follows:

\[ Y = 10.77X + 2.33 \quad \text{(where } Y \text{ was SE, and } X \text{ was FPR, } R^2 = 0.77) \]

Thus, when FPR is 5%, SE is 56.2%, resulting in LR+ of 11.2. The regression line in 8 pairs when the FPR was ≥10 was as follows:

\[ Y = 0.384X + 62.04 \quad \text{(where } Y \text{ was SE, and } X \text{ was FPR, } R^2 = 0.79) \]

Thus, when FPR is 10%, SE is 65.2%, resulting in LR+ of 6.6.

For UAD alone in the 2nd trimester in unselected or low-risk women (Figure 2B), the regression line in 6 pairs when the FPR was <10 was as follows:

\[ Y = 9.28X + 2.33 \quad \text{(where } Y \text{ was SE, and } X \text{ was FPR, } R^2 = 0.73) \]

Thus, when FPR is 5%, SE is 55.0%, resulting in LR+ of 11.0. The regression line in 5 pairs when the FPR was ≥10 was as follows:

\[ Y = 0.267X + 73.08 \quad \text{(where } Y \text{ was SE, and } X \text{ was FPR, } R^2 = 0.54) \]
Figure 3 The relationship between the positive likelihood ratio (LR+) and the change from pre-test probability to post-test probability to predict EO-PE, for UAD alone in the 1st trimester in unselected or low-risk women (A), UAD alone in the 1st trimester in high-risk women (B), UAD alone in the 2nd trimester in unselected or low-risk women (C), UAD alone in the 2nd trimester in high-risk women (D), the combination use of UAD and other risk factors in the 1st trimester in unselected or low-risk women (E), the combination use of UAD and other risk factors in the 1st trimester in high-risk women (F), the combination use of UAD and other risk factors in the 2nd trimester in unselected or low-risk women (G), and the combination use of UAD and other risk factors in the 2nd trimester in high-risk women. The post-test probability was calculated using the pre-test probability and the LR+. The pre-test and post-test probabilities are connected by a thin arrow.
Thus, when FPR is 10%, SE is 75.7%, resulting in LR+ of 7.6.

With the combination use of UAD and other risk factors in the 1st trimester in unselected or low-risk women (Figure 2C), the regression line in 8 pairs when the FPR was <10 was as follows:

\[ Y = 13.62X + 3.18 \text{ (where } Y \text{ was SE, and } X \text{ was FPR, } R^2 = 0.91) \]

Thus, when FPR is 5%, SE is 71.3%, resulting in LR+ of 14.3. The regression line in 9 pairs when the FPR was ≥10 was as follows:

\[ Y = 0.130X + 87.03 \text{ (} R^2 = 0.41 \text{)} \]

Thus, when FPR is 10%, SE is 90.0%, resulting in LR+ of 9.0.

With the combination use of UAD and other risk factors in the 2nd trimester in unselected or low-risk women (Figure 2D), the regression line in 2 pairs when the FPR was <10 was as follows:

\[ Y = 15.61X + 1.22 \text{ (} R^2 = 0.98 \text{)} \]

Thus, when FPR is 5%, SE is 79.3%, resulting in LR+ of 15.9. The regression line in 3 pairs when the FPR was ≥10 was as follows:

\[ Y = 0.123X + 87.51 \text{ (} R^2 = 0.46 \text{)} \]

Thus, when FPR is 10%, SE is 88.7%, resulting in LR+ of 8.9.

Comparing LR+ using UAD alone between the 1st and 2nd trimesters, LR+ at the level of 5% FPR was almost identical (11.2 and 11.0, respectively). Comparing LR+ with the combination use of UAD and other risk factors between the 1st and 2nd trimesters, LR+ at the level of 5% FPR was also almost identical (14.3 and 15.9, respectively). Comparing LR+ between UAD alone and the combination use of UAD, LR+ was higher for the prediction of EO-PE using the combination use of UAD than for that using UAD alone.

**LR+ and the change from pre-test probability to post-test probability for predicting EO-PE**

We firstly assessed the change from pre-test probability to post-test probability according to the LR+ for predicting EO-PE using UAD alone (Figure 3A-D). For unselected or low-risk women with UAD alone in the 1st trimester (Figure 3A), although two studies showed post-test probability of >0.2 [33,44], the post-test probabilities in the other 9 studies were <0.1. For high-risk women with UAD alone in the 1st trimester (Figure 3B), the post-test probabilities in two studies were between 0.1 and 0.2, suggesting that screening for EO-PE in the 1st trimester in high-risk women might be better than that in unselected or low-risk women. For unselected or low-risk women with UAD alone in the 2nd trimester (Figure 3C), all the post-test probabilities in 8 studies except for that in one study [56] were <0.1. For high-risk women with UAD alone in the 2nd trimester (Figure 3D), the post-test probabilities in 3 studies were all high: 0.194 [58], 0.216 [59] and 0.237 [43], suggesting that the prediction of EO-PE by UAD alone in the 2nd trimester in high-risk women is promising.

Next, we assessed the change from pre-test probability to post-test probability according to the LR+ for predicting EO-PE using the combination of UAD and other risk factors (Figure 3E-H). For unselected or low-risk women with the combination use of UAD and other risk factors in the 1st trimester (Figure 3E), the post-test probabilities in 14 studies except for those in two studies [24,41] were all <0.1. For high-risk women with the combination of UAD and other risk factors in the 1st trimester (Figure 3F), the post-test probabilities in 2 studies were >0.1: 0.121 [43] and 0.405 [38]. For unselected or low-risk women with the combination use of UAD and other risk factors in the 2nd trimester (Figure 3G), the post-test probabilities in all 4 studies were <0.1. For high-risk women with the combination use of UAD and other risk factors in the 2nd trimester (Figure 3H), the post-test probabilities in 2 studies were all high: 0.234 [59] and 0.553 [60], suggesting that the combination use of UAD and other risk factors, such as soluble endoglin (sEng), or soluble fms-like tyrosine kinase 1 (sFlt-1), in the second trimester in high-risk women selected by abnormal UAD is promising for predicting EO-PE.

In view of the predictive value for EO-PE, high-risk women showed better post-test probabilities than unselected or low-risk women. Post-test probabilities in two studies by UAD alone in the 1st trimester in high-risk women were >0.10, while those in the majority of studies by UAD alone in the 1st trimester in unselected or low-risk women were <0.10; post-test probabilities in three studies by UAD alone in the 2nd trimester in high-risk women were >0.18, while those in the majority of studies by UAD alone in the 2nd trimester in unselected or low-risk women were <0.10; post-test probabilities in two studies by combination use of UAD and other risk factors in the 1st trimester in high-risk women were >0.10, while those in the majority of studies by combination use of UAD and other risk factors in the 1st trimester in unselected or low-risk women were <0.10; and post-test probabilities in two studies by combination use of UAD and other risk factors in the 2nd trimester in high-risk women were >0.20, while those in 4 studies by a combination of UAD and other risk factors in the 2nd trimester in unselected or low-risk women were <0.10.

**DISCUSSION**

In this systematic review, 40 articles with SE and FPR data were finally used for calculating LR+ and post-test probability for predicting EO-PE. We made two important findings. First, in unselected or low-risk women, the average LR+ using UAD alone in the 1st and 2nd trimesters, and the combination use of UAD in the 1st and 2nd trimesters was 11.2, 11.0, 14.3, and 15.9, respectively. Thus, the prediction of EO-PE using UAD indices at a cut-off level of 5% FPR in unselected or low-risk women appears to be clinically useful. Second, in view of the predictive value for EO-PE, high-risk women showed better post-test probabilities than unselected or low-risk women. In particular, the combination use of UAD and other risk factors in the 2nd trimester in high-risk women yielded post-test probabilities of >0.20 in three studies. Thus, the prediction of EO-PE using the combination of UAD and other risk factors in the 2nd trimester in high-risk women is promising.

The prediction of EO-PE with individual/combination use of UAD indices at a cut-off level of 5% FPR in the 1st and 2nd trimesters in unselected or low-risk women appears to be clinically useful, because LR+ was >10. In particular, in 8 studies using the combination of UAD and other risk factors in the 1st/2nd trimesters for predicting EO-PE in unselected or low-risk women, the SE was ≥80% [20,22,24,27,30,38,41,52]. Pedrosa et al. [10]
systemically reviewed the combination use of UAD and other risk factors to predict PE in 2011, and suggested that in the 1st trimester, accurate screening for EO-PE probably requires the combination of several markers; however, it was also suggested that in the 2nd trimester, screening for early PE probably requires the combination of fewer markers. In our review, high LR+ of ≥10 in screening was achieved by the combination of UAD with one other risk factor [11,53] or two other risk factors [41,52] in the 1st trimester. High LR+ of ≥10 was also achieved by the combination of UAD and one other risk factor [26,28,36] or two other risk factors [16,18,19,25,29] in the 2nd trimester. Therefore, the combination of UAD and one or two risk factors might be sufficient to yield LR+ of ≥10 for predicting EO-PE in the 1st and 2nd trimesters.

In view of the predictive value for EO-PE, high-risk women showed better post-test probabilities than unselected or low-risk women. In particular, the combination of UAD and other risk factors in the 2nd trimester yielded post-test probabilities of >0.20 in three studies. To the best of our knowledge, the post-test probability for predicting PE using UAD has not been evaluated in the systematic review articles [7,10,12-14]. The knowledge of post-test probability is more useful for evaluating the risk of EO-PE rather than LR+, because the incidence rate of EO-PE is often very low. If the post-test probability is ≥0.20, obstetric professionals will judge that women with such a high post-test probability of EO-PE should be closely monitored for the occurrence of PE by increasing maternal checkups or by using home blood pressure monitoring [9]. If the incidence rate of EO-PE in some populations is only 0.2%, the post-test probability even with a high LR+ of 10 is only 2%; thus, obstetric professionals will not pay much attention to such a moderate risk. Thus, post-test probability of ≥0.20 for predicting EO-PE by the combination of UAD and other risk factors in the 2nd trimester in high-risk women was very promising.

In conclusion, prediction of EO-PE using UAD was very promising. In particular, in high-risk women in the 2nd trimester, the post-test probability using the combination of UAD and other risk factors was ≥0.20.

CONTRIBUTORS
A.O. systemically searched for articles, and selected eligible articles, and wrote the manuscript. K.T., C.H., R.J., S.M. and M.S. critically reviewed the manuscript.

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