OJOG

The diagnostic accuracy of the usage of the Fetal Medicine Foundation's (FMF) on-line risk calculator with first-trimester ultrasound for screening for pre-eclampsia in high-risk pregnant Brazilian population

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ABSTRACT

To evaluate the sensitivity and specificity of the usage of the FMF On-Line Risk Calculator with first-trimester ultrasound, in screening assessment for pre-eclampsia (PE), without serum markers. To define the best risk cut-off values for early, intermediate and late pre-eclampsia. Diagnostic accuracy study of pregnant women who had first-trimester ultrasounds between 11 and 13 weeks. The index test was the first-trimester ultrasound scan plus the FMF On-Line Risk Calculator to assess the risk for PE. The reference standard was the confirmation of actual development of early, intermediate or late PE. For calculations of sensitivity and specificity to determine the best cut-off values for early, intermediate and late PE, all the information were processed into ROC curves. The assessment of pre-eclampsia risk in the first trimester using an ultrasound plus the FMF On-Line Risk Calculator demonstrated a significant ($p < 0.05$) area under the ROC curve for early, intermediate and late pre-eclampsia. The best risk cut-off values were defined as 2.1% for early, 2.5% for intermediate and 3.5% for late pre-eclampsia. The first trimester US plus the FMF On-Line Risk Calculator tool was useful and applicable when assessing the risk for pre-eclampsia in a specific pregnant Brazilian population.

Keywords: Accuracy; Sensitivity; Specificity;
Pre-Eclampsia; First Trimester; Risk

1. INTRODUCTION

Pre-Eclampsia (PE) is a multisystem disorder exclusive to pregnancy characterized by hypertension and protein-uria that develops after 20 weeks of gestation [1-4]. PE affects 2% - 10% of all pregnancies and is an important cause of morbidity and maternal and perinatal mortality [1-3,5,6]. Early screening of women with a potential risk of developing pre-eclampsia is justified because it allows the possibility of early intensive maternal and fetal monitoring, thereby avoiding adverse outcomes. Furthermore, there is evidence that prophylactic usage of aspirin may reduce the incidence of PE in 50% of women when the treatment is started before 16 weeks [7,8].

Advances in fetal medicine and ultrasound imaging techniques have allowed extensive research on the role of first-trimester screening for several maternal and fetal conditions [4,9-14]. This new assessment of risk factors using fetal, maternal and biochemical markers suggests new approaches for prenatal care that are more focused on the first rather than third trimester [14,15].

Many current studies have demonstrated the possibility of pre-eclampsia screening between 11 and 13 weeks with promising results [4,13,16-22]. This screening focuses on the multivariate analysis of risk associating maternal data, clinical, obstetric, ultrasound and serum marker measurements [19,20].

It was recently demonstrated that first-trimester ultrasound scanning can predict early PE by identifying women who will require delivery before 34 weeks' gestation, intermediate PE by identifying women requiring delivery at 34 - 37 weeks and late PE by identifying women requiring delivery after 37 weeks. This study concluded that effective prediction of PE can be achieved at 11 - 13 weeks' gestation [4]. Based on these results, the Fetal Medicine Foundation (FMF) provides an on-line risk calculator for the assessment of risk for early, inter-mediate and late PE using information from the ultrasound scan as well as clinical and serum biochemical markers.

Considering the paucity of studies using ultrasound

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screening to assess the risk of pre-eclampsia in pregnant women in Brazil, the objective of this study was to evaluate the sensitivity and specificity of the usage of the FMF On-Line Risk Calculator and first trimester ultrasound scan in assessment of risk for pre-eclampsia, but not serum markers. The actual development of pre-eclampsia was the reference standard. This study also aimed to define the best risk cut-off values for early, intermediate and late pre-eclampsia, using the FMF on-line risk calculator.

2. METHODS

We followed the STARD (Standards for Reporting of Diagnostic Accuracy) recommendations for reporting the accuracy of a diagnostic procedure [23]. This involved completing a checklist of items to ensure that all pertinent information was present in the text, thus allowing the reader to detect the potential for bias and to judge the applicability of the results.

This was a study of diagnostic accuracy among pregnant women who had first-trimester ultrasound between 11 and 13 weeks at the High Risk Pregnancy Service, University Hospital (UH), School of Medicine (FAMED), Federal University of Mato Grosso do Sul (UFMS) between October 2010 and May 2011. All pregnant women who had first-trimester ultrasound examinations during the study period and whose obstetric and perinatal clinical information were available in the medical records were included. We excluded patients who were under 18 years of age or who had indigenous heritage and twin pregnancies. All patients included in study signed an informed consent. The study and its informed consent were approved by the Ethics Committee on Human Research, Protocol 1859, on September 30, 2010.

The index test considered in this series was the first-trimester ultrasound scan plus the FMF On-Line Risk Calculator (https://courses.fetalmedicine.com/calculator/pe?locale=en). Together, they were used to assess the risk for early, intermediate and late PE. The theoretical 3.0% cut-off risk for pre-eclampsia was defined for the index test (the ultrasound scan + the FMF On-Line Risk Calculator), based upon previous pre-eclampsia prevalence studies in different populations [1-3], before confirmation using the reference standard.

The reference standard was the confirmation of actual development of early, intermediate or late PE after patient delivery. This study was planned after the patients had performed the index test and after they had delivered; therefore, this was a retrospective analysis of diagnostic accuracy.

For the confirmation of maternal pre-eclampsia development (reference standard), we considered women who presented with the diagnostic criteria of two or more blood pressure measurements exceeding 140/100 mmHg and proteinuria exceeding 300 mg/24 h [2,3], as recorded in the medical record during prenatal care. If PE developed and required delivery before 34 weeks, this was defined as early PE. If PE developed and required termination of pregnancy between 34 - 37 weeks, we considered this intermediate PE. Finally, patients that developed late PE were those whose diagnosis required delivery after 37 weeks [4].

To calculate the risk of pre-eclampsia, we used the FMF On-Line Risk Calculator for Pre-eclampsia, available on the FMF web site. We also considered maternal clinical variables (e.g., age, ethnicity, weight, height, body mass index, mode of conception, smoking history, illicit drug use, history of hypertension, history of diabetes and history of systemic lupus erythematous), obstetrical variables (e.g., parity, history of PE in the woman's mother, history of previous PE, history of miscarriages and stillbirths), ultrasound data (e.g., fetal crown-rump length and pulsatility index of uterine arteries) and blood pressure (BP) measured at the time of examination [13, 17-22]. No maternal serum biochemical markers were used in the risk assessment for pre-eclampsia; only the clinical information, obstetric ultrasound and BP measurements were used. Blood pressure was measured twice in each arm, and the mean BP was calculated according to the criteria established for the implementation of this examination by FMF [21,22]. All the ultrasound scanning data were collected by FMF-certified sonographers. The Ultrasound used to acquire the images were Nemio 17, TOSHIBA, with preset of first trimester scan default.

Clinical and obstetrical information, as well as ultrasound data and blood pressure values, were included in the respective fields requested on the online risk calculator homepage from the FMF website. The risks were registered on the patient's record in the same format in which they were presented as percentages values for the following: risk for early, intermediate and late pre-eclampsia. The assessment risks from the index test were acquired blindly, without knowledge of the patient's actual development of pre-eclampsia; the latter information was only available after delivery. Because each patient could have more than one risk factor according to the screening test, indicating their elevated risk for early, intermediate or late PE, they were grouped by the earliest possibility of developing PE. For example, if a patient was assessed to have a risk higher than 3.0% for early, intermediate and late PE, this patient was considered only in the early PE group.

The design of the study is outlined in a flowchart (**Figure 1**). For calculations of sensitivity and specificity and to determine the best cut-off values for early, inter-
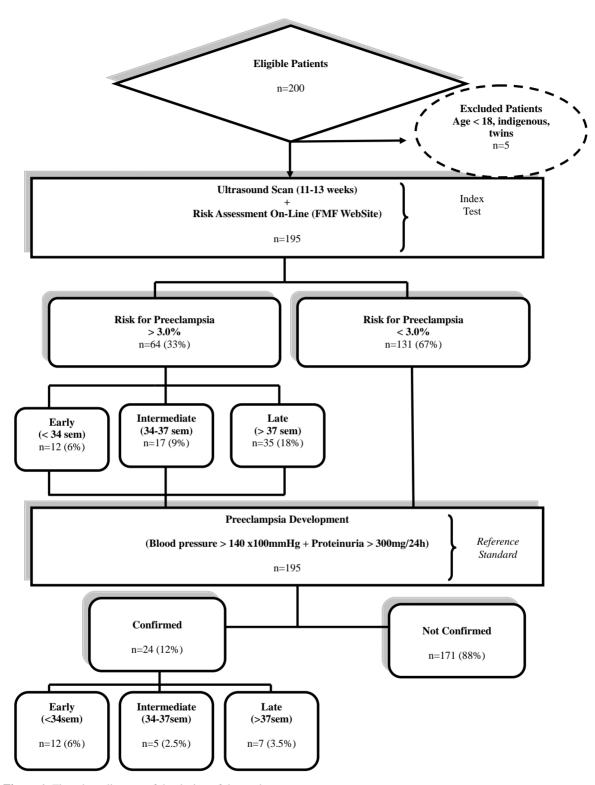
Figure 1. Flowchart diagram of the design of the study.

mediate and late PE, all the information was processed into ROC curves. To create the ROC curves, the risk values from patients with unconfirmed PE (n = 171) were compared to the risk values from patients with con-

firmed early (n = 12), intermediate (n = 5) and late (n = 7) PE. For statistical calculations, we used the area under the ROC curve and considered a significant p value to be less than 0.05. The calculated Odds Ratio (OR) and con-

fidence intervals (CI) greater than 95% were also presented. The calculations were processed with Prism 5 software for Windows (GraphPad Software Inc., 1992-2007©).

3. RESULTS

Initially, the eligible patients included 200 pregnant women who underwent ultrasound screening in their first trimester from October 2010 to May 2011. Five patients were excluded because they had not met the inclusion criteria. The final sample studied (n = 195) corresponded to 97.5% of pregnant women who submitted to ultrasound screening during the study period (**Figure 1**).

The patients' mean age was 32 ± 4.5 years, and most of the subjects were Caucasian (62.5%). The average weight of the pregnant women studied was 64.7 ± 12.2 kg, and the mean height was 163 ± 0.6 cm. The mean parity was 1.69 ± 0.9 children. The mean gestational age at examination was 12 ± 0.6 weeks, and the mean fetal crown-rump length (CRL) was 60.2 ± 9.5 mm. The mean gestational age at delivery was 37.4 ± 2.4 weeks, with newborns having a mean weight of 3046 ± 515 g and a mean height of 47.7 ± 3.17 cm.

Of the 195 pregnant women screened for PE by the index test (first-trimester US + FMF On-Line Risk Calculator, considering the theoretical cut-off risk of 3.0%, 131 (67%) were selected not to developed PE, considering their risk lower than 3.0%. Alternatively, 64 (33%) were identified to developed PE when their risk was greater than or equal to 3.0%. Among these screened patients with a positive risk for PE (n = 64), 12 (6%) were high-risk for early PE, 17 (9%) were high-risk for intermediate PE, and 35 (18%) were high-risk for late PE.

Pre-eclampsia was really confirmed in 12% of the study population (24/195): 6% (12/195) with early pre-eclampsia, 2.5% (5/195) with intermediate pre-eclampsia and 3.5% (7/195) with late pre-eclampsia. These data are presented in a flowchart (**Figure 1**).

The assessment of risk for pre-eclampsia in the first trimester, with an ultrasound scan plus the FMF On-Line Risk Calculator, demonstrated a significant (p < 0.05) area under the ROC curve for early (area = 0.84 95% IC: 0.67 - 1.0), intermediate (area = 0.89 95% IC: 0.72 - 1.0) and late (area = 0.88 95% IC: 0.73 - 1.0) pre-eclampsia, as presented in **Figures 2-4** and in **Table 1**.

For women for whom PE was not confirmed, the median and 25th - 75th percentile risks are as follows: early PE, 0.04% (0.01% - 0.14%); intermediate PE, 0.49% (0.1% - 1.0%) and late PE, 1.0% (0.54% - 3.0%). For patients for whom PE was confirmed, the median and 25th - 75th percentile risks are as follows: early PE, 5.0% (0.95% - 22.0%); intermediate PE, 12.0% (2.2% - 16.0%) and late PE, 12.0% (4.0% - 25.0%). These data are presented in **Table 1**.

After the statistical calculations of specificity and sensitivity, the best risk cut-off risk values were defined as greater than 2.1% for early, greater than 2.5% for intermediate and greater than 3.5% for late pre-eclampsia. The sensitivity, specificity and likelihood ratio for each cut-off value are presented in **Table 1**.
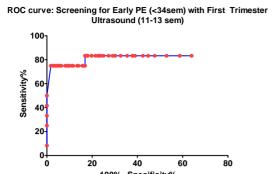
4. DISCUSSION

The assessment of pre-eclampsia risk using maternal-fetal parameters is a novel topic in prenatal diagnosis. Most of the studies concerning this subject are dated after 2009 [4,18-20,24]. Maternal characteristics associated with biochemical and biophysical tests at 11 - 13 weeks' gestation can identify 90%, 80% and 60% of pregnancies that will result in early, intermediate and late PE, respectively [4]. Based on these results, the Fetal Medicine Foundation website gives free access to research materials and online tools that facilitate the assessment of the PE risk factors [4]. The question raised was if this assessment of calculated risks could be useful and applicable in different populations of pregnant women.

Our results demonstrate that the reference test studied (assessment of risk for PE with a first-trimester ultrasound + the FMF On-Line Risk Calculator) could accurately screen for early (cut-off risk value: >2.1%, 75%
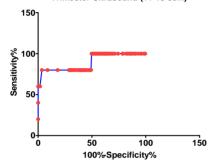
Table 1. The median risk values, best risk cut-off values, sensitivity, specificity, likelihood ratio and area under the ROC curve for the assessment of risk for pre-eclampsia with a first-trimester ultrasound in pregnant women.

Assessment of risk for pre-eclampsia in first-trimester (ultrasound + FMF on-line risk calculator)	Median risk values (25th - 75th percentile) of patients without PE (%)	Median risk values (P25 - P75) of confirmed PE patients (%)	Best risk cut-off value (%)	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio	Area under ROC curve (95% CI)	p value
Early **(<34 weeks)**	0.04 (0.01 - 0.14)	5.0 (0.95 - 22.0)	>2.1	75.0% (42.8 - 94.5)	98.2% (94.9 - 99.6)	43.0	0.84 (0.67 - 1.0)	<0.0001
Intermediate **(34 - 37 weeks)**	0.49 (0.1 - 1.0)	12.0 (2.2 - 16.0)	>2.5	80.0% (28.3 - 99.4)	91.2% (85.9 - 95.0)	9.12	0.89 (0.72 - 1.0)	0.002
Late **(>37 weeks)**	1.0 (0.54 - 3.0)	12.0 (4.0 - 25.0)	>3.5	85.7% (42.1 - 99.6)	82.4% (75.9 - 87.8)	4.89	0.88 (0.73 - 1.0)	0.0005

ROC curve: Screening for Early PE (<34sem) with First Trimester Ultrasound (11-13 sem)
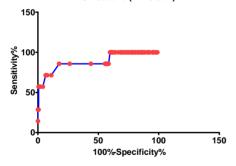

Figure 2. ROC curve: screening for early PE (<34 weeks) with first-trimester ultrasound (11 - 13 weeks).

ROC curve: Screening for Intermediate PE (34-37sem) with First Trimester Ultrasound (11-13 sem)

Figure 3. ROC curve: screening for intermediate early PE (34 - 37 weeks) with first-trimester ultrasound (11 - 13 weeks).

ROC curve: Screening for Late PE (>37sem) with First Trimester Ultrasound (11-13 sem)

Figure 4. ROC curve: screening for late PE (>37 weeks) with first-trimester ultrasound (11 - 13 weeks).

sensitivity, 98.2% specificity); intermediate (cut-off risk value: >2.5%, 80.0% sensitivity, 91.2% specificity) and late (cut-off risk value: >3.5%, 85.7% sensitivity, 82.4% specificity) PE. The advantage of this method is that it is low-cost and applicable to daily clinical practice. The free provision of FMF On-Line Risk Calculator and the ease of acquiring an ultrasound scan and maternal clinical data give this method good reproducibility. Moreover, because maternal biochemical serum markers were not used, this method is applicable in developing countries like Brazil.

Our results also demonstrate a high frequency (12%; 24/195) of confirmed pre-eclampsia diagnoses among the pregnant patients studied: 6.0% (12/195) early PE, 2.5% (5/195) intermediate PE and 3.5% (7/195) late PE. These rates are elevated when compared to other studies. Among the 35,000 singleton pregnancies included in a recent study [4], it was reported the prevalence of early, intermediate and late PE at 0.3%, 0.6% and 1.3%, respectively. In our study, the assessed risk using the first-trimester ultrasound scan plus the FMF On-Line Risk Calculator for patients who did not have confirmed pre-eclampsia showed median risk values of 0.04%, 0.49% and 1.0% for early, intermediate and late PE, respectively. This finding is in agreement with the Akolekar *et al.* 2011 study [4].

The most probable explanation for the high frequency of PE development in our population was that we recruited from a High Risk Pregnancy Referral Center. This supports the accuracy rates of the first-trimester screening for PE demonstrated herein, considering that assessed risk rates for early, intermediate and late PE > 3.0% was calculated for 6% (12/195), 9% (17/195) and 18% (35/195) of patients, respectively, according to the index test before confirmation with the reference standard. After confirmation, the rates of early, intermediate and late pre-eclampsia were 6% (12/195), 2.5% (5/195) and 3.5% (7/195).

The accuracy of the index test presented in this retrospective study was not 100%, as we failed to identify all patients that developed PE [25]. However, retrospective accuracy tests may reflect routine clinical practice better than a prospective study [23,25], as demonstrated in the flowchart (**Figure 1**). We have demonstrated the applicability of this PE screening technique, which relies on first-trimester ultrasound and the FMF On-Line Risk Calculator, but not on maternal serum biochemical markers, for use in daily practice.

Despite the short period of evaluation, our results suggest that the FMF On-Line Risk Calculator tool is useful and applicable for PE risk assessment in a high-risk pregnant Brazilian population. These results, however, demonstrate that new research should be conducted on the early assessment of patient-specific risk factors for pre-eclampsia to prevent complications and improve pregnancy outcomes by shifting prenatal care from a series of routine visits to a more individualized approach [4]. In the case of PE, the assessment of risk by first-trimester ultrasound requires future studies to determine the role of pharmacological intervention, such as starting an aspirin regimen during the first trimester, to decrease subsequent development of the disease [4].

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