Comparison of the diagnostic accuracy of early screening for preeclampsia by NICE guidelines, ACOG guidelines and comprehensive first trimester screening using maternal characteristics, ultrasonographic findings and maternal serum biochemical markers in the prediction of the development of preeclampsia in a tertiary hospital*

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ABSTRACT

Introduction: Preeclampsia remains to be a major cause of both fetal and maternal morbidity and mortality, particularly in severe forms leading to preterm birth. There is a lack of consensus, however, on the preferred screening test for early diagnosis with the aim of reducing the prevalence and morbidity of the disease.

Objective: To compare the performance of the comprehensive first trimester screening using maternal characteristics, ultrasonographic findings and serum biochemical markers, with the NICE and ACOG guidelines in predicting the development of preeclampsia. The study also aims to determine the compliance rate of clinicians in giving aspirin prophylaxis using the different screening tests.

Methodology: This is a retrospective, analytical, cross sectional study of all pregnant patients between 11 to 13 6/7 weeks referred for comprehensive first trimester screening for preeclampsia from January 2014 to January 2018. Maternal factors were assessed to determine the risk of preeclampsia using NICE guidelines, ACOG guidelines and comprehensive first trimester screening. The compliance on aspirin administration for high-risk patients was also determined. The outcome measure was diagnosis of preeclampsia and the detection rate (DR) of the three screening tests were compared.

Results: A total of 202 women were included in the analysis where 24 (11.9%), 11 (5.4%) and 13 (6.4%) developed preeclampsia, early-onset preeclampsia (EO-PE) and late-onset preeclampsia (LO-PE) respectively. The NICE and ACOG guidelines were able to detect preeclampsia with an accuracy of 76.73% (Sn 75%, Sp 77% PPV 30.5%) and 43.07% (Sn 83.3%, Sp 37.6% PPV 15.3%) respectively. The comprehensive first trimester screening was able to detect preeclampsia with an accuracy of 89.60% (Sn 83.3%, Sp 90.5% PPV 54.1%). EO-PE and LO-PE were detected with an accuracy of up to 97.2% using the comprehensive screening (Sn 90.9%, Sp 97.9% PPV 71.4%), compared with the NICE guideline (up to 74.26%, Sn 81.8%, Sp 73.8% PPV 15.3%) and the ACOG guideline (up to 39.6%, Sn 90.9%, Sp 36.6, PPV 7.63%). Compliance with the NICE and ACOG recommendation on aspirin administration was only 42.37% and 33.33%, respectively, and this increased to up to 62% when comprehensive first trimester screening was used.

Conclusion: This study confirmed that the performance of screening for PE, and therefore appropriate selection of the patients that would benefit from prophylactic use of aspirin and closer surveillance, is by far superior if the comprehensive first trimester screening is used than the method advocated by ACOG and NICE.

Keywords: ACOG Guidelines; Early-Onset Preeclampsia; Late-Onset Preeclampsia; NICE Guidelines; Preeclampsia; Preeclampsia screening; PAPP-A; PIGF

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INTRODUCTION

Preeclampsia, defined as a pregnancy-specific syndrome characterized by the onset of hypertension (≥ 140/90) and either proteinuria or end organ dysfunction after the 20th week of gestation in previously normotensive women, remains to be a major cause of perinatal morbidity and mortality for both the mother and the baby.[1-3] The risk for such complications is particularly high when the disease is severe leading to preterm birth at < 37 weeks' gestation which can result in serious long-term medical and developmental problems, with tremendous individual, family and societal cost, hence it remains to be a critical public health issue in this country.

The current approach to screening for preeclampsia (PE) is to identify maternal risk factors based on demographic characteristics and medical history. According to the National Institute for Health and Care Excellence (NICE), in the United Kingdom, women should be considered to be at high risk of developing PE if they have any one high-risk factor (hypertensive disease in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus or autoimmune disease) or any two moderate-risk factors (nulliparity, age ≥ 40 years, body mass index (BMI) ≥ 35 kg/m2, family history of PE or interpregnancy interval > 10 years).[2] In the United States, according to the American College of Obstetricians and Gynecologists (ACOG), women are at high-risk of developing PE if they fulfill any of the following factors: PE in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus, systemic lupus erythematosus or thrombophilia, nulliparity, age > 40 years, BMI ≥ 30 kg/m^2, family history of PE or conception by in-vitro fertilization.[3] The purpose of screening is be able to identify women who can benefit from additional management and allow proper planning, monitoring and antenatal management to prevent hypertensive complications. Recent evidences suggest that the risk of EO-PE can be substantially reduced by the prophylactic use of aspirin as early as 12 weeks age of gestation until the third trimester.[1-5] However, the recommendation of when to prescribe aspirin for prevention of preeclampsia varies. According to NICE, all high-risk pregnancies should be offered low dose aspirin. According to ACOG, use of aspirin should be reserved for women with history of preeclampsia in two or more pregnancies or preeclampsia requiring delivery at less than 34 weeks of gestation. Because historical risk factors only predict about 30-40% of women who will develop preeclampsia[3,5,16], use of laboratory and imaging tests in combination with maternal factors to calculate the risk of developing preeclampsia is an active area of investigation.

The Fetal Medicine Foundation (FMF) developed a first trimester screening utilizing maternal characteristics, uterine artery pulsatility index (UtA PI) and maternal serum biochemical markers such as pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PIGF) to determine pregnant patients at risk of developing PE.[6-7] According to recent studies, this screening method, which is used in women at 11 weeks to 13 weeks and 6 days age of gestation, had the highest detection rate for preeclampsia compared to the methods recommended by ACOG and NICE guidelines.[6,16] In this institution, preeclampsia is the second most common condition among high risk mothers, comprising 16% of all high risk mothers who delivered here in 2017 (Source: 2017 Census). Because of this high prevalence of preeclampsia in our population, this institution adapted the FMF algorithm for the screening of preeclampsia by providing a comprehensive first trimester screening using maternal demographic characteristics, ultrasound findings and serum biochemical markers in order to contribute to the reduction of maternal and perinatal complications. A preliminary study on the first two years of its implementation showed a relatively high prevalence rate of 22.5% of preeclampsia, with a detection rate of 80% for early onset preeclampsia and 62.5% of late onset preeclampisa.[8] It is worthwhile to note that there are differences in the demographic characteristics of the preliminary study of Geronimo et al compared to the findings of O'Gorman et al. Geronimo et al found a higher prevalence rate of preeclampsia, with women at more advanced age and with previous history of hypertension developing preeclampsia more frequently. In comparison, O'Gorman found a 2.7% prevalence of preeclampsia and only about 8% of the study population of 8,792 women were of Southeast Asian origin. Thus, this study sought to determine the best method of screening for preeclampsia for the Filipina women.

The aim of this study is to compare the performance of the comprehensive first trimester screening using maternal characteristics, ultrasonographic findings and maternal serum biochemical markers with the NICE and ACOG recommendations in predicting the development of preeclampsia in a local private tertiary hospital. Specifically, it aims to:

1. To compare the diagnostic performance of NICE guidelines, ACOG guidelines and comprehensive FTS in the prediction of early and late onset preeclampsia in terms of sensitivity, specificity, PPV, NPV, LR+, LR-, overall accuracy
2. To determine the association of selected maternal characteristics, uterine artery pulsatility index, and biochemical markers with the development of preeclampsia
3. To determine the proportion of referring obstetricians who comply with the recommendation of aspirin administration for the prevention of preeclampsia

among women who screened positive for preeclampsia using the different screening guidelines

METHODOLOGY

Population and Sample

This is a retrospective, analytical, cross sectional study of all pregnant patients between 11 to 13 6/7 weeks referred to Women's Health Care Center (WHCC) for combined first trimester screening for preeclampsia in a private tertiary hospital from January 2014 to January 2018. In this institution, combined first trimester screening refers to comprehensive screening for both preeclampsia and aneuploidy. All patients referred during the study period and who subsequently delivered in the same institution were included in the study. Exclusion criteria are those who have multifetal pregnancy, those found to have high risk for aneuploidy based on the first trimester screening, and those who delivered non-institutionally whose data cannot be retrieved in the hospital or their respective attending physician's clinic. Using the specificity of different FTS for predicting pre-eclampsia, a minimum of 213 subjects was required for this study based on a level of significance of 5%, an estimated prevalence of 5.3% of women with preeclampsia, a specificity of UtA-PI in predicting preeclampsia at 84.52%1 with a width of the 95% confidence interval of 0.05 (Table 1).[9-10]

METHODS

Study Setting

The first trimester screening program is offered routinely in the institution to patients regardless of their maternal history. The prevalence of patients who developed preeclampsia among those screened was determined and the risk factors were analyzed in terms of their association with the development of preeclampsia. Each patient's risk for preeclampsia was assessed retrospectively based on ACOG and NICE guidelines. The proportion of referring obstetricians who comply with the recommendation of aspirin administration for the prevention of preeclampsia among women who screened positive for preeclampsia using the different screening guidelines was determined.

Clinical Assessment

All pregnant patients between 11 to 13 6/7 weeks referred to WHCC for first trimester screening were interviewed and assessed by the FMF resident rotator or FMF fellow. Maternal characteristics and medical, obstetric and drug histories were obtained using a specific collection form. Blood pressure (BP) was taken simultaneously on both arms using a calibrated, automated device (Dynamap) while the patient is on a sitting position, and the mean arterial pressure (MAP) was then obtained according to the recommendation for proper BP recording by the FMF.[11] All clinical data were analyzed by the researcher to define the screen-positive patients who are at high risk for developing preeclampsia according to ACOG and NICE guidelines.

Clinical Laboratory And Ultrasound Measurements

All ultrasound measurements were carried out by FMF-certified perinatologists according to standardized protocols.[12-14] Gestational age was determined from the measurement of the fetal crown–rump length. Maternal serum concentrations of PAPP-A, PlGF, and b-HCG were measured using an automated device (DELFIA® Xpress analyzer from PerkinElmer Life and Analytical Sciences, Waltham, USA). Quality control was applied to achieve consistency of measurement of biomarkers throughout the duration of the study. The final risk for each woman was determined and analysed using the risk calculation LifeCycle software from PerkinElmer Life and Analytical Sciences.

Outcome measurement

Data on pregnancy outcome, including medications given antenatally, mode of delivery, and age of gestation upon delivery, were collected from the hospital medical records or the attending physician's records. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine the diagnosis of PE. This was based on the finding of hypertension (systolic BP of ≥ 140 mmHg or diastolic BP of ≥ 90 mmHg on at least two occasions 4 hours apart, developing after 20 weeks' gestation in a previously normotensive women) and at least one of the following: proteinuria (≥ 300 mg/24 h or protein to creatinine ratio ≥30mg/mmol or ≥2+ on dipstick testing), renal insufficiency (serum creatinine > 1.1 mg/dL or two-fold increase in serum creatinine in the absence of underlying renal disease), liver involvement (blood concentration of transaminases to twice the normal level), neurological complications (e.g. cerebral or visual symptoms), thrombocytopenia (platelet count < 100 000/μL), or pulmonary edema.[1-2] Early onset preeclampsia (EO-PE) was defined as preeclampsia at less than 34 weeks of gestation, which may be associated with preterm delivery, intrauterine growth restrictions (IUGR), abnormal uterine and umbilical artery Doppler wave forms and adverse maternal and neonatal outcomes. On the other hand, late onset preeclampsia (LO-PE) was defined as preeclampsia that developed later in pregnancy and necessitated delivery after 34 weeks age of gestation.[15] The detection rate of screening recommended by the NICE and ACOG guidelines in comparison to the detection rate of the comprehensive first trimester screening were assessed.

ANALYSIS

Univariate analysis

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables.

Bivariate analysis

One – way ANOVA, Kruskal – Wallis test and Fisher's exact/Chi square test were used to determine the difference of mean, median and frequency, respectively.

Exact logistic regression

Crude odds ratio and the corresponding 95% confidence interval from exact logistic regression was computed to determine the association between selected maternal characteristics, uterine artery pulsatility index, and biochemical markers with the development of pre-eclampsia. Adjusted odds ratios from stepwise regression was not calculated because assumptions were not met due to a low event rate (i.e. less than 20% of the total population).

Diagnostic accuracy

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratio (LR+, LR –) with their corresponding 95% CI were reported.

All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

Table 1. Minimum Sample Size at 0.05 Level of Significance

Specificity	Minimum Sample Size
	L = 0.05
UtA PI = 84.52%	213
PIGF = 91.26%	130
PAPP – A = 92.94%	107

$$n \geq \frac{Z^2{}_{\alpha} \times S_P \times (1 - S_P)}{L^2 \times (1 - \mathrm{Pr}\,evalence)}$$

$$n \geq \frac{1.96^2 \times 0.8452 \times (1 - 0.8452)}{0.05^2 \times (1 - 0.053)}$$

$$n \geq 212.3 \cong 213$$

RESULTS

During the study period, 224 patients underwent comprehensive first trimester screening for preeclampsia in this institution. A total of 202 women were included in the analysis. Reasons for exclusion are the following: 14 were screen positive for aneuploidy, and 8 had no maternal outcomes available. Preeclampsia developed in 24 (11.9%) of the 202 pregnancies, with 11 (5.4%) having EO-PE and 13 (6.4%) LO-PE. Nineteen (9.4%) of the population developed gestational hypertension. Table 2 shows the maternal demographic characteristics of our patients by preeclampsia status and the association of these characteristics to the development of preeclampsia. The groups did not appear to be significantly different in age profile, with women being mostly in their mid-30s. Majority of women who developed hypertension belonged to the 31-40 year range; the youngest and oldest were aged 24 and 44 years respectively. Women who developed preeclampsia were more likely to be obese, multiparous, with history of hypertension, diabetes mellitus and prior preeeclampsia.

Table 3 shows that cesarean delivery was more likely among women with PE than among those with no hypertension (38.39% vs 61.64%, p=0.003). Preterm delivery was likewise more likely among women with EO-PE (81.82% vs 18.18%, p=<0.001). EO-PE was noted to be more likely associated with higher BP (72.73% vs 84.62%, p=0.001), gestational diabetes (54.55% vs 23.08%,p=0.15), significant proteinuria (100% vs 92.31%, p=<0.001), and neurologic symptoms (27.27% vs 7.69%, p=<0.001) compared with LO-PE.

On bivariate analysis, the factors which appeared to increase the risk for preeclampsia were weight, BMI, history of hypertensive disease, diabetes mellitus, family history of preeclampsia, MAP MoM ≥1.0, and PAPP-A MoM ≥1.0 (Table 4). Age, smoking and pregnancy outcome were not found to be significantly associated (p-value >0.5). There were 8 (33.3%) obese and 10 (41.67 %) overweight patients who developed preeclampsia. The odds of developing preeclampsia among those obese patients were 5x the odds of those with normal BMI and this was statistically significant (OR 9.934 95%CI 0.95–Inf p<0.001). Out of 22 smokers, only 3 (12.50%) developed preeclampsia, but this was not statistically significant (OR 1.266 95%CI 0.22-4.92 p=0.937). The proportion of those who developed preeclampsia was significantly higher among those with previous hypertension compared to those with no previous hypertension (62.50% vs 7.30%). The odds of developing preeclampsia among those who had previous hypertension was 20.5 times the odds of those having

no previous hypertension (95%CI 6.95–65.04 p<0.001), 19.8 times among those having chronic hypertension (95%CI 5.61–77.21), and 24 times among those with history of preeclampsia in a prior pregnancy (95%CI 8.06–80.23). The odds of developing preeclampsia among those with history of diabetes mellitus were almost 9 times the odds of non-diabetics. (OR 8.921 95%CI 1.87–42.71 p<0.005). The proportion of patients who developed preeclampsia during the course of pregnancy were significantly higher if the MAP MoM ≥ 1.0 than those with MAP MoM < 1.0 (91.67% versus 8.33%). The odds of developing preeclampsia among those having MAP MoM ≥ 1.0 was 8.5 times the odds of those with MAP MoM <1.0. (95%CI 1.6–60.8 p<0.001). There was no significant difference, however, in the proportion of patients who developed preeclampsia if the UtA-PI MoM ≥ 1.0 than those with UtA-PI MoM < 1.0 (54,17% versus 45.83% OR 0.922 95%CI 0.36–2.41 p-value=1). Of the three biochemical markers, only PAPP-A was significantly associated with PE, with a decreasing trend noted on preeclamptic women, with lesser odds of developing PE if MoM is ≥1.0.

The rate of compliance with the recommendation to prescribe aspirin to prevent preeclampsia is shown in Table 5. Women found to be at high risk for preeclampsia based on the comprehensive first trimester screening were more likely to be prescribed aspirin (62.16% all-PE, 56.52% of LO-PE and 71.43% of EO-PE). When either the NICE or the ACOG recommendations were used as basis for prescribing aspirin for preeclampsia prevention, more women were likely not given aspirin (57.63% with NICE and 66.67% with ACOG guidelines).

Table 6 compares the diagnostic accuracy of the different screening methods for preeclampsia. The NICE and ACOG guidelines were able to detect preeclampsia with an accuracy of 76.73% (Sn 75%, Sp 77% PPV 30.5%) and 43.07% (Sn 83.3%, Sp 37.6% PPV 15.3%) respectively. The comprehensive first trimester screening was able to detect preeclampsia with an accuracy of 89.60% (Sn 83.3%, Sp 90.5% PPV 54.1%). When broken down into onset of the condition, EO-PE was detected with a higher accuracy using the comprehensive screening (97.52%, Sn 90.9%, Sp 97.9% PPV 71.4%), compared with the NICE guideline (74.26%, Sn 81.8%, Sp 73.8% PPV 15.3%) and the ACOG guideline (39.6%, Sn 90.9%, Sp 36.6, PPV 7.63%). Similarly, LO-PE was detected with higher accuracy using the comprehensive screening (85.15%, Sn 76.9%, Sp 85.7% PPV 27%) compared with the NICE guideline (73.27%, Sn 73.5%, Sp 73.5% PPV 15.3%) and the ACOG guideline (38.61%, Sn 76.9%, Sp 36% PPV 7.63%). The false positive rate is highest for ACOG guideline (62.4%), followed by NICE guideline (23%) and comprehensive test (9.5%). The false negative rate is similar across the screening methods, 2.97% for NICE guideline, 1.98% for ACOG guideline and 2.02% for comprehensive screening.

DISCUSSION

Main findings

The prevalence of preeclampsia in this study was found to be 11.88%. While lower than the prevalence found by Geronimo et al in a similar population in 2015, this prevalence rate is still higher than that reported in literatures.[1,3-7,16] Similarly, our study population has been consistently older, more obese and multiparous compared to other studies. The highest risk for our population was noted in patients with history of PE in a previous pregnancy, history of hypertensive disease and diabetes mellitus, which were associated with a 24-fold, 20-fold and almost 9 fold increase, respectively. The higher prevalence rate in this study population may be explained by the higher proportion of women with advanced maternal age, higher BMI, history of hypertension and diabetes mellitus.

Currently, the prevailing local practice is to screen for preeclampsia by maternal history. However, screening using this traditional approach has not shown a good detection rate. In our study, the comprehensive method had the highest DR and PPV for both EO-PE and LO-PE, compared to NICE and ACOG guidelines both of which had a very high FPR of up to 62.4%. This was similar to the prospective multicenter study by Gorman et al, which assessed the DR for PE when the NICE guidelines, the ACOG recommendations and the FMF algorithm were used. Screening by NICE guidelines detected only up to 41% of EO-PE and 34% of LO-PE at 10.2% FPR. Although screening by ACOG recommendations can detect up to 94% of EO-PE and 89% of LO-PE, the FPR was high at 64.2% and only 6% of this population were eligible for aspirin prophylaxis.[6] FMF screening algorithm detected 100% of PE < 32 weeks, 75% of PE < 37 weeks and 43% of PE ≥ 37 weeks, at a 10% FPR. Another prospective multicenter study, also known as Screening Program for Preeclampsia (SPREE), supports the superior performance of the comprehensive screening. In this study, the DR of the NICE method for EO-PE was 40.8% (95% CI, 32.8 – 48.9%), which was lower than that using maternal factors, MAP and PAPP-A (53.5%; 95% CI, 45.3 – 61.7%), maternal factors, MAP and PlGF (69.0%; 95% CI, 61.4 – 76.6%) and maternal factors, MAP, PlGF and UtA-PI (82.4%; 95% CI, 76.1 – 88.7%).[16] The SPREE study has demonstrated that the performance of first-trimester screening for PE by a combination of maternal factors and biomarkers can double the detection rate, at the same screen-positive, compared to that achieved

by the method recommended by the current NICE guidelines. This better performance in detection for EO-PE may be attributed to the addition of ultrasound and serum biomarkers which can primarily detect features of primary placental disorder, maladaptation of the uteroplacental spiral arteries, and syncytiotrophoblast damage as in the case of EO-PE.[15]

Our study also aimed to determine the compliance of obstetricians in the administration of aspirin to women found to be high-risk for preeclampsia using the different screening tests. Aspirin has been shown to reduce the risk of preterm PE by 67% (95% CI, 43 – 81%), but not term preeclampsia, provided that the daily dose was ≥ 100 mg and the onset of therapy was <16 weeks.[5,7,11,12]. In this study, however, compliance with the NICE and ACOG recommendation that women at high risk for PE should be treated with aspirin from the first trimester to the end of pregnancy was only 42.37% and 33.33%, respectively. This low compliance rate may be in part be attributed to the absence of a standardized local guideline in our country with regards to the administration of aspirin in women who are found to be at high risk for developing preeclampsia. If the selection for aspirin prophylaxis was based on the comprehensive first trimester screening-positive for high risk EO-PE, 6.93% (n=14) of the pregnant population would receive aspirin, and this population would contain 90.91% of those that will develop preterm PE. If selection was based on the NICE guidelines, 29.21% (n=59) of the pregnant population would receive aspirin and this population would contain 81.82% of those that will develop preterm PE. In the case of the ACOG recommendations, 2.97% (n=6) of the population would receive aspirin and only 54.5% of cases of preterm PE that would potentially benefit from such therapy would be targeted. Although aspirin administration has only minimal to negligible effect on both mother and baby and the principal studies on its side effects are reassuring, a more accurate and targeted screening can avoid the routine and extensive prescription of aspirin, which can lessen the potential exposure to potential gastrointestinal and hemorrhagic side effects. [4, 18-19]

Implications in practice

First trimester screening for preeclampsia is a novel approach in the Philippines. This institution is the first and only institution that utilizes a comprehensive approach to the screening for preeclampsia with the use of combined maternal factors and biomarkers. The high prevalence rate of preeclampsia at 11.58% in our local population is one reason why screening for early prevention is important. The traditional approach using the NICE guideline can miss up to 1/3 of women who will develop preeclampsia while the approach using the ACOG guideline can miss up to 2/3 of these women. In comparison, the comprehensive approach can identify up to 83% of women who will develop preeclampsia with a FPR of only 9.5%. In addition, using the comprehensive screening test, up to 91% of women who will develop EO-PE and who are candidates for aspirin administration are accurately identified. Although it is reassuring that prophylactic use of aspirin has no negative maternal and perinatal effects[4,18-19], it is still essential to put in place a targeted screening tool that can limit the needless exposure of pregnant women to aspirin. This study confirmed that the performance of screening for EO-PE, and therefore appropriate selection of the patients that would benefit from prophylactic use of aspirin and closer surveillance, is by far superior if the comprehensive first trimester screening is used than the method advocated by ACOG and NICE.

The main limitation of the study is the limited number of subjects included compared to the dataset used in other validation studies. Nevertheless, the detection rates obtained were very similar to those reported in literatures. The effect of aspirin in the prevention of preeclampsia among women who screened positive in the comprehensive screening was not analyzed in this study and will be the subject of a subsequent analysis. Currently, new best practice recommendations are greatly needed to guide clinicians in the care of women with all forms of preeclampsia and hypertension that occur during pregnancy, particularly women with acute severe hypertension and superimposed preeclampsia. ■

Table 2. Demographic and clinical characteristics, by preeclampsia status

	No Hypertension (n = 159)	Early Preeclampsia (n = 11)	Late Preeclampsia (n = 13)	Gestational Hypertension (n = 19)	
	Frequency (%); Mean ± SD; Median (Range)				*P*
Age (y)	34.36 ± 4.79	35.82 ± 2.48	33.38 ± 4.79	33.38 ± 4.79	.589*
<24	2 (1.26)	0	0	0	.568†
24–30	30 (18.87)	0	4 (30.77)	4 (21.05)	
31–40	113 (71.07)	11 (100)	9 (69.23)	12 (63.16)	
41–44	13 (8.18)	0	0	3 (15.79)	
≥45	1 (0.63)	0	0	0	
Height (cm)	157.5 (130–180)	157 (140–173)	157.5 (136–165.1)	157.5 (150–179.1)	.856‡
Weight (kg)	62 (39–106)	**70 (55–99.5)**	69 (57.7–84)	59 (49–92)	**.048‡**
BMI (kg/m^2)	24.5 (16–40.4)	**26.6 (22.9–37.9)**	**27.4 (23.3–38.1)**	23.1 (18.4–34.8)	**.006‡**
<19	11 (6.92)	0	0	2 (10.53)	.123†
19–24.9	76 (47.8)	3 (27.27)	3 (23.08)	9 (47.37)	
25–29.9	56 (35.22)	5 (45.45)	5 (38.46)	5 (26.32)	
≥30	16 (10.06)	3 (27.27)	5 (38.46)	3 (15.79)	
Gravidity					**.023†**
G1	59 (37.11)	3 (27.27)	1 (7.69)	12 (63.16)	
G2–G4	96 (60.38)	7 (63.64)	**11 (84.62)**	7 (36.84)	
G5 above	4 (2.52)	1 (9.09)	1 (7.69)	0	
Parity					**.026†**
P0	70 (44.03)	4 (36.36)	1 (7.69)	**13 (68.42)**	
P1	55 (34.59)	3 (27.27)	**8 (61.54)**	4 (21.05)	
≥P2	34 (21.38)	4 (36.36)	4 (30.77)	2 (10.53)	
AOG at delivery (wks)	38 (20–41)	**35 (22–39)**	**37 (37–39)**	38 (37–40)	**<.001‡**
AOG at screening (wks)	12.5 (11–13.6)	12.5 (11–13.6)	12.6 (11.6–13.4)	13 (10.5–13.6)	.636‡
Major risk factors					
History of hypertensive disease	7 (4.4)	**6 (54.55)**	**9 (69.23)**	6 (31.58)	**<.001†**
Chronic hypertension	5 (3.14)	**5 (45.45)**	**5 (38.46)**	1 (5.26)	**<.001†**
Diabetes mellitus	5 (3.14)	**3 (27.27)**	**2 (15.38)**	0	**.005†**
Autoimmune disease	6 (3.77)	1 (9.09)	0	0	.552†
Chronic kidney disease	2 (1.26)	1 (9.09)	0	0	.217†
Moderate risk factors					
First pregnancy at ≥40y (n=26)	4 (19.05)	0	0	1 (33.33)	.691†
Interpregnancy interval >10y	3 (1.89)	1 (9.09)	1 (7.69)	0	.134†
First visit BMI ≥35 kg/m^2	2 (1.26)	1 (9.09)	1 (7.69)	1 (5.26)	.066†
Family history of PE	8 (5.03)	**7 (63.64)**	2 (15.38)	5 (26.32)	**<.001†**
PE in a prior pregnancy	7 (4.4)	**6 (54.55)**	**9 (69.23)**	4 (21.05)	**<.001†**
Smoking	17 (10.69)	2 (18.18)	1 (7.69)	1 (5.26)	.719†
Developed Gestational Diabetes Mellitus	25 (15.72)	**6 (54.55)**	3 (23.08)	5 (26.32)	**.015†**
Beta-hCG	42.85 (4.9–317.7)	46.5 (7.7–91.4)	33 (6.2–67.2)	40.8 (12.9–146.1)	.678‡
Multiple of median	1.14 (0.16–9.95)	1.38 (0.28–1.9)	1.03 (0.17–1.9)	1.04 (0.31–4.33)	.940‡
<1	66 (41.51)	4 (36.36)	5 (38.46)	9 (47.37)	.924†
≥1.0	93 (58.49)	7 (63.64)	8 (61.54)	10 (52.63)	
MAP (mmHg)	83 (64.8–117.5)	**102.3 (84.8–110.7)**	**96.3 (81.3–114.5)**	87.7 (65.8–107.5)	**<.001‡**
MoM	1 (0.53–1.42)	1.23 (1.02–1.34)	1.12 (0.98–1.38)	1.09 (0.81–1.22)	**<.001‡**
<1	73 (45.91)	0	2 (15.38)	5 (26.32)	**.001†**
≥1.0	86 (54.09)	11 (100)	11 (84.62)	14 (73.68)	
PAPP-A	3006.5 (595.6–15872.6)	**1454.5 (922.9–3552.9)**	**2672.2 (558.5–6502.7)**	4154.9 (350.3–10850.2)	**.030‡**
MoM	1.05 (0.21–10.21)	0.81 (0.3–1.88)	0.72 (0.35–2.41)	1.07 (0.32–2.67)	.153‡
<1	76 (47.80)	8 (72.73)	9 (69.23)	6 (31.58)	.074†
≥1.0	83 (52.20)	3 (27.27)	4 (30.77)	13 (68.42)	
PlGF	30.5 (4.8–79.9)	26.8 (5.9–39.5)	33.3 (4.7–82.3)	29.6 (9.6–50.9)	.167‡
MoM	1.12 (0.16–3.02)	0.94 (0.18–1.51)	1.28 (0.15–2.36)	1.1 (0.33–1.67)	.290‡
<1	64 (40.25)	6 (54.55)	5 (38.46)	8 (42.11)	.831†
≥1.0	95 (59.75)	5 (45.45)	8 (61.54)	11 (57.89)	
UtA-PI, left	1.71 (0.45–4)	1.99 (1.6–3.17)	1.4 (0.6–3.06)	1.64 (0.93–3.04)	.066‡
UtA-PI, right	1.66 (0.45–3.48)	2.06 (1.22–3.33)	1.41 (0.4–2.65)	1.51 (0.72–2.83)	.057‡
UtA Doppler MoM	1.04 (0.3–2.39)	**1.39 (0.83–1.9)**	0.94 (0.3–1.91)	1.07 (0.53–1.58)	**.016‡**
<1	70 (44.03)	2 (18.18)	9 (69.23)	8 (42.11)	.097†
≥1.0	89 (55.97)	9 (81.82)	4 (30.77)	11 (57.89)	
Nuchal translucency (mm)	1.56 (0.09–10.76)	1.59 (1.2–2.08)	1.24 (1.04–2.88)	1.71 (0.99–3.22)	.413‡
MoM	1.01 (0.07–6.57)	1.1 (0.7–1.6)	0.74 (0.64–1.81)	1.17 (0.64–1.84)	.152‡
<1	73 (45.91)	4 (36.36)	9 (69.23)	7 (36.84)	.290†
≥1.0	86 (54.09)	7 (63.64)	4 (30.77)	12 (63.16)	
Nasal bone	159 (100)	11 (100)	13 (100)	19 (100)	-

MAP, mean arterial pressure; MoM, multiple of the median; PAPP-A, pregnancy associated plama protein A ; PE, preeclampsia; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.
Statistical tests used: * - ANOVA; † - Fisher's exact test; ‡ - Kruskal Wallis H test.

Table 3. Delivery outcomes, by preeclampsia status

	No Hypertension (n = 159)	Early Preeclampsia (n = 11)	Late Preeclampsia (n = 13)	Gestational Hypertension (n = 19)	P
	Frequency (%)				
Mode of delivery					**.003**
NSD	61 (38.36)	1 (9.09)	1 (7.69)	2 (10.53)	
CS	98 (61.64)	10 (90.91)	12 (92.31)	17 (89.47)	
AOG at delivery					**<.001†**
Term	147 (92.45)	2 (18.18)	13 (100)	19 (100)	
Preterm	12 (7.55)	9 (81.82)	0	0	
PE severity					**<.001†**
Not applicable	159 (100)	0	0	19 (100)	
Severe	0	7(63.64)	11 (84.61)	0	
Non-severe	0	4 (36.36)	2 (15.39)	0	
Maternal complications					
BP ≥160/110 mmHg	1 (0.63)	**8 (72.73)**	**11 (84.62)**	0	**<.001†**
Developed Gestational Diabetes Mellitus	25 (15.72)	**6 (54.55)**	3 (23.08)	5 (26.32)	**.015†**
Proteinuria	2 (1.26)	**11 (100)**	**12 (92.31)**	1 (5.26)	**<.001†**
Renal insufficiency	0	1 (9.09)	0	0	.054†
Liver involvement	0	1 (9.09)	0	0	.054†
Neurologic	0	**3 (27.27)**	1 (7.69)	0	**<.001†**
Thrombocytopenia	0	0	0	0	-
Pulmonary edema	0	0	0	0	-

Statistical test used: † - Fisher's exact test

Table 4. Binary logistic regression for predictors of preeclampsia

	+ Preeclampsia (n = 24)	- Preeclampsia (n = 178)	Crude Odds Ratio (95% CI)	p value
	Frequency (%); Mean ± SD; Median (Range)			
Age (y)	34.5 ± 4.02	34.43 ± 4.77	1.003 (0.92–1.10)	.971
<24	0	2 (1.12)	(reference)	-
24–30	4 (16.67)	34 (19.10)	0.264 (0.02–Inf)	1.000
31–40	20 (83.33)	125 (70.22)	0.380 (0.03–Inf)	1.000
41–44	0	16 (8.99)	1 (0–Inf)	-
≥45	0	1 (0.56)	1 (0–inf)	-
Height (cm)	157.48 (136–173)	157.5 (130–180)	0.951 (0.89–1.01)	.129
Weight (kg)	69.5 (55–99.5)	62 (39–106)	1.050 (1.01–1.09)	**.007**
BMI (kg/m2)	27 (22.9–38.1)	24.3 (16–40.4)	1.177 (1.07–1.30)	**<.001**
<19	0	13 (7.30)	(reference)	-
19–24.9	6 (25)	85 (47.75)	1.205 (0.16–Inf)	.879
25–29.9	10 (41.67)	61 (34.27)	2.842 (0.41–Inf)	.412
≥30	8 (33.33)	19 (10.67)	6.934 (0.95–Inf)	.947
Gravidity				
G1	4 (16.67)	71 (39.89)	(reference)	-
G2–G4	18 (75)	103 (57.87)	3.087 (0.96–13.07)	.061
G5 above	2 (8.33)	4 (2.25)	8.40 (0.59–85.73)	.121
Parity				
P0	5 (20.83)	83 (46.63)	(reference)	-
P1	11 (45.83)	59 (33.15)	3.073 (0.92–11.90)	.070
≥P2	8 (33.33)	36 (20.22)	3.648 (0.98–15.20)	.055

Risk factors				
History of hypertensive disease	15 (62.50)	13 (7.30)	20.503 (6.95–65.04)	**<.001**
Chronic hypertension	10 (41.67)	6 (3.37)	19.813 (5.61–77.21)	<.001
Diabetes mellitus	5 (20.83)	5 (2.81)	8.921 (1.87–42.71)	**.005**
Autoimmune disease	1 (4.17)	6 (3.37)	1.245 (0.03–11.00)	1.000
Chronic kidney disease	1 (4.17)	2 (1.12)	3.787 (0.06–75.43)	.634
First pregnancy at ≥40y (n=26)	0	5 (20.83)	1.091 (0–8.32)	1.000
Interpregnancy interval >10y	2 (8.33)	3 (1.69)	5.230 (0.42–48.32)	.217
First visit BMI ≥35 kg/m2	2 (8.33)	3 (1.69)	5.230 (0.42–48.32)	.217
Family history of PE	9 (37.50)	13 (7.30)	7.486 (2.41–22.87)	**<.001**
PE in a prior pregnancy	15 (62.50)	11 (6.18)	24.42 (8.06–80.23)	<.001
Smoking	3 (12.50)	18 (10.11)	1.268 (0.22–4.92)	.937
Beta-hCG				
<1	9 (37.50)	75 (42.13)	(reference)	-
≥1.0	15 (62.50)	103 (57.87)	1.212 (0.47–3.32)	.840
MAP MoM				
<1	2 (8.33)	78 (43.82)	(reference)	-
≥1.0	22 (91.67)	100 (56.18)	8.514 (1.99–76.90)	**<.001**
PAPP-A MoM				
<1	17 (70.83)	82 (46.07)	(reference)	-
≥1.0	7 (29.17)	96 (53.93)	0.353 (0.12–0.95)	**.038**
PlGF MoM				
<1	11 (45.83)	72 (40.45)	(reference)	-
≥1.0	13 (54.17)	106 (59.55)	0.804 (0.31–2.10)	.771
UtA-PI MOM				
<1	11 (45.83)	78 (43.82)	(reference)	-
≥1.0	13 (54.17)	100 (56.18)	0.922 (0.36–2.41)	1.000
Nuchal translucency				
<1	13 (54.17)	80 (44.94)	(reference)	-
≥1.0	11 (45.83)	98 (55.06)	0.692 (0.26–1.78)	.526

MAP, mean arterial pressure; MoM, multiple of the median; PAPP-A, pregnancy associated plama protein A ; PE, preeclampsia; PlGF, placental growth factor; UtA PI, uterine artery pulsatility index.

Table 5. Aspirin prescription, by positive results in different screening tests

	NICE Guideline (n = 59)	High-Risk ACOG Guideline (n = 131)	For Aspirin ACOG Guideline (n = 6)	Comprehensive FTS	
				High Risk for Late PE (n = 23)	High Risk for Early and Late PE (n = 14)
Aspirin given	25 (42.37)	30 (22.90)	2 (33.33)	13 (56.52)	10 (71.43)
Aspirin not given	34 (57.63)	101 (77.10)	4 (66.67)	10 (43.48)	4 (28.57)

Table 6. Diagnostic accuracy measures of different screening tests for preeclampsia

	Sensitivity Detection Rate	Specificity	PPV Bayesian Detection Rate NPV	NPV	+ LR	- LR	Accuracy
NICE							
All preeclampsia	75 (53.3–90.2)	77 (70.1–82.9)	30.5 (19.2–43.9)	95.8 (91.1–98.4)	3.26 (2.28–4.64)	0.32 (0.16–0.65)	76.73 (70.29–82.38)
Early preeclampsia	81.8 (48.2–97.7)	73.8 (67–79.9)	15.3 (7.22–27)	98.6 (95–99.8)	3.13 (2.17–4.51)	0.25 (0.07–0.87)	74.26 (67.65–80.14)
Late preeclampsia	73.5 (66.7–79.7)	73.5 (66.7–79.7)	15.3 (7.22–27)	97.2 (93–99.2)	2.62 (1.7–4.04)	0.42 (0.18–0.95)	73.27 (66.6–79.23)
ACOG							
All preeclampsia	83.3 (62.6–95.3)	37.6 (30.5–45.2)	15.3 (9.6–22.6)	94.4 (86.2–98.4)	1.34 (1.08–1.65)	0.44 (0.18–1.10)	43.07 (36.14–50.20)
Early preeclampsia	90.9 (58.7–99.8)	36.6 (29.8–43.9)	7.63 (3.72–13.6)	98.6 (92.4–100)	1.44 (1.16–1.78)	0.24 (0.04–1.62)	39.6 (32.81–46.71)
Late preeclampsia	76.9 (46.2–95)	36 (29.1–43.3)	7.63 (3.72–13.6)	95.8 (88.1–99.1)	1.2 (0.88–1.65)	0.64 (0.23–1.76)	38.61 (31.86–45.70)
Comprehensive FTS							
All preeclampsia	83.3 (62.6–95.3)	**90. (8–94.)**	**54.1 (–)**	97. (9–99.)	8.3 (5.–1.9)	0.1 (0.08–0.45)	89. (84.5–93.)
Early preeclampsia	90.9 (58.7–99.8)	**(–)**	**(–)**	99.4 (96.6–)	(–)	0. (0.0–0.6)	(–9)
Late preeclampsia	(4.2–95)	**85. (79.–90.)**	**27 (1–)**	98. (9–99.6)	5. (3.–8.)	0.27 (0.1–0.73)	8 (79.8–89.)

Table 6.1.1 Diagnostic accuracy of NICE guidelines for all pre-eclampsia

		True Positive	True Negative	Total
		Frequency (%)		
Positive on test		18 (8.91)	41 (20.30)	59 (29.21)
Negative on test		6 (2.97)	137 (67.82)	143 (70.79)
Total		24 (11.88)	178 (88.12)	202 (100)
Sensitivity	75 (53.3–90.2)	Positive LR	3.26 (2.28–4.64)	
Specificity	77 (70.1–82.9)	Negative LR	0.32 (0.16–0.65)	
PPV	30.5 (19.2–43.9)	Accuracy	76.73 (70.29–82.38)	
NPV	95.8 (91.1–98.4)			

Table 6.1.2. Diagnostic accuracy of NICE guidelines for early pre-eclampsia

		True Positive	True Negative	Total
		Frequency (%)		
Positive on test		9 (4.46)	50 (24.75)	59 (29.21)
Negative on test		2 (0.99)	141(69.80)	143 (70.79)
Total		11 (5.45)	191 (94.55)	202 (100)
Sensitivity	81.8 (48.2–97.7)	Positive LR	3.13 (2.17–4.51)	
Specificity	73.8 (67–79.9)	Negative LR	0.25 (0.07–0.87)	
PPV	15.3 (7.22–27)	Accuracy	74.26 (67.65–80.14)	
NPV	98.6 (95–99.8)			

Table 6.1.3 Diagnostic accuracy of NICE guidelines for late pre-eclampsia

		True Positive	True Negative	Total
		Frequency (%)		
Positive on test		9 (4.46)	50 (24.75)	59 (29.21)
Negative on test		4 (1.98)	139 (68.81)	143 (70.79)
Total		13 (6.44)	189 (93.56)	202 (100)
Sensitivity	73.5 (66.7–79.7)	Positive LR	2.62 (1.7–4.04)	
Specificity	73.5 (66.7–79.7)	Negative LR	0.42 (0.18–0.95)	
PPV	15.3 (7.22–27)	Accuracy	73.27 (66.6–79.23)	
NPV	97.2 (93–99.2)			

Table 6.2.1. Diagnostic accuracy of ACOG guidelines for all pre-eclampsia

		True Positive	True Negative	Total
		Frequency (%)		
Positive on test		20 (9.90)	111 (54.95)	131 (64.85)
Negative on test		4 (1.98)	67 (33.17)	71 (35.15)
Total		24 (11.88)	178 (88.12)	202 (100)
Sensitivity	83.33 (62.6–95.3)	Positive LR	1.34 (1.08–1.65)	
Specificity	37.6 (30.5–45.2)	Negative LR	0.44 (0.18–1.10)	
PPV	15.3 (9.6–22.6)	Accuracy	43.07 (36.14–50.20)	
NPV	94.4 (86.2–98.4)			

Table 6.2.2. Diagnostic accuracy of ACOG guidelines for early pre-eclampsia

		True Positive	True Negative	Total
		Frequency (%)		
Positive on test		10 (4.95)	121 (59.9)	131 (64.85)
Negative on test		1 (0.5)	70 (34.65)	71 (35.15)
Total		11 (5.45)	191 (94.55)	202 (100)
Sensitivity	90.9 (58.7–99.8)	Positive LR	1.44 (1.16–1.78)	
Specificity	36.6 (29.8–43.9)	Negative LR	0.24 (0.04–1.62)	
PPV	7.63 (3.72–13.6)	Accuracy	39.6 (32.81–46.71)	
NPV	98.6 (92.4–100)			

Table 6.2.3. Diagnostic accuracy of ACOG guidelines for late pre-eclampsia

		True Positive	True Negative	Total
		Frequency (%)		
Positive on test		10 (4.95)	121 (59.9)	131 (64.85)
Negative on test		3 (1.49)	68 (33.6)	71 (35.15)
Total		13 (6.44)	189 (93.56)	202 (100)
Sensitivity	76.9 (46.2–95)	Positive LR	1.2 (0.88–1.65)	
Specificity	36 (29.1–43.3)	Negative LR	0.64 (0.23–1.76)	
PPV	7.63 (3.72–13.6)	Accuracy	38.61 (31.86–45.70)	
NPV	95.8 (88.1–99.1)			

Table 6.3.1 Diagnostic accuracy of comprehensive FTS for all pre-eclampsia

		True Positive	True Negative	Total
		Frequency (%)		
Positive on test		20 ()	17 (8.)	37 (18.)
Negative on test		4 ()	1 (79.)	16 (81.)
Total		24 (1)	17 (8.)	(100)
Sensitivity	83. (62.6–95.3)	Positive LR	8.3 (5.–1.9)	
Specificity	90. (8–94.)	Negative LR	0.1 (0.08–0.45)	
PPV	54.1 (–)	Accuracy	89. (84.5–93.)	
NPV	97. (9–99.)			

Table 6.3.2. Diagnostic accuracy of comprehensive FTS for early pre-eclampsia

		True Positive	True Negative	Total
		Frequency (%)		
Positive on test		10 (5.05)	)	()
Negative on test		1 (0.51)	()	()
Total		11 (5.56)	1 (94.)	(100)
Sensitivity	90.9 (58.7–99.8)	Positive LR	6.3 (–)	
Specificity	(–9)	Negative LR	(0.0–0.6)	
PPV	(–)	Accuracy	()	
NPV	99.4 (96.6–)			

Table 6.3.3. Diagnostic accuracy of comprehensive FTS for late pre-eclampsia

		True Positive	True Negative	Total
		Frequency (%)		
Positive on test		10 ()	27 (13.)	37 (18.)
Negative on test		3 (1.)	1 ()	16 (81.)
Total		13 (6.)	18 (93.)	(100)
Sensitivity	7 (4–9)	Positive LR	5. (3.–8.)	
Specificity	85. (79.–90.)	Negative LR	0.27 (0.1–0.73)	
PPV	27 (1–)	Accuracy	8 (79.8–89.)	
NPV	98. (9–99.)			

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