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Comparison of FMF and NICE Algorithms in Early Preeclampsia Screening at 11-13 Weeks Gestation

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Abstract

Background:Approximately 3% of pregnant women develop preeclampsia at some time during their pregnancy. Preeclampsia is a common cause of maternal and fetal morbidity and mortality worldwide. Currently there are 3 assessment tools for preeclampsia: the National Institute for Health and Care Excellence (NICE) guidelines, the American College of Obstetricians and Gynecologist (ACOG) and the Fetal Medicine Foundation (FMF) algorithm. Both NICE and ACOG guidelines use maternal demographics and medical history as a screening tool. The more recent approach, FMF uses Bayes theorem utilizes biophysical and biochemical markers in addition to maternal risk factors. Methods: An exhaustive search of the available medical literature was performed using the search engines MEDLINE- PubMed, Google Scholar, and Science of Web. Keywords included: "Preeclampsia" AND "NICE guidelines" AND "fetal medicine foundation" and "Preeclampsia screening guidelines". The GRADE Working Group was used to assess the quality of relevant studies. Results: During the search, 2 articles were found to meet the eligibility criteria. Both were prospective multicenter cohort studies. Conclusion: The FMF algorithm which combines maternal factors with biophysical and biochemical markers is superior in screening for preeclampsia during weeks 11-13 gestation compared to the NICE algorithm. The quality of evidence is at a low to very low due to risk of publication bias and incomplete blinding.

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First trimester screening, preeclampsia, NICE algorithm, FMF algorithm, mean arterial pressure, placental growth factor, pregnancy associated plasma protein A, uterine artery Doppler

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Comparison of FMF and NICE Algorithms in Early Preeclampsia Screening at 11-13 Weeks Gestation

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Biography

Mergitu Gemeda was born and raised in Ethiopia, East Africa. She moved to the U.S in 2006 and started pursuing her education at local community college in MN. She graduated with A.A.S in Respiratory Therapy from Northland community and Technical College, later earned her B.S with Emphasis on Respiratory Care from University of Minnesota. She worked as a Registered Respiratory Therapist before returning to school to pursue her PA education at Pacific University.

Lauren Voelker was born and raised in Indianapolis, Indiana. She attended Indiana University in Bloomington where she received in B.S in Biology and a minor in Spanish. She worked as a medical scribe before starting PA school at Pacific University.

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Approximately 3% of pregnant women develop preeclampsia at some time during their pregnancy. Preeclampsia is a common cause of maternal and fetal morbidity and mortality worldwide. Currently there are 3 assessment tools for preeclampsia: the National Institute for Health and Care Excellence (NICE) guidelines, the American College of Obstetricians and Gynecologist (ACOG) and the Fetal Medicine Foundation (FMF) algorithm. Both NICE and ACOG guidelines use maternal demographics and medical history as a screening tool. The more recent approach, FMF uses Bayes theorem utilizes biophysical and biochemical markers in addition to maternal risk factors.

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List of Abbreviations

FMF   Fetal Medicine Foundation
NICE   National Institute for Health and Care Excellence
ACOG   American College of Obstetricians and Gynecologist
MAP   Mean Arterial Pressure
PAPP-A   Serum pregnancy associated plasma protein-A
UtA-PI   Uterine artery pulsatility index
PlGF   Serum placental growth factor
PE   Preeclampsia
DR   Detection rate
FPR   False positive rate
SPREE   Screening program for pre-eclampsia
UCL-CCTU   University College London Comprehensive Clinical Trials Unit

Comparison of FMF with NICE and ACOG Algorithm in Early Preeclampsia Screening at 11-13 Weeks Gestation

BACKGROUND

Preeclampsia is a complication of pregnancy that is characterized by high blood pressure with signs of end organ damage especially the liver and kidney. Despite intense years of research over the years the etiology of preeclampsia remains unknown.[1] According to the American College of Obstetrics and Gynecologists Preeclampsia is defined as blood pressure greater than 140/90 mmHg on two occasions, at least four hours apart and proteinuria (greater than 300mg per 24hr urine collection or +1 on a dipstick or protein/creatinine ratio greater than or equal to 0.3) in pregnant women who were previously normotensive. In the absences of proteinuria, a new onset of hypertension with a presence of one of the following: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema or cerebral/visual disturbance will meet diagnostic criteria. Preeclampsia occur as early as 20 weeks of pregnancy and can last up to six weeks into the postpartum period.[2]

Despite extensive research and advance in the field of medicine preeclampsia remains the leading cause of mortality and morbidity worldwide resulting in thousands of death of both the mother and fetus every year.[2] Over the last decade many studies have been conducted in an effort to find a better screening tool to reduce the disease prevalence by initiating pharmacological intervention for those at high risk[3] and minimize the adverse events in those who are already experiencing preeclampsia by planning delivery in timely manner at appropriate facility.[4] The general approach, based on the National Institute for Health and Care Excellence (NICE) and the American College of Obstetricians and Gynecologists (ACOG) recommendation has been to identify risk based on maternal demographics and medical history as a way to screen for

preeclampsia, whereas Fetal Maternal Foundation (FMF) approach utilizes biophysical and biochemical markers in addition to prior maternal risk factors.[5]

The NICE guideline uses maternal risk factors such as history of hypertensive disease in previous pregnancy, chronic kidney disease, autoimmune disease, diabetes mellitus and chronic hypertension, first pregnancy, age ≥ 40 years, interpregnancy interval > 10 years, body mass index (BMI) at first visit of ≥ 35 kg/m^2 or family history of preeclampsia to determine the risk of developing preeclampsia. Whereas according to ACOG nulliparity, age > 40 years, BMI ≥ 30 kg/m^2, *in-vitro* fertilization, history of previous pregnancy complicated by PE, family history of PE, chronic hypertension, chronic renal disease, diabetes mellitus, systemic lupus erythematosus or thrombophilia are all considered maternal risk factors for developing PE. In addition to maternal risk factors the FMF screening model utilizes Mean Arterial Pressure (MAP), serum pregnancy associated plasma protein-A (PAPP-A), Uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PlGF) to determine women who are at high risk for developing PE. The goal of this review is to determine whether NICE guideline or FMF algorithm is superior in detecting risk of developing preeclampsia early in the pregnancy.[5]

METHODS

After an extensive search using MEDLINE- PubMed, Google Scholar, and Science of Web articles were narrowed down using the search phrase "Preeclampsia AND "NICE guidelines" AND "fetal medicine foundation". Eligible studies included English language articles, comparison of FMF algorithm to NICE and/or ACOG algorithm, screened during the first trimester, large population size, and documented statistical analysis. Studies failing to compare the FMF screening tool with the current NICE guidelines, screening taking place in the second or third trimester, and studies focusing on therapy were excluded. The qualities of the eligible

articles were evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.[6]

RESULTS

The initial search using MEDLINE- PubMed revealed 3 articles to review. Using the eligibility criteria only 1 was found to be relevant.[5] A search of Google Scholar resulted in 89 articles. Only 2 meet the eligibility criteria[5,7] One of the 2 included the same article by O'Gorman was found in MEDLINE- PubMed. The remaining 87 articles were excluded. Web of Science resulted in zero results. In total 2 articles[5,7] were analyzed for this systematic review. Both articles were prospective multicenter cohort studies. (See Table 1.)

O'Gorman et al. (2017)

The purpose of this prospective multicenter study[5] was to compare the new FMF algorithm with the current standard practice NICE and ACOG method to determine if one is superior in detecting preeclampsia early. This study included 8775 women who are 11-13 weeks gestation at 12 maternity hospitals in 5 different countries. These countries were the UK, Spain, Belgium, Greece, and Italy. Patients were recruited between February and September 2015. These women completed a written informed consent to participate in the trial and were approved by National Health Service Research Ethics Committee in the UK.[5]

The detection rate (DR) was calculated for NICE, ACOG and FMF in every patient.[5] NICE and ACOG DR was determined by inquiring medical history and maternal factors.[8] Then each risk factor which was used as a separate screening test and added together to calculate the detection rate and positive screening rate. The results were viewed using statistical software

package R. With the FMF algorithm, maternal factors were collected, MAP and UtA-PI were measured using standardized protocols[9,10] and PAPP-A and PlGF concentrations were collected. The collected data were combined with the use of Bayes' theorem to determine individual patient specific risks of PE.[5]

The results revealed that with the use of the FMF algorithm a detection rate of PE 100% at <32 weeks, 75% at <37 weeks, and 43% at ≥ 37 weeks and a 10.0 % FPR. The NICE algorithm detected 41% of PE <32 weeks, 39% of PE <37 weeks, and 34% of PE ≥ 37 weeks. (See Table 2.) In comparison, of the 2 algorithms for early screening, FMF is the more accurate screening in determining pregnancies at high risk for developing pre-eclampsia.[5] Limitations of this study include failure to blind the patients and physicians, small population size that developed PE which lead to a wide confidence intervals, and publication bias due to funding by FMF.[5]

Tan et al. (2018)

The prospective multicenter study[7] compared the current screening method, NICE and ACOG, to the new algorithm FMF for detecting PE. There were 16 747 patients at 11-13 weeks gestation from seven different maternity hospitals who were recruited between April 2016 to December 2016 to participate in the study. Inclusion criteria included age ≥ 18 years, singleton pregnancy, and live fetus. Exclusion criteria were women who were unconscious or severely ill, had learning difficulties or serious mental illness, and major fetal abnormality at the 11-13 week scan.[7] Each participant had to meet the inclusion criteria, sign a formed consent to agree to participate in the study, and receive approval from the London Surrey Borders Research Ethics Committee.[7]

Maternal characteristics as well as biomarkers including MAP, UtA-PI, PlGF, and PAPPA-A were obtained from each participant. Standardized protocols were used to measure MAP and

UtA-PI to keep measurements consistent across the different participating hospitals.[11,12] MAP was measured by either health care assistant or sonographers while the UtA PI was completed only by the sonographers. PAPP-A and PlGF were measured using either DELFIA Xpress analyzer or KRYPTOR analyzer. Quality control was used to make sure measured markers were consistent across the seven hospitals. The results were blinded to participants and their physicians. The measurements were sent to UCL-CCTU where the statisticians analyzed the data using both NICE and FMF algorithm as well as identifying those who were treated with aspirin and the association between aspirin and baseline results.[7]

The first comparison included mini combined test vs NICE algorithm. The mini combined test collected maternal factors, MAP, and PAPP-A and used Bayes' theorem. The reason for including these specific biomarkers was due no extra cost associated with it. The second comparison used the NICE guidelines vs three subgroups of markers and Bayes' theorem. These groups included maternal factors, MAP, and PAPP-A; maternal factors, MAP, and PlGF; and maternal factors, MAP, UtA-PI and PlGF. PlGF was selected because it has a better success rate than PAPPA-A marker in predicting PE in previous studies. The maternal factors, MAP, UtA-PI and PlGF was found to be the most accurate combination in detecting preterm PE in previous studies which is why it was also selected.[7]

The study found that using the combination of maternal factors and biomarkers were far more accurate in detecting PE when compared to the NICE guidelines. The NICE guidelines detected approximately 30% of pregnancies that would go on to develop PE and approximately 40% of pregnancies that would develop severe PE with a FPR of 10.0%.[1] (See Table 2.) The FMF algorithm which included maternal factors, MAP, and serum PAPP-A detected 42.5% of all PE.

The combination of maternal factors, MAP, UtA-PI and PlGF detected 82.4% of preterm PE with a FPR of 10.0%.[7]

DISCUSSION

Undiagnosed preeclampsia can lead to very serious, even fatal, complications for both the mother and the fetus. It's clear that a more accurate and sensitive screening tool is needed to identify pregnant women who are at risk for developing preeclampsia and plan intervention appropriately in order to decrease the mortality and morbidity related to preeclampsia. Analyzing the data from the 2 studies[5,7] shows that using biophysical and biochemical markers in combination with pre-existing maternal risk factors is superior in detecting preeclampsia early on when compared to the traditional approach which only uses maternal risk factors. These additional measurements can be completed in the office during a routine visit at 11-13 weeks gestation. MAP measurement requires inexpensive equipment and minimal training of a health care assistant.[5] Though it does require adherence to the appropriate protocol in order to obtain an accurate result.[9] UtA-PI is measured by a sonographer and also requires adherence to protocol.[10] Each exam only takes a few minutes to perform. PlGF and PAPP-A which are found in the serum can be collected with routine labs during the initial visit. The additional labs can be completed using the same machine which is commonly used to test for free B-human chorionic gonadotropin.[5] These measurements are put into the FMF risk assessment tool which then calculates the PE risk. The FMF risk assessment tool developed by FMF is available for free online at www.fetalmedicine.com.

Both studies[5,7] that were reviewed concluded that the FMF screening tool was superior to the standard NICE and ACOG method in detecting PE during 11-13 weeks gestation. O'Gorman et

al (2017)[5] detected in a population size of 8775 singleton pregnancies, 100% (95% CI, 80-100%) of PE <32 weeks, 75% (95% CI, 62-85%) of PE < 37 weeks and 43% (95% CI, 35-50%) of PE ≥ 37 weeks and a FPR of 10.0%[2] with the use of FMF algorithm. Using the same population, NICE[13] and ACOG[14] guidelines were also applied. NICE screening detected 41% (95% CI, 18-67%) of PE <32 weeks, 39% (95% CI, 27-53%) of PE < 37 weeks, and 34% (95% CI, 27-41%) of PE ≥37 weeks at a 10.2% FPR. ACOG screening revealed 94% (95% CI, 71-100%) of PE <32 weeks, 90% (95% CI, 79-96%) of PE < 37 weeks, and 89% (95% CI, 84-94%) of PE ≥ 37 weeks at a 64.2% FPR.

Tan et al[7] detected 31.5% (95% CI, 27.3-35.7%) of all PE and 40.8% (95% CI, 32.8-48.9%) of preterm PE via the NICE algorithm. Note the effect of aspirin used in some patients was adjusted. The FMF algorithm detected 42.5% (95% CI, 38.0-46.9%) of all PE. Screening for preterm PE via FMF screening tool revealed maternal factors, MAP and PAPP-A detected 53.5% (95% CI, 27.3-35.7%) of PE, maternal factors, MAP and PlGF detected 69.9% (95% CI, 61.4-76.6%) of PE, and maternal factors, MAP, PlGF, and UtA-PI detected 82.4% (95% CI, 76.1-88.7%) of PE.

The main limitations of the two studies was the fact that it was funded by FMF which can be considered biased. However, FMF is not benefiting financially from their screening tool as it is offered free for any health care provider via their website. One of the limitations of the study conducted by O'Gorman et al[5] was the wide confidence intervals. This is due to the small number of patients who developed PE. However, O'Gorman et al[5] noted these values and the results were similar to the data collected in an earlier study[15] which included a larger population size of 35 948 participants. Other limitations of the O'Gorman et al study[5] included the lack of

blinding of the participants and their health care providers to the measurements and outcomes of the screening tools.

In general, the additional measurements to complete the FMF screening tool appears to be only require minimal additional training, equipment, time, and cost. However, no study has been conducted to assess these factors and the practicality of the additional measurements. It would be recommended to further study the potential cost to determine if it would be practical and beneficial to implement in the clinics. Also, it would be important to conduct studies that evaluate the early and accurate detection of high risk patients for PE using FMF algorithm would decrease morbidity and mortality in both mother and child.

CONCLUSION

The FMF algorithm which combines maternal factors with biophysical and biochemical markers, MAP, UtA-PI and PIGF is superior in screening for preeclampsia during weeks 11-13 gestation compared to the standard NICE guidelines. Based on current low to very low evidence available more studies are warranted. However FMF algorithm is a promising approach to screening for preeclampsia. Further study, assess the financial implication of implementing this algorithm into clinical practice is also necessary.

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Table 1: Quality Assessment of Reviewed Articles

Study	Design	Downgrade Criteria					Quality
		Limitations	Indirectness	Inconsistency	Imprecision	Publication bias	
O'Gorman et al[5]	Prospective Cohort	Not Serious[a]	Not Serious	Not Serious	Serious	Likely[b]	Very Low
Tan et al[7]	Prospective Cohort	Not Serious[a,c]	Not Serious	Not Serious	Serious	Likely[b]	Very Low

[a] Both studies had large sample sizes
[b] Both studies were funded by FMF and other agencies
[c] Lack of blinding

Table 2 Summary of Study Findings

O'Gorman et al[5]			
Outcome	NICE (n=8775)	FMF (n=8775)	ACOG (n=8775)
DR of PE < 32 weeks of delivery	41% (95% CI, 27-53)	100% (95% CI, 80-100)	94% (95% CI, 71-100%
DR of PE < 37 weeks of delivery	39% (95% CI, 27-53)	75% (95% CI, 62-85)	90% (95% CI, 79-96%
DR of PE $\geq$ 37 weeks of delivery	34% (95% CI, 27-41)	43% (95% CI, 35-50)	89% (95% CI, 84-94%)
FPR	10.2%	10%	64.2%

Tan et al[7]		
Outcome	NICE (n= 16747)	Baye Theorem Based Method (n=16747)
DR for all PE	30.4% (95% CI, 26.3-34.6)	42.5% (95% CI, 38.0-46.9)
DR for preterm PE	40.8% (95% CI, 32.8-48.9)	82.4% (95% CI, 76.1-88.7%)