Prediction of Pre-Eclampsia in Advanced-Age Pregnant Women by use of a Uterine Artery Doppler Combination with Maternal Serum fms-like Tyrosine Kinase (sflt-1), Placental Growth Factor (PlGF) and Pregnancy-Associated Plasma Protein-A (PAPP-A)

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Objective: To study the efficacy of using Doppler ultrasound to measure blood flow within the uterine artery through the determination of soluble fms-like tyrosine kinase-1 (sflt-1) levels, placenta growth factor (PlGF), and pregnancy-associated plasma protein-A (PAPP-A) in the plasma to predict the risk of preeclampsia in pregnant women over 35 years old at high risk of developing this condition.

Materials and Methods: Data were collected from pregnant women aged over 35 years who attended the antenatal clinic at the Department of Obstetrics and Gynecology, Thammasat University Hospital at gestational ages of 8 to 20 weeks. The patient information included age, parity, gestational age, past pregnancy history and the risk factors of preeclampsia development. All the participants had measured plasma levels of sflt-1, PlGF, and PAPP-A, followed by assessment through the ultrasound Doppler examination.

Results: Of a total of 296 participants, only 276 pregnant women were able to be tracked with enough data for analysis. There were 15 cases (5.43%) of pregnant women with preeclampsia, while the remaining 261 cases (94.57%) showed no complications of preeclampsia. In a comparison of average age, weight, body-mass index, parity and risk of preeclampsia history in the two groups, no statistically significant differences were found. There were also no statistically significant differences in gestational age at delivery or the birth weight of newborns. The ratio of blood-flow abnormalities in the uterine arteries of pregnant women who had preeclampsia was 26.67% (4/15 cases), which was higher than in the group that had no preeclampsia; the ratio for this latter group was found to be 16.48% (43/261 cases). However, there was no significant difference between the two groups ($p = 0.31$). The average ratio of sflt-1 to PlGF was higher in the pregnancies with preeclampsia, but there were no statistically significant differences (8.60±4.79, 8.09±5.24, $p = 0.71$). The multiple of median (MoM) of PAPP-A in pregnant women with preeclampsia was less than in those without preeclampsia, but no statistically significant differences were found. When all three factors were evaluated and appraised in statistical form for the prediction of preeclampsia, it was found that abnormalities of uterine artery blood flow increased the risk of preeclampsia by a factor of 1.78. A sflt-1-to-PlGF ratio greater than 14 increased the risk of preeclampsia by a factor of 2.54 and a PAPP-A less than 0.5 MoM increased the risk of preeclampsia by a factor of 2.5, respectively, while the prediction of total preeclampsia from all three factors was 64.62%.

Conclusion: In pregnant women over 35 years of age with these factors, there was a greater chance of preeclampsia. However, the combination of factors in predicting the likelihood of preeclampsia was not significant enough and was not worthwhile for use in clinical practice in this high-risk group.

Keywords: Preeclampsia, Prediction, sflt-1, PlGF, PAPP-A

Two to five percent of pregnancies are reported to have the occurrences of preeclampsia or pregnancy-induced hypertension. It is one of the leading causes of death and disability of both mother and newborn by causing many of the obstetric complications that have been known to occur, such as intrauterine growth restriction, stillbirth, and placental abruption. From the available medical evidence, there are indications that the cause of preeclampsia is probably the result of abnormal placental development in the trophoblast portion of the blastocyst. The pathogenesis involves an abnormality in trophoblastic cell division and the invasion of

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trophoblastic cells into the mother's uterine spiral arteries and includes an imbalance of antiangiogenic and angiogenic factors causing placenta cells to become ischemia and eventually suffer deterioration. Those determinants result in increased vascular resistance in the circulatory system between the mother and fetus[1].

Currently, there is no effective method to prevent the occurrence of preeclampsia. Therefore, there is much consideration being devoted to the search for risks of preeclampsia in pregnant women to enable detection of the disease in its initial stages so that the effects on the mother and fetus will not be severe, and to plan for treatment in a minimum amount of time. Nowadays, there are several preeclampsia screenings, such as history-related risks of disease, Doppler ultrasound of the uterine artery and the measurement of serum-plasma levels markers, which include many types of markers[2]. Doppler ultrasound is a very popular method for evaluating the circulatory system of mother and fetus. Because of its low-cost and absence of adverse effects, the uterine artery examination has been widely studied. The previous studies found that it can predict the occurrence of high blood pressure during pregnancy[3]. There are many serum plasma markers associated with preeclampsia, such as placental protein-13 (PP-13), A disintegrin and metalloprotease 12 (ADAM-12), pregnancy-associated plasma protein-A (PAPP-A) and soluble fms-like tyrosine kinase 1 (sflt-1)[4,5].

The evaluation of high blood-vessel resistance by the Doppler ultrasound is performed by measuring the pulsatility index (PI; peak systolic flow-end-diastolic flow divided by mean flow), resistant index (RI; peak systolic flow-end diastolic flow divided by peak systolic flow) and early diastolic notching detection. In addition, the imbalance of angiogenic proteins includes pro-angiogenic factors, vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), which correlate with blood-vessel formation and development. All of these are found to be lower when the pregnancy is complicated with preeclampsia. On the other hand, a substance that inhibits angiogenesis, including sflt-1, increases with hypoxia or ischemia. Trophoblast placental proteins such as PP-13 and PAPP-A contribute to the development of the placenta through the mechanisms of IGF1 and IGF2. In a normal pregnancy, these proteins are high in their content throughout pregnancy, but it was found that PP-13 and PAPP-A were at lower levels in pregnant women with preeclampsia. This abnormality can be detected from the first trimester of a pregnancy prior to the onset of symptoms of preeclampsia[6].

The assumed causes of preeclampsia have led to the practice of screening by the use of serum-plasma markers as a term of prediction for the occurrences of this condition. In a woman who is at risk of preeclampsia, the sflt-1 tend to be at a higher level, contrary to the trend of the PlGF, which tends to be at a lower level in serum plasma. These serum-plasma markers can occur before the appearance of preeclampsia symptoms. Nevertheless, with regard to the current information, there is still some debate and no clear conclusion about the best indicator to be used in predicting the appearance of preeclampsia symptoms. Accordingly, the research team has focused its attention on studying the new preeclampsia-screening tool. The tool would be used in combination with a Doppler ultrasound of the uterine artery, together with measurements of serum-plasma levels of sflt-1, PlGF, and PAPP-A in pregnant women who are at risk of preeclampsia. There are no previous studies being conducted by combining predictors among patients at risk of preeclampsia. Therefore, this knowledge may provide new information for utilization in clinical applications of the future.

Objective

To study the efficacy of using Doppler ultrasound for uterine artery blood flow measurement combined with plasma sflt-1, PlGF and PAPP-A levels in plasma to predict the risk of preeclampsia in pregnant women over 35 years of age.

Materials and Methods

This prospective study was approved by the Ethics Committee, Faculty of Medicine, Thammasat University, and MTU-EC-OB-4-079/58. The present study was conducted at the antenatal care clinic of Thammasat University Hospital. Two hundred and ninety-seven Thai pregnant women were recruited. The study period took place from July 2015 to June 2016. The participants were Thai pregnant women above 35 years of age as determined by their estimated dates of confinement. They came to the antenatal clinic by appointment with the intention of delivering at the Thammasat University Hospital. Inclusion criteria were singleton pregnancies, with gestational ages of 8 to 20 weeks. The exclusion criteria were pregnant women who had renal disease, chronic hypertension or autoimmune disease.

The participants who were enrolled in the present study were advised to recognize certain recommendations and detailed explanations essential to the research program. Those who agreed to sign the consent form were allowed to participate in the project.

The demographic characteristic data collected included age, gestation number, gestational age, previous obstetrics history and factors identified as high risk for preeclampsia. Included among these factors was a history of hypertension, especially when accompanied by an adverse outcome such as chronic hypertension, type 1 or 2 diabetes, renal disease, autoimmune disease, obesity (body mass index greater than 30), family history of preeclampsia and previous adverse pregnancy outcomes.

Gestational age was identified by the last menstrual period and was then confirmed by ultrasound biometry measurement. After gestational age was confirmed and the fetal anomaly was scanned, uterine arteries Doppler waveforms were obtained using the Voluson E8 Expert ultrasound machine at 3.5 or 5 MHz. A transducer was placed on the left and right lower quadrants of the maternal abdominal wall to identify the external iliac arteries and the uterine

artery medial to it, and flow-velocity waveforms were then obtained from each uterine artery near to the external iliac artery before division into branches. Recordings were performed in the absence of fetal breathing or movement. Uterine artery PI, RI, systolic/diastolic ratio (SD ratio) and diastolic notch of the uterine artery were recorded.

A five-milliliter blood collection was drawn from the participants for serum levels of soluble tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A) results.

The criteria for diagnosis of preeclampsia are the first episode of blood pressure higher than 140/90 mmHg after 20 weeks of gestation in previously normotensive women plus proteinuria ($\geq$300 mg/24 hours, or protein/creatinine ratio of 0.3 mg/dL or more) or thrombocytopenia (platelet count <100,000/µl), renal deficiency (creatinine level >1.1 mg/dl, or doubling of baseline), liver involvement (serum transaminase level twice normal) and cerebral symptoms (headache, visual disturbances, and convulsions)[1].

Statistical analysis was performed using Stata, version 14 (Stata Corp LLC, College Station, Texas). Continuous variables were expressed as means and standard deviations. Category variables were analyzed either by Chi-square or Fisher's exact test with the appropriate condition (depending on the satisfied condition). A receiver operating characteristic curve (ROC) curve was used for the prediction of disease by a discrimination threshold of the combination tests.

Results

A total of 276 pregnant women who attended the antenatal care clinic at Thammasat University Hospital from July 2015 to June 2016 were enrolled in the present study.

Of these, 15 pregnant women were diagnosed with preeclampsia, and 261 were found to have no preeclampsia. The incidence of preeclampsia was 5.43 percent. As shown in Table 1, demographic data of the two groups revealed no significant differences in baseline clinical characteristics.

The rates of abnormalities found by Doppler flow measurement of the uterine artery between the two groups were not significantly different. However, Doppler measurements of the uterine artery in pregnant women with preeclampsia demonstrated an abnormal waveform that was higher than in pregnant women without preeclampsia (26.67% and 16.48%, respectively: $p = 0.31$).

The average ratio of sflt-1 to PlGF in pregnant women with preeclampsia was higher than in those without preeclampsia, but with no significant difference (8.60$\pm$4.79 vs. 8.09$\pm$5.2, respectively: $p = 0.71$), as shown in Table 2.

Mean PAPP-A among pregnant women with preeclampsia was lower than in pregnant women without preeclampsia, as shown in Figure 1. Multiple of the median (MoM) was applied to adjust the data in a more appropriate form. It is found that PAPP-A (MoM) of pregnant women with preeclampsia was less than in pregnant women without preeclampsia, but with no statistically significant differences, as shown in Table 2. The MoM values of PAPP-A were used to create a prenatal prediction graph, as shown in Figure 1.

Risk factors for prediction of preeclampsia were analyzed by multivariate logistic regression analysis. The data showed that the abnormalities in the blood flow of uterine arteries increased the risk of preeclampsia by a factor of 1.78. A ratio of sflt-1-to-PlGF greater than 14 increases the risk of preeclampsia by a factor of 2.58, while a MOM of

Table 1. Comparing baseline characteristics of patients between pregnant women with preeclampsia and women without preeclampsia
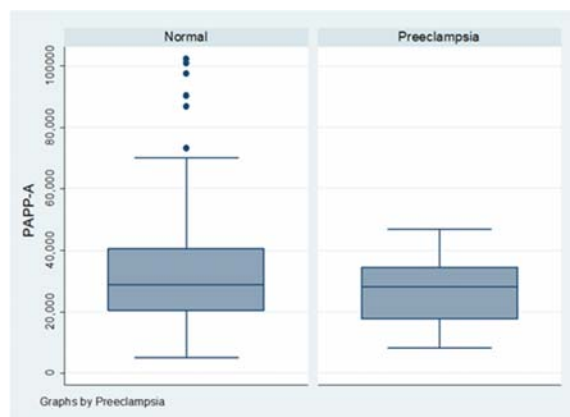
	Pregnant women with preeclampsia (n = 15)	Pregnant women without preeclampsia (n = 261)	p-value
Age (years)	38.00$\pm$0.79	37.13$\pm$0.15	0.29
Bodyweight (kg)	63.69$\pm$10.87	60.95$\pm$10.90	0.36
Height (cm)	159.80$\pm$5.43	158.14$\pm$5.76	0.27
Body mass index (kg/m^2)	24.89$\pm$3.78	24.25$\pm$4.29	0.54
GA at first ANC (weeks)	10.33$\pm$3.11	9.83$\pm$3.45	0.58
Parity			0.24
0	6 (40%)	90 (34.48%)	
1	7 (46.67%)	132 (50.57%)	
2	2 (13.33%)	29 (11.11%)	
3	0 (0%)	10 (3.83%)	
History of high blood pressure	0	1 (0.38%)	0.81
Smoking	0	0	-
Family history of high blood pressure	2 (13.33%)	74 (28.35%)	0.21
Calcium used	12 (80.00%)	215 (83.01)	0.76
GA at getting blood sample	18.20$\pm$1.32	18.14$\pm$1.16	0.87
GA at delivery	37.80$\pm$1.52	38.87$\pm$1.25	0.84
Newborn birthweight (gm)	3,224.67$\pm$681.38	3,076.88$\pm$435.19	0.42

Number are mean $\pm$ SD, or n (%)

Table 2. Comparison of women with preeclampsia with women without preeclampsia using Doppler ultrasound of uterine artery in conjunction with maternal serum

	Pregnant women with preeclampsia (n = 15)	Pregnant women without preeclampsia (n = 261)	p-value
Abnormal blood flow of the uterine artery	4 (26.67)	43 (16.48)	0.31
PAPP-A (mIU/ml)	26,365.07±11,618.68	31,973.87±16,685.88	0.11
PAPP-A MoM	0.61, 1.18	0.70, 1.40	0.28
Sflt-1 mIU/mL	225.37±122.48	266.92±137.13	0.24
PlGF mIU/mL	1,470.79±465.29	1,788.70±835.95	0.15
Sflt-1/PlGF	8.60±4.79	8.09±5.24	0.71

PAPP-A = pregnancy-associated plasma protein-A, MoM = multiple of the median report as the interquartile range, sflt-1 = soluble fms-like tyrosine kinase-1, PlGF = Placenta growth factor

Figure 1. Demonstration of the distribution of PAPP-A levels in a comparison between pregnant women with preeclampsia and pregnant women without preeclampsia.

PAPP-A less than 0.5 increases the risk of preeclampsia by a factor of 2.5 (Table 3). However, the increased risk of these three factors has not demonstrated a statistical significance. The prediction of preeclampsia of all three factors was found to be 64.62 percent, as shown in Figure 2.

Discussion

The present study found that the incidence of preeclampsia in singleton pregnant women who are older than 35 years was 5.43%. This number is close to the average worldwide incidence reported by the World Health Organization, which had a reported incidence of around 2 to 5%[7]. The data demonstrated that the occurrence of preeclampsia among the studied pregnant women was likely to occur during the near-term gestational age. The average gestational age was 37 weeks and most of the cases were of the non-severe type.

An age of more than 35 years of pregnant women is a significant risk factor in incidences of preeclampsia. The researchers were particularly interested in conducting a study of this group because pregnant women over the age of 35 would be screened and diagnosed for Down's syndrome. Currently, the use of the serum cell-free DNA test as the screening tool is widely accepted. Therefore, if the predictions of occurrences of preeclampsia are truly reliable, these screening tools could be used in combined tests together at the same time to increase the value of the examination and reduce duplication of blood collection.

When comparing the measurement of the Doppler uterine artery between pregnant women with preeclampsia and normal pregnant women, there was a tendency toward higher abnormalities of the Doppler uterine artery, but the difference was not statistically significant. These findings are the same as in the report from Pongrojpaw et al[8]. Their study reported the detection of abnormalities in the uterine artery Doppler. Further, their study showed a PI greater than 1.58 or a diastolic notching with a high sensitivity of 59.25 to 81.48 percent, in their predictions of preeclampsia. However, the ability to predict when the test results would be positive (positive predictive value) was only 12.42 to 13.67 percent. Also, this outcome was consistent with the systematic review and bivariable meta-analysis designed study of Cnossen et al[9], which reported that the findings of Doppler uterine artery abnormalities, such as a higher PI or the detection of diastolic notching in pregnant women who are at risk of developing preeclampsia, have a predictive capability of approximately 2.2 times (positive likelihood ratio = 2.2). This ratio is consistent with our study, which found that such factors as vascular circulatory disorders increase the risk of preeclampsia by a factor of 1.78. However, the significant limitation of the Doppler artery-uterine examination arose from variations and discrepancies between the examining persons and the interpretation of results that were mainly positive or negative, depending on the opinions of the inspectors.

The present study evaluated the use of pregnancy-associated plasma protein-A (PAPP-A) in predicting preeclampsia, which was examined during the second trimester of pregnancy. It was found that the levels of PAPP-A were lower in pregnant women with preeclampsia as compared to levels in normal pregnant women, although there was no statistically significant difference. This finding is consistent with the report from Monte el al[10] that PAPP-A

Table 3. Prediction of preeclampsia calculated as risk ratio by use of multivariate logistic regression analysis model

	Risk ratio to preeclampsia	95% CI	*p*-value
Abnormalities of Doppler flow measurement of uterine artery	1.78	0.53 to 5.97	0.35
Ratio of sflt-1 to PlGF >14	2.58	0.76 to 8.72	0.13
MoM of PAPP-A <0.5	2.50	0.65 to 9. 65	0.18

CI = confidence interval
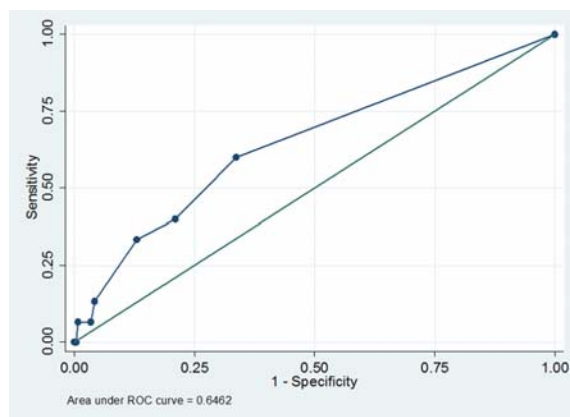
Figure 2. Graph of the prediction of preeclampsia, as calculated from the abnormalities of blood flow of uterine arteries, with a ratio of sflt-1-to-PlGF above 14 and a MOM of PAPP-A below 0.5.

levels are lower every trimester in pregnant women with preeclampsia. Also, Saxena et al[11] reported the use of PAPP-A levels in the first trimester to predict preeclampsia. The levels of PAPP-A and PAPP-A MOM are relatively low in the group of pregnant women with preeclampsia with significantly lower levels, and a lower PAPP-A MOM in the first trimester indicates a 5-times statistically significant higher chance of being pregnant with preeclampsia. Therefore, in several studies with results in the same direction as the results of the present study, a PAPP-A MOM value less than 0.5 indicated a trend in the chances of becoming pregnant with preeclampsia of up to 2.5 times higher.

When comparing the ratio of sflt-1-to-PlGF among pregnant women with preeclampsia, it was found that the average ratio was higher than in pregnant women without preeclampsia. This result was the same as that of the previous study of Vivo et al[12], which reported the use of sflt-1-to-PlGF ratios at 38.47 in their predictions of preeclampsia. This ratio indicated a sensitivity of 88.5 percent. Likewise, reports from Zeisler el al[13] indicated that the use of the cut-off level of the sflt-1-to-PlGF ratio at 38 or lower can predict the chance of not contracting preeclampsia within two weeks. Through the use of this value, it is possible to predict a negative predictive value of up to 99.3%. In the present

study, the selected cut-point ratio at 14 is used, because it gives a specificity of 88.37%, which is high enough to differentiate normally pregnant women from those women who become diseased. At this point, a negative predictive value (NPV) at 95.10 percent (confidence interval 93.76-96.17) and positive predictive value (PPV) at 9.68 percent (confidence interval 3.54 to 23.8) have been established. One of the explanations of low PPV values was the low incidence of the disease in our studied population.

Previous studies[14-16] have reported the use of the sFlt-1-to-PlGF ratio to predict disease incidence. The value of prediction was a reliable result only in the high-risk groups but was still not satisfactory in low-risk groups. In this study, we have added the level of PAPP-A into the combination. After adjustment for multivariate analysis and creation of a predictive model to forecast the occurrence of preeclampsia, the ability of the combination test in detecting the abnormalities of the uterine artery Doppler was combined with the PAPP-A MOM and sflt-1-to-PlGF ratio in the second quarter during the gestational age of 18 to 20 weeks in pregnant women aged over 35 years was at 64.62 percent, which is not yet high enough for application in clinical use, possibly because the studied population in our study had a low incidence of disease and the number of samples may not have been sufficient to show statistical results or significant implications. Moreover, in women at high risk who had histories of preeclampsia, there may have only been small amounts of this disease and too little for further analysis. However, the study has shown trends and possibilities in using these tests. They show promise for predicting incidences of preeclampsia and in identifying women who are at high risk for the disease. These tests can thus help prevent future occurrences of the disease.

Conclusion

Preeclampsia predictive tests that are designed to forecast possible occurrences of the disease constitute an important method for preventing or reducing the severity of the disease. Low-dose aspirin is currently accepted as an efficient preventive method, but the selected group of high-risk pregnant women is still controversial. Our study demonstrated the possibility for utilization of the combination test, in which the abnormalities of the uterine artery Doppler are combined with the PAPP-A MOM level and the sft-1-to-PlGF ratio in the second trimester in pregnant women aged over 35 years. The ultimate purpose of this combination

test is to predict possible occurrences of preeclampsia.

What is already known on this topic?

Like the previous study, pregnant women with age of more than 35 years are a significant risk factor in incidences of preeclampsia. Therefore, if the predictions of occurrences of preeclampsia are truly reliable, these screening tools could be used in combined tests together at the same time to increase the value of the examination. When comparing the measurement of the Doppler uterine there was a tendency toward higher abnormalities of the Doppler uterine artery, but the difference was not statistically significant. It was found that the levels of PAPP-A were lower in pregnant women with preeclampsia as compared to levels in normal pregnant women, although there was no statistically significant difference. When comparing the ratio of sflt-1-to-PlGF among pregnant women with preeclampsia, it was found that the average ratio was higher than in pregnant women without preeclampsia. The value of prediction was a reliable result only in the high-risk groups, but was still not satisfactory in low-risk groups.

What this study adds?

In the present study, the authors have combined the uterine artery Doppler and the sflt-1-to-PlGF ratio including the level of PAPP-A into the combination for the creation of a predictive model to forecast the occurrence of preeclampsia in pregnant women aged over 35 years was at 64.62 percent, which is not yet high enough for application in clinical use. It is possible because the studied population in the present study had a low incidence of disease.

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Potential conflicts of interests

The authors declare no conflict of interest.

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การทำนายการเกิดภาวะครรภ์เป็นพิษในกลุ่มสตรีตั้งครรภ์อายุมากกว่า 35 ปี โดยการตรวจดอพเลอร์หลอดเลือดแดงยูเทอรีนร่วมกับการวัดระดับของ fms-like tyrosine kinase (sflt-1), placental growth factor (PlGF) และ pregnancy-associated plasma protein-A (PAPP-A)

นิพัทธา วินะยานุวัติคุณ, ต้องตา นันทโกมล, จรินทร์ทิพย์ สมประสิทธิ์, ชำนาญ แท่นประเสริฐกุล

วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพของการใช้ดอพเลอร์อัลตราซาวน์ ตรวจระบบไหลเวียนเลือดของหลอดเลือดแดงยูเทอรีนร่วมกับการตรวจวัดระดับของ sflt-1 (soluble fms-like tyrosine kinase-1) PlGF (Placenta growth factor) และPAPP-A (pregnancy-associated plasma protein A) ในพลาสมา เพื่อช่วยทำนายความเสี่ยงต่อการเกิดภาวะครรภ์เป็นพิษในกลุ่มสตรีตั้งครรภ์ที่มีความเสี่ยงสูงต่อการเกิดภาวะนี้ได้แก่ สตรีตั้งครรภ์อายุมากกว่า 35 ปี

วัสดุและวิธีการ: ทำการศึกษาโดยเก็บข้อมูลในสตรีตั้งครรภ์ที่มีอายุมากกว่า 35 ปีขึ้นไป ที่มาฝากครรภ์ที่แผนกสูตินรีเวช โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ ในช่วงอายุครรภ์ 8 ถึง 20 สัปดาห์ ทำการบันทึกข้อมูลพื้นฐานของผู้ป่วยได้แก่ อายุ จำนวนการตั้งครรภ์ อายุครรภ์ และประวัติการตั้งครรภ์ในอดีต ปัจจัยพื้นฐานของความเสี่ยงต่อการเกิดภาวะครรภ์เป็นพิษ และเก็บตัวอย่างเลือดเพื่อวัดระดับของ sflt-1, PlGF และ PAPP-A พร้อมส่งตรวจดอพเลอร์อัลตราซาวน์ เพื่อดูระบบไหลเวียนเลือดของหลอดเลือดแดงยูเทอรีนทั้งสองข้างและทำการบันทึกไว้ในแบบบันทึกข้อมูล ติดตามผลลัพธ์ของการตั้งครรภ์ และภาวะครรภ์เป็นพิษที่เกิดขึ้น นำข้อมูลมาวิเคราะห์ทางสถิติเพื่อหาโอกาสการทำนายการเกิดภาวะครรภ์เป็นพิษ

ผลการศึกษา: ในจำนวนสตรีที่เข้าร่วมการศึกษาจำนวนทั้งสิ้น 296 ราย สามารถติดตามและมีข้อมูลเพียงพอต่อการวิเคราะห์ 276 ราย โดยมีสตรีตั้งครรภ์ร้อยละ 5.43 หรือ 15 รายเกิดภาวะครรภ์เป็นพิษ และสตรีตั้งครรภ์ร้อยละ 94.57 หรือ จำนวน 261 ราย ไม่พบภาวะครรภ์เป็นพิษ เมื่อเปรียบเทียบ อายุเฉลี่ย น้ำหนัก ดัชนีมวลกาย จำนวนบุตร ประวัติความเสี่ยงต่อภาวะครรภ์เป็นพิษของทั้งสองกลุ่มพบว่า ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ โดยอายุครรภ์ที่วัดการไหลเวียนเลือดของหลอดเลือดแดงยูเทอรีน และอายุครรภ์ที่คลอด รวมทั้งน้ำหนักทารกแรกคลอด ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ในขณะที่อัตราส่วนความผิดปกติของการไหลเวียนเลือดของหลอดเลือดแดงยูเทอรีน ในกลุ่มสตรีตั้งครรภ์ที่เกิดภาวะครรภ์เป็นพิษพบร้อยละ 26.67 (4/15 ราย) สูงกว่าในกลุ่มสตรีตั้งครรภ์ที่ไม่เกิดภาวะครรภ์เป็นพิษซึ่งพบร้อยละ 16.48 (43/261 ราย) แต่ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ (*p* = 0.31) ค่าเฉลี่ยของอัตราส่วน sflt-1 ต่อ PlGF ในกลุ่มสตรีตั้งครรภ์ที่เกิดภาวะครรภ์เป็นพิษ สูงกว่า สตรีตั้งครรภ์ ที่ไม่เกิดภาวะครรภ์เป็นพิษ แต่ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ (8.60±4.79, 8.09±5.24, *p* = 0. 71) และค่า Multiple of median ของ PAPP-A ในกลุ่มสตรีตั้งครรภ์ที่เกิดภาวะครรภ์เป็นพิษ น้อยกว่ากลุ่มสตรีตั้งครรภ์ที่ไม่เกิดภาวะครรภ์เป็นพิษ แต่ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ

เมื่อนำปัจจัยทั้งสามมาคำนวณประเมินเข้ารูปแบบทางสถิติเพื่อการทำนายภาวะครรภ์เป็นพิษ พบว่าปัจจัยความผิดปกติของการไหลเวียนของหลอดเลือดยูเทอรีน เพิ่มโอกาสเสี่ยงที่จะเกิดภาวะครรภ์เป็นพิษ 1.78 เท่า ปัจจัยการมีอัตราส่วนของ sflt-1 ต่อ PlGF ที่มากกว่า 14 เพิ่มโอกาสเสี่ยงที่จะเกิดภาวะครรภ์เป็นพิษ 2.54 เท่า และปัจจัยการมีค่า MOM ของ PAPP-A น้อยกว่า 0.5 เพิ่มโอกาสเสี่ยงที่จะเกิดภาวะครรภ์เป็นพิษ 2.5 เท่าตามลำดับ โดยมีค่าการทำนายภาวะครรภ์เป็นพิษรวมของทั้งสามปัจจัยที่ร้อยละ 64.62

สรุป: ในสตรีตั้งครรภ์อายุมากกว่า 35 ปี ที่มีปัจจัยดังกล่าวพบว่าจะมีโอกาสการเกิดภาวะครรภ์เป็นพิษสูงขึ้น แต่การใช้ปัจจัยร่วมกันเพื่อทำนายโอกาสภาวะครรภ์เป็นพิษยังมีค่าการทำนายที่ไม่สูงเพียงพอและยังไม่คุ้มค่าที่จะนำมาใช้ในเวชปฏิบัติ