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PREDICTION OF PREECLAMPSIA USING PLACENTAL GROWTH FACTOR AS AN ADJUNCT MARKER AT (11-13) WEEK GESTATION IN A SAMPLE OF PREGNANT WOMEN IN IRAQ

***[1]Dr. Zubaida Adnan Abdullah and [2]Dr. Anne Khazal Yaseen**

[1]Babylon Health Directorate, Babylon, Iraq.
[2]Medical City, Baghdad, Iraq.

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***Corresponding Author: Dr. Zubaida Adnan Abdullah**

Babylon Health Directorate, Babylon, Iraq.

ABSTRACT

Introduction: Preeclampsia complicate ≤10% of pregnancies and it a major cause of maternal and perinatal morbidity and mortality. The aim of the study to evaluate the use of placental angiogenic marker (PlGF) as early predictor of preeclampsia and its related adverse outcome. **Methods:** Fifty-four lady between 11th and 13th week of their gestation attending their antenatal complicated pregnancies involving Rh isoimmunization, thyroid dysfunction, connective tissue disorders, liver or kidney diseases and chronic hypertension were excluded. All women were informed about the nature of the study, and all who agreed to participate provided verbal informed consent. The study was approved by the Ethics Committee of the institution. **Results:** Of the enrolled and followed 54 subjects, 5 (9%) women contracted PE, including 3 delivered before 37 weeks (preterm labor). Apart from body mass index (BMI) and mean arterial pressure (MAP), other risk factors such as advance maternal age, parity, diabetes mellitus and conception method were not found to have a significant association with the occurrence of PE. Receiver operating characteristic curve (ROC) analysis showed PlGF cutoff point of 79.85pg/dl (area under the curve (AUC) = 0.798; P ≤ 0.029) had the maximum sensitivity and specificity of (80%) for PE prediction. 80% of patients who develop PE have low PlGF. **Conclusion**: Maternal serum PlGF between 11th and 13th week gestation can be used together with other maternal characteristic (MAP and BMI) as early predictor of PE and PE adverse outcome to identify fetuses requiring increased surveillance and possibly urgent delivery.

KEYWORDS: Preeclampsia, placental growth factor, an adjunct marker, (11-13) week gestation, pregnant women.

INTRODUCTION

Hypertensive disorders of pregnancy (HDPs) are a common complication of pregnancy that put women and their fetuses at disproportionate risk for further complications, as well as life-long sequelae.[1] The major hypertensive disorders that occur in pregnant patients as identified by The American College of Obstetricians and Gynecologists (ACOG).[2] Hypertensive disorders of pregnancy, including preeclampsia and eclampsia (PE/E), are the second leading cause of maternal death in women under age 35. Mortality related to PE/E can be prevented with swift diagnosis, effective management, and timely delivery. However, evidence-based interventions are sparsely implemented in many low- and middle-income country settings, leading to poor outcomes for both mothers and neonates.[3,4] Preeclampsia is a pregnancy-specific multisystem disorder4 and continues to be a major cause of both maternal-fetal morbidity and mortality, with reported incidences in the range of 2%–18%. Early identification of women at high risk of developing such disorders could help physicians to provide appropriate care.[5] Depending on time, the condition is classified as early-onset preeclampsia (EOP) (placental), which requires delivery before 34 weeks' gestation, or late-onset preeclampsia (LOP) (maternal), with delivery at or after 34 weeks or later. Although the diagnostic criteria for EOP and LOP are the same, there are some uncertainties about the maternal and fetal outcomes. It is thought that EOP poses a high risk to both mother and fetus, whereas LOP may present with less severe clinical symptoms.[6] The management of PE depends on the gestation at onset, the severity—both maternal and fetal—and the rate of progression.[7] However, the ultimate treatment of PE is

removal of the offending organ—the placenta. This is why PE remains a leading cause of prematurity because delivery of the placenta requires, of course, delivery of the fetus. Timing delivery is then a balance between the interests of the mother and the interests of the fetus. The interests of the woman with preeclampsia are always best served by delivery. Delivery prevents worsening hypertension and thereby avoids related complications including stroke, liver failure and kidney failure. However, early delivery may not best serve the baby, particularly if very preterm. Beyond neonatal demise, preterm delivery is a risk factor for a host of conditions that will affect a baby well into their adult life, including cerebral palsy, visual and hearing problems, respiratory difficulties, cardiovascular compromise, renal impairment, and learning and behavioral problems.[8] Even late preterm delivery (<37 weeks) increases the risk of lifelong cardiovascular and renal complications.[9] The aim of study is to evaluate the use of placental angiogenic marker placental growth factor as an early predictor of PE and PE-related adverse outcome.

METHOD

Cross sectional follows up study had been performed between September 1st 2020, and April 1st, 2021, which included pregnant women who attending their first antenatal visit with singleton pregnancy at Baghdad Teaching Hospital / Gynecology and Obstetrical Department and a private clinic at Babil Governmet, Al-Kifil. Fifty-four pregnant women at their 11th -13th week of pregnancy were recruited. However, Complicated pregnancies involving Rh isoimmunization, thyroid dysfunction or collagen, liver or kidney diseases were excluded. After obtaining verbal consent an accurate interview with each participant was conducted during their antenatal visit. The following data were recorded: age, parity, smoking during pregnancy, type of conception (spontaneous or assisted), family history (including pre-eclampsia affecting mothers), hypertension before pregnancy, diabetes mellitus, pre-eclampsia in a previous pregnancy, systemic diseases, kidney disorders or antiphospholipid syndrome. Ultrasound scanning was performed by one expert (Radiologist) to reduce inter-observer variation using the Philips Ultrasound to confirm the gestational age by measuring crown – rump length (CRL). Blood pressure measurement was done using standard mercury sphygmomanometer with an appropriately sized cuff and stethoscope with the subject in a seated position with arm kept on table so that arm and heart were nearly at the same level. After resting for 1 to 2 min, blood pressure was measured in both arms, and a series of recordings were made at 5-min intervals for two times [10]. Height (m2) and body weight (Kg) were recorded for calculation of body mass index (BMI). The measuring tape was used to measure height in centimeter, which was converted to meter square and weight in kg measured by digital scale, according to recommendations of SI unit.[11] A five milliliters of Maternal peripheral venous blood were aspirated from the median cubital vein to measure serum PlGF of each participant. The syringe samples were pulled into a clean disposable gel tubes and allowed to clot at room temperature for 30 minutes before separation of serum by centrifugation at 1000×g for 15 minutes. Separated serum then stored at ≤ -20 °C according to manufacturer's instruction. Pregnancy outcome was collected from gynecologist and radiologist of involved women. Based on the definition from ACOG, PE was characterized by 'development of hypertension of 140/90mmHg or more, with proteinuria ≥300 mg/24 h after the 20th week of gestation in a previously normotensive and non-proteinuria patient [1]. The enzyme linked immunosorbent assay (ELISA) is an immunological assay commonly used to measure **antibodies, antigens, proteins** and **glycoproteins** in biological samples. ELISA assays are generally carried out in 96 well plates, allowing multiple samples to be measured in a single experiment. These plates need to be special absorbent plates to ensure the antibody or antigen sticks to the surface. Each ELISA measures a specific antigen, and kits for a variety of antigens are widely available. Statistical analysis was performed with SPSS 22 (Statistical package for social sciences) and also Excel 2010 programs. Data analysis was done using chi-square test and Fisher's exact test for categorical, also calculate frequencies, percentages, ranges, means standard deviation and standard errors of mean. ROC curve used to assessment the more sensitive and specific cutoff point of PLGF. Values were considered statistically significant when p-value is equal or less than 0.05.

RESULTS

Cross sectional study of 54 patients, the age range of participant was 18-40 years, mean and SD of maternal age (26.1± 6), age mean and SD of gestational age (87.7 ± 5.2) days. Mean and SD of CRL (63.9 ± 11.5) mm. Mean and SD of weight of pregnant women (73 ± 15.8) Kg. Mean and SD of height (161.5 ± 5.3) cm. Mean and SD of BMI (28 ± 6.1) Kg/m2. Mean and SD of MAP (96.8 ± 10.5), Mean and SD of PLGF (92 ± 15) pg/ml.

Table (1): baseline characteristics of the studied participants.

Characteristic	Range	Mean	SD
Maternal age (years)	18 - 40	26.1	6
Gestational age (days)	78 - 92	87.7	5.2
CRL (mm)	45 - 75	63.9	11.5
Maternal weight (kg)	50 – 114.5	73	15.8
Maternal height (cm)	152 - 173	161.5	5.3
BMI	20 - 43	28	6.1
MAP (mmHg)	72.08 – 130.5	96.8	10.5
PlGF (pg/dl)	67.5 – 128.7	92	15

According to table (2) there is (98%) of patients have no D.M., (100%) of patients are not smoking, (94%) of patients with spontaneous conception method, (100%) of patients with no family history of PE, (80%) of patients are parous with no previous PE, (69%) of patients at age less than 35 years old, (2%) of patients end with complication of emergency cesarean section at 35 weeks, and at 36 weeks and intrauterine death at 31 weeks respectively.

Table (2): frequency and percentage of variables.

D.M	frequency	percentage
No	**53**	**98**
yes	**1**	**2**
smoking		
No	**54**	**100.0**
Conception method		
Ovulation drugs	**3**	**6**
Spontaneous	**51**	**94**
Patient mother had PE		
No	**54**	**100.0**
Parity		
Nulliparous	**11**	**20**
Parous no previous PE	**43**	**80**
age		
< 35 years	**37**	**69**
≥ 35 years	**17**	**31**
complication		
emergency c/s at 35	**1**	**2**
emergency c/s at 36	**1**	**2**
IUD at 31	**1**	**2**
no	**51**	**94**

According to fig (1, 2 and 3) (9%) of patients with preeclampsia as outcome and (91%) of them with no PE, (43%) of patients with optimal MAP and (17%) of patients with high grade 1 and (4%) of patients with high grade 2. (30%) of patients are obese while (33%) of them are overweight.

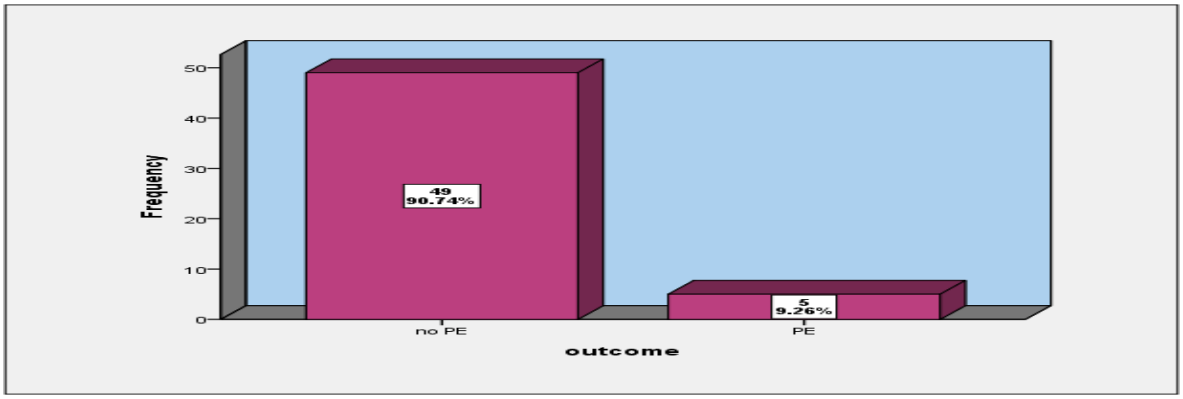

Fig. (1): distribution of patients according to outcome.

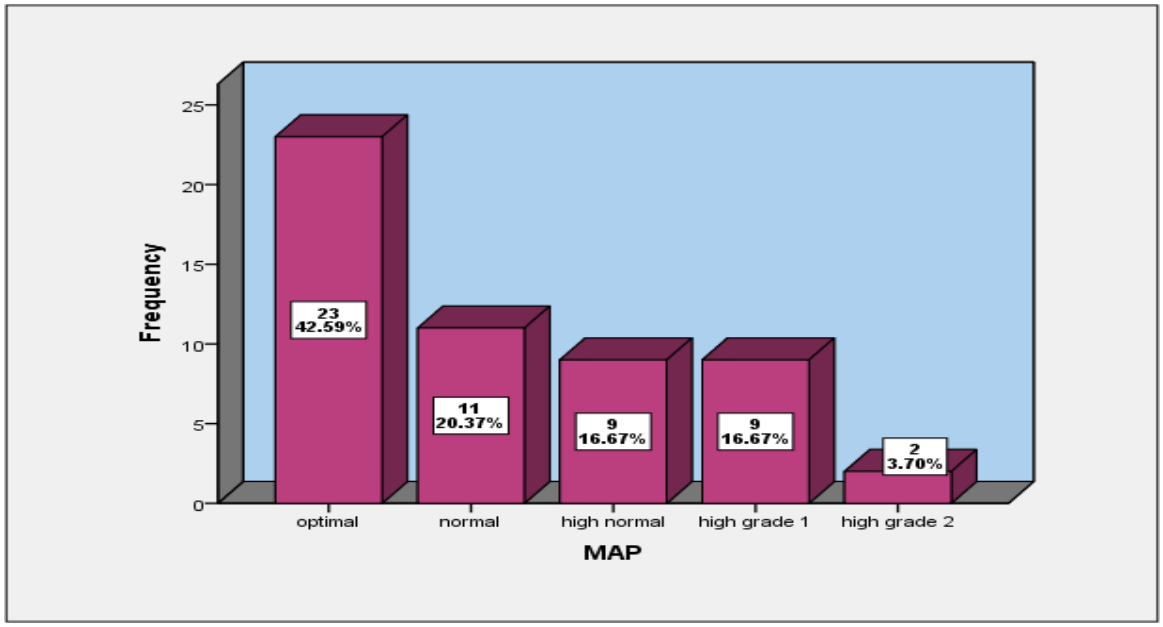

Fig. (2): distribution of patients according to MAP.

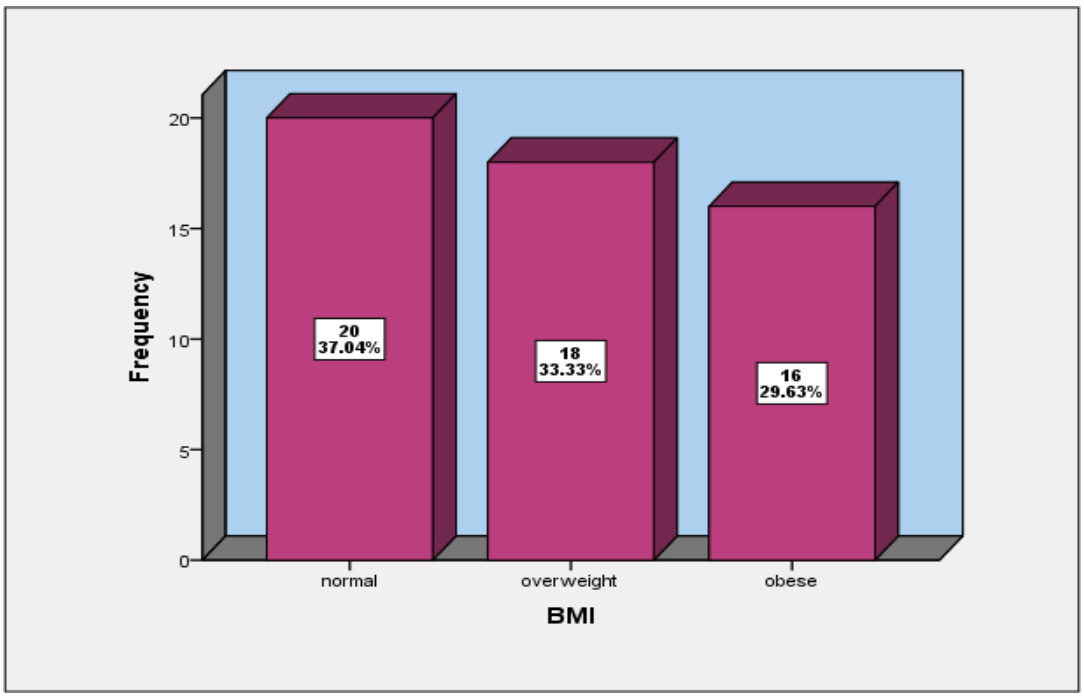

Fig. (3): distribution of patients according to BMI.

There is significant association between outcome and complication, (100%) of patients have emergency cesarean section at 35 weeks, and 36 week and intrauterine death at 31-week associate with outcome PE respectively. In addition, there significant association between gestational outcome and BMI, (25%) of patients have with obesity associate with outcome PE. Further that there is significant association between gestational outcome and MAP, (100%) of patients with high-grade (2) MAP associate outcome PE.

There is no significant association between gestational outcome and (D.M, Conception method, parity and age of mother). As in table 3.

Table (3): Distribution of gestational outcome and (D.M, Conception method, parity, complication, age of mother, BMI and MAP).

variables		Outcome		P-value
		No PE	PE	
D.M	No	48	5	1.00
	%	90.6%	9.4%	
	Yes	1	0	
	%	100.0%	0.0%	
	total	49	5	
	%	90.7%	9.3%	
Conception method	Ovulation drugs	3	0	1.00
	%	100.0%	0.0%	
	Spontaneous	46	5	
	%	90.2%	9.8%	
	Total	49	5	
	%	90.7%	9.3%	
Parity	Nulliparous	10	1	1.00
	%	90.9%	9.1%	
	Parous no previous PE	39	4	
	%	90.7%	9.3%	
	Total	49	5	
	%	90.7%	9.3%	
complication	emergency c/s at 35	0	1	0.0001
	%	0.0%	100.0%	
	emergency c/s at 36	0	1	
	%	0.0%	100.0%	
	IUD at 31	0	1	
	%	0.0%	100.0%	
	no PE	49	2	
	%	96.1%	3.9%	
	Total	49	5	
	%	90.7%	9.3%	
Age	< 35 years	34	3	0.65
	%	91.9%	8.1%	
	≥ 35 years	15	2	
	%	88.2%	11.8%	
	Total	49	5	
	%	90.7%	9.3%	
BMI	normal	19	1	0.03
	%	95.0%	5.0%	
	overweight	18	0	
	%	100.0%	0.0%	
	obese	12	4	
	%	75.0%	25.0%	
	Total	49	5	
	%	90.7%	9.3%	
MAP	optimal	23	0	0.0001
	%	100.0%	0.0%	
	normal	11	0	
	%	100.0%	0.0%	
	high normal	8	1	
	%	88.9%	11.1%	
	high grade 1	7	2	
	%	77.8%	22.2%	
	high grade 2	0	2	
	%	0.0%	100.0%	
	Total	49	5	
	%	90.7%	9.3%	

According to fig (4), significant ROC curve for sensitivity and specificity of PLGF cutoff points according to outcome, show (78.85pg/dl) is more sensitive and specific cutoff point with area under curve (0.798).

AUD= 0.798, 0.029 (significant).

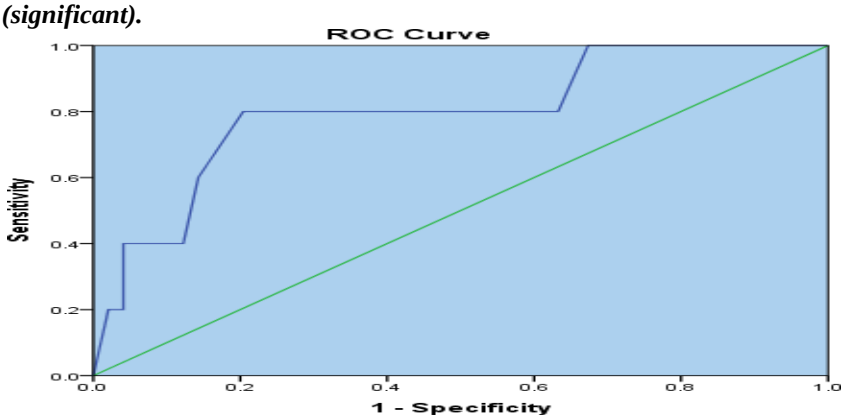

Fig. (4): ROC curve for sensitivity and specificity of PLGF cutoff points according to outcome.

According to fig (5), the distribution of patients according to PLGF show (74.07%) of patients with PLGF more than (79.85pg/dl) and (25.93%) of patients with PLGF equal or less (79.85pg/dl).

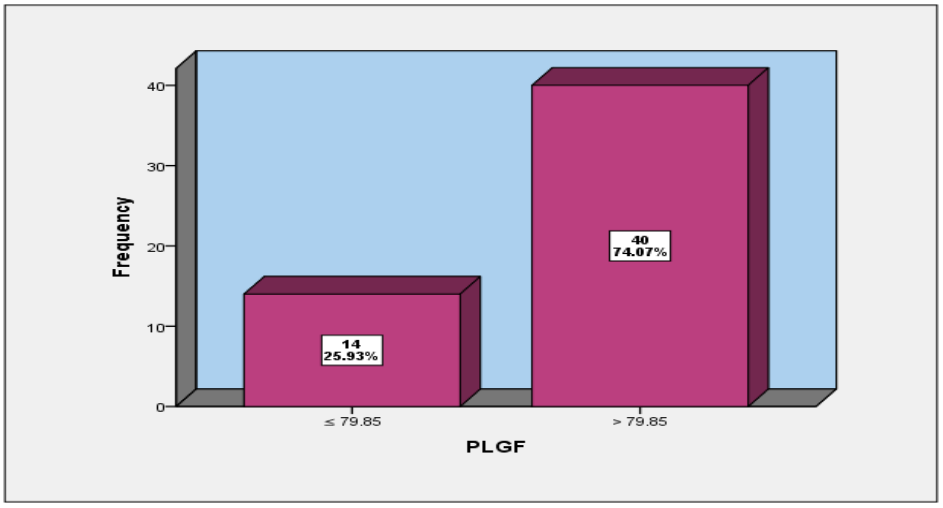

Fig. (5): distribution of patients according to PLGF.

According to table (4), there is significant association between gestational outcome and PLGF, (80%) of patients have outcome PE associate with level of PLGF equal or less (79.85pg/dl) in other hand (20%) of patients have outcome PE associate with level of PLGF more than (79.85pg/dl).

Table (4): Distribution of gestational outcome and PLGF.

variable		Outcome		P-value
		No PE	PE	
PLGF	≤ 79.85pg/dl	10	4	0.013
	%	20.4%	80.0%	
	> 79.85pg/dl	39	1	
	%	79.6%	20.0%	
	Total	49	5	
	%	100.0%	100.0%	

DISCUSSION

Preeclampsia (PE) is a multisystem progressive disorder affecting up to5–8% of all pregnancies and is part of the spectrum of hypertensive disorders of pregnancy.[12] Accordingly, low PlGF in first trimester was observed in women who subsequently develop PE (80%), This finding agrees **chin et al. 2021.**[13] with their finding of PlGF in women at risk of developing PE is lower than in women with a normal pregnancy outcome. Among 5 participants who develop PE, 3 had delivery before 37 weeks' gestation, reflecting significant association between low maternal PlGF and occurrence of such adverse outcome, such finding consistent with **Cetin et al 2017,**[14] who found an association between low PlGF and lower gestational age at delivery, with a significantly increased rate of urgent cesarean sections. A significant association between increased MAP in the first trimester with the occurrence of PE ($p < 0.0001$) shows an agreement with **Gallo et al 2014** [15] and by their finding

of MAP as being a good predictor of preeclampsia with high specificity and negative predictive value. A significant association ($p<0.03$) in this study was found between obesity and PE occurrence which goes with **Fernández Alba et al 2018** by their finding of strong direct correlation between an increasing BMI and the risk of developing preeclampsia and pregnancy induced hypertension. Further contributing to the relationship between preeclampsia and obesity, a study found that weight loss reduces the risk of developing preeclampsia **Magdaleno et al. 2012.[16]** Obesity is considered a risk factor for preeclampsia and there are many common mechanisms that link obesity with a higher risk of developing preeclampsia by: *1*) acting on the placenta causing cytotrophoblast dysfunction and placental ischemia; *2*) enhancing ischemia/hypoxia-induced release of soluble placental factors; and *3*) by increasing the sensitivity by which placental ischemia-factors are able to promote endothelial dysfunction and hypertension.[17] The present study showed that there was no significant association between preeclampsia and diabetes and this result disagree with who found that diabetes is a strong risk factor for PE. This disagreement might be at least partly explained by the small number of patients in the diabetic subgroup which could have interfered with statistical power of the analysis. There was no significant association between PE and parity such result disagrees with **Pogačnik et al. 2020 [18]** who found a strong association with null parity, and **Moon et al. 2015 [19]** who found significant differences in prediction between nulliparous and multiparous women. There was no significant association with method of conception whether it was spontaneous or assisted reproductive technology (ART) which disagrees with **Maman et al. 1998.[20]** in their finding of a significant higher prevalence of mild to moderate pregnancy-induced hypertension among singleton pregnancies in the IVF and ovulation induction groups compared with the spontaneous conception control groups. while, **Martin et al. 2016[21]** found women exposed to ovarian stimulation (OS) medications known to increase serum estrogen levels, such as clomiphene and exogenous gonadotropins, have an increased risk of preeclampsia regardless of ART use. In contrast, stimulation with aromatase inhibitors that do not cause supraphysiologic estrogen levels was not associated with preeclampsia after adjusting for age, parity, and comorbid conditions. These findings may explain result of the present study supported by the hypothesis of increased risk of preeclampsia among ART pregnancies may be due, in part, to elevated estrogen levels associated with certain types of OS. Supraphysiologic estrogen during implantation may contribute to abnormal placentation and subsequent aberrant or inadequate uteroplacental circulation that plays a central role in the pathogenesis of preeclampsia. This hypothesis is supported by a study in baboons that found vascular invasion of uterine spiral arteries was markedly decreased after exposure to serum estradiol levels threefold above normal in the first trimester.[22] On the other hand, **Chen et al. 2009.[23]** found a higher incidence of preeclampsia among pregnancies conceived by IVF, but no significant association was found in intrauterine insemination and ovulation induction. The present study demonstrated that there was no significant relation between age and development of preeclampsia in contrast to **Luealon et al. 2010.[24]** who found that women ≥ 35 years were 1.5 times more likely to have preeclampsia compared to women under 35 years of age. This disagreement due to small sample size of group ≥ 35 years' age. Findings of this study highlights the importance of early identification of women in need of early treatment with preventive measures such as aspirin and increased obstetrical surveillance.

CONCLUSION

The use of maternal serum placental growth factor between 11th and 13th week of gestation found to be of value for early prediction of pregnant women at high risk of subsequent PE and its adverse outcome.

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