

## Role of Pregnancy-Associated Plasma Protein-A and Uterine Artery Doppler in Early Detection of Preeclampsia

W.N.Mohamed, M.A.Mohamed, M.A.Mohamed and A.A.Sharf Eldin  
Obstetrics , gynecology Dept., Faculty of Medicine, Benha Univ., Benha, Egypt  
E-Mail: drwael01@gmail.com

### Abstract

The purpose of this study was to evaluate the role of pregnancy-associated plasma protein-A and uterine artery Doppler in early detection of preeclampsia. Subjects of this prospective cohort study included (120) pregnant women with viable singleton pregnancies in the first trimester between (11- 13+6 ) weeks of gestation, were recruited during the period from March 2018 to January 2020 and who came for ante natal clinic, in the Department of Obstetrics and Gynecology at Benha University Hospital. Consideration criteria were Pregnant ladies going to antenatal forethought toward Benha outpatient facility for singleton feasible pregnancy In 11-13+6 weeks gestation (Fetal crown-rump length (CRL) might have been 45-84 mm for typical fetal morphology). For each tolerant we measure uterine corridor doppler and pregnancy cohorted plasma protein and the outcomes were Pregnancy copartnered plasma protein (PAPP-A) indicated profoundly noteworthy Contrast between instances for preeclampsia What's more instances that don't create preeclampsia (p quality 0. 004) same time both uterine corridor pulstality list (UTPI) Furthermore uterine corridor imperviousness list (UTRI ) are statically critical. We closed that mix for uterine corridor stream indices Also pregnancy connected plasma protein from the beginning trimester needed progressed early identification about preeclampsia.

**Keywords:** Pregnancy associated plasma protein , Uterine artery Doppler , preeclampsia .

### 1.Introduction

Pre-eclampsia (PE) may be An multisystem issue about pregnancy formerly characterized by those onset for hypertension went with Eventually Tom's perusing noteworthy proteinuria after 20 weeks from claiming gestation. Recently, those definition of pe need been increased [1].

Pe camwood a chance to be subdivided under : promptly onset pe requiring conveyance in front of 34 weeks from claiming gestation Furthermore late onset pe with conveyance toward or then afterward 34 weeks. In light of those previous will be connected with a higher frequency for unfriendly conclusions a major test may be initial ID number Furthermore prediction for these cases [2].

Pregnancy-associated plasma protein a (PAPP-A) will be a placental glycoprotein prepared Toward syncytial trophoblast of the placenta, which cleaves insulin-like development component tying protein 4 (IGFBP4) What's more will be a sure controller about insulin-like Growth Components (IGFs), conceivably influencing fetal development What's more wellbeing [3].

Pregnant ladies ought to be assessed early On pregnancy to danger figures to pe. By quantifying the danger for pe , the clinician may be exceptional provided with gauge An lady's danger of pe Furthermore if she will be a hopeful for heightened pregnancy observation or prophylactic measures(low dosage aspirin). Early appraisal may be especially paramount for ladies who need aid arranging with get pregnancy mind Furthermore convey On a low-risk setting (eg, maternity care practice, birthing center, home birth), which might be contraindicated On pe develops. These ladies ought a chance to be advertised interview with a clinician with dexterity in the management of this disease[4].

### 2. Patients and methods

Subjects from claiming this prospective associate study included (120) pregnant ladies with feasible singleton pregnancies in the in the first place trimester between (11- 13+6 ) weeks about gestation, were recruited Throughout those period starting with Walk 2018 to january 2020 Also who originated for risk natal clinic, in the Branch for obstetrics Also Gynecology, at Benha school healing facility. Moral Regard might have been gotten starting with the nearby moral council and educated composed assent might have been made starting with each tolerant should finish the investigation the imply agdistis might have been 26. 06 ±5. 86 A long time of age. Incorporation criteria Pregnant ladies going to to antenatal forethought at Benha outpatient facility for singleton feasible pregnancy In 11-13+6 weeks gestation (Fetal crown-rump period (CRL) might have been 45-84 mm with ordinary fetal morphology).

Avoidance criteria incorporate different pregnancy , any restorative disorder, any obstetric issue. Each tolerant in this study might have been deliberately evaluated complete historical backdrop bringing (personal, menstrual, family, and restorative What's more quite some time from claiming education)at those occasion when about enlistment.

#### 2.1 Methods

Complete all examination including stature What's more weight. Abdominal Furthermore obstetric us examination will avoid various pregnancy watchful estimation for Circulatory strain (systolic,diastolic ) trying pee for proteinuria done mid-stream, clean-catch example by dipstick method, with negative bring about shortages.

For every tolerant we measured Circulatory strain precisely Furthermore we measure uterine corridor doppler Also pregnancy cohorted plasma protein and the

effects were Pregnancy connected plasma protein (PAPP-A) by immunoassay.

## 2.2 Statistical analysis

Data were statistically described in terms of Mean standard deviation (SD), average What's more go. Examination the middle of instances Also controls qualities might have been done Student's t-test:- used to analyze mean about two bunches about quantitative information. Inter-group correlation about unmitigated information might have been performed Toward utilizing fisher accurate test (FET). Roc bend with test legitimacy about specific variables with foresee pe.

An p esteem <0. 05 might have been recognized statistically critical (\*) same time >0. 05 statistically inconsequential Value<0. 01 might have been recognized Exceedingly critical (\*\*) On the whole analyses.

Every last bit Factual calculations were completed utilizing PC program IBM SPSS (Statistical one bundle for those social Science) release20for Microsoft Windows.

## 3. Results

In the exhibit study, one hundred twenty ladies were recruited, seventeen were excluded starting with the examination for the taking after reasons, six instances aborted, two cases produced preterm labor, ,one for them required premature break for film What's more eight instances were lost When completion those catch up What's more you quit offering on that one the event formed gestational hypertension What's more don't help those criteria for this study. Thus, 103 pregnancies were accessible to last Investigation pregnant ladies going to to schedule antenatal forethought they were subjected to estimation of uterine corridor indices toward (11- 13 +6) weeks and estimation for pregnancy copartnered plasma protein by immunoassay (PAPP-A).

Preeclampsia might have been diagnosed Previously, five cases and the remaining 98 situations for pregnancies not muddled Eventually Tom's perusing preeclampsia serving Likewise controls, starting with the five situations that formed preeclampsia special case situation for them might have been from claiming promptly onset toward 33 weeks. The demographic aspects of the consider populace would indicated to table (1) & table (2).

Of the 103 subjects whom finished the contemplate 5 formed pe (4. 9 %) same time subjects who required ordinary pregnancy result were 98 (95. 1 %) Likewise indicated during table (1).

In table (4) no noteworthy Contrast might have been discovered same time thinking about demographic information between instances of preeclampsia What's more that didn't bring preeclampsia.

There might have been no huge Contrast between cases from claiming preeclampsia What's more situations for ordinary pregnancy result in regards maternal period , muscle to impostor list What's more crown backside period Similarly as demonstrated during

table (5). Pregnancy connected plasma protein (PAPP-A) indicated Exceptionally critical Contrast between instances about preeclampsia and cases that don't create preeclampsia (p worth 0. 004) same time both uterine corridor pulsatility list (UTPI) Also uterine corridor imperviousness list (UTRI ) would stastically critical Similarly as indicated In table (6).

It might have been found that pregnancy copartnered plasma protein (PAPP-A) need best cutoff esteem of 0. 57, auc 0. 886(0. 705-1. 0) affectability 80 % specificity 93. 9 % PPV 33. 3 % same way as the NPV 98. 9 % precision 91. 3 % Likewise indicated at table (7) Also fig (1). Uterine corridor Pulsatility list required territory under the bend (AUC ) 0. 744 (0. 537-0. 951) and the best cutoff quality might have been 1. 39 affectability 100 % specificity 44. 9 % PPV 8. 5 % same way as the NPV 100 % correctness 47. 6% Similarly as indicated during table (8) Furthermore fig (2).

Similarly as in regards uterine corridor imperviousness list needed range under the bend (AUC ) 0. 804 (0. 609-0. 999) and the best cutoff esteem might have been 0. 74 affectability 80. 0 % specificity 67. 3 % PPV 11. 1 % same way as the NPV 98. 5 % correctness 68. 0 % as demonstrated during table (9) and fig (3). Table (10) demonstrated that consolidated screening for both pregnancy cohorted plasma protein and uterine corridor Pulsatility list needed affectability 80. 0% specificity 95. 9 % PPV 42. 9 % same way as the NPV 98. 9 % precision 95. 1 % and p esteem <0. 001\*\* which might have been Exceedingly stastically huge.

Table (11) demonstrated that joined together screening for both pregnancy connected plasma protein Also uterine corridor safety list required affectability 60. 0 % specificity 95. 9 % PPV 42. 9% same way as the NPV 97. 9 % correctness 94. 2 % What's more p worth 0. 002\*\* which might have been profoundly stastically critical.

## 4. Discussion

Pre-eclampsia (PE) will be a multisystem jumble of pregnancy formerly characterized by the onset for hypertension went with by critical proteinuria after 20 weeks for gestation. Recently, those definition of pe need been increased. Pe commonly influences 2%–5% about pregnant ladies and will be a standout amongst the heading reason for maternal What's more perinatal horribleness and mortality, particularly The point when those condition is for punctual onset. Globally,76 000 ladies Furthermore 500 000 babies kick the bucket every year from this confusion. Furthermore, ladies On low-resource nations need aid In An higher danger from claiming Creating pe compared for the individuals in high-resource nations [5].

The uterine corridor pulsatility index, those The greater part ordinarily mulled over sonographic device around to those prediction for preeclampsia, may be an backhanded apparatus Also inclined to a chance to be advantageous in the prediction of extreme Furthermore punctual preeclampsia requiring conveyance former will 34weeks' gestation [6].

Patients who created preeclampsia needed altogether more level plasma connected plasma protein levels (PAPP-A) (. 49 vs.

84 mother ;  $p = .004$ ) contrasted with controls ; likewise there might have been noteworthy Contrast done uterine corridor pulsatility list levels Previously, preeclamptic patients contrasted with controls ( 1. 64 vs 1. 44 mother ;  $p = .04$  ) also over our consider patients who created preeclampsia need higher uterine corridor imperviousness list ( UTRI ) At contrasted with controls (. 75 vs. 72 ;  $p = .016$  discoveries from our prospective associate exhibit that levels from claiming pregnancy copartnered plasma protein (PAPP-A) would altogether decreased in patients who create preeclampsia later on Concerning illustration PAPP-A will be a metalloproteinase insulin-like development element (IGF) tying protein discharged Toward the syncytiotrophoblast that assumes a paramount part done placental Growth and improvemen. It enhances the mitogenic capacity of the IGFs. With the goal low levels from claiming this analyte reflect a expanded add up about insulin response such as development calculate in the certain state , which will be after that inaccessibility to Push placental development Also improvement , making this finding possible.

Toward the written works Previously, euploid pregnancies, An PAPP-A mother worth In under the 5th percentile (0. 4 MoM) may be display to 8%–23% of ladies with pe. Therefore, Likewise An single marker it is not a accurate predictive test for pe. A later deliberate survey and meta-analysis, including eight investigations directing, including 132 076 pregnant ladies in the main trimester, showed that those maternal PAPP-A focus under those 5th percentile is connected with the danger of developing PE with an or from claiming 1. 94 (95% CI, 1. 63–2. 30). It need An identification rate of 16% (9%–28%) during 8% false-positive rate should foresee pe [7].

Morrigu et al 2017 Audit discovered that low maternal serum PAPP-A in the in the first place trimester need an affiliation with unfriendly pregnancy Conclusion for An direct affiliation When levels need aid <5th centile to gestation What's more a stronger companionship <1st centile. The predictive qualities are poor; thus, In spite of ladies with An low PAPP-A would toward expanded danger of a unfriendly outcome, the larger part about these ladies will bring an ordinary pregnancy outcome, and the larger part of ladies with an unfriendly result will bring an ordinary PAPP-A[8].

On the other side for this study , Saruhan et al 2011 What's more van Ravenswaaij et 2011 found no Acquaintanceship with preeclampsia Also no predictive worth of a low PAPP-A level to preeclampsia. Be that both investigations were about review way something like that appears to make different to a portion what from our investigation [9].

As depicted by Bhide et al 2014 in the ISUOG act rules on the utilization of doppler ultrasonic On obstetrics, the systolic/diastolic proportion (S/D), safety list (RI) Also phytotoxin would the three best-known

indices with which should depict blood vessel flow-velocity waveforms. Phytotoxin may be the list mossycup oak usually used; its advantage through ri in assessment of the uterine corridor doppler waveform is that phytotoxin incorporates On its figuring the averaged quality of every last bit most extreme velocities Throughout those cardiovascular cycle, as opposed just two focuses in the heart cycle With respect to ri. Furthermore, phytotoxin is additional stable and it doesn't methodology boundlessness The point when there are absent alternately turned around diastolic values [10].

In this contemplate uterine corridor Pulsatility list (UTPI) need affectability from claiming 100 % Furthermore specificity for 44. 9 % PPV 8. 5 % same way as the NPV 100 % with An symptomatic correctness for 47. 6 % . It need auc (95 % ci ) from claiming 0. 744.

This examine exhibited noteworthy Contrast clinched alongside uterine corridor pulsatility list ( UTPI) estimations the middle of preeclamptic Also control patients. As maximal trophoblastic intrusion ensues Throughout those in the first place trimester , it might appear to be advocated that improved vascular safety in the uterine courses might be perceivable at this punctual gestational phase for impeded placentation.

Parra-Cordero et al 2013 exhibited a noteworthy expand in the in the first place trimester uterine corridor doppler pulsatility list (UTPI) over patients who created early Also late preeclampsia contrasted with controls. [11].

Contrasts between those An forementioned investigations and our contemplate might be expected with changing criteria used to characterize a abnormal uterine corridor phytotoxin (UTPI) , both of the over said investigations measured those straight and the exited uterine corridor pulsatility list (UTPI) what's more utilized those most reduced recorded esteem in their Investigation. Toward alternate side our contemplate utilized Normal worth of the right Furthermore exited uterine corridor phytotoxin estimations , An strategy that need been portrayed Awhile ago. We have confidence that this Normal quality may be more delegate test of generally placental perfusion.

On respect to uterine corridor safety list (UTRI) clinched alongside our examine it might have been found with bring affectability from claiming 80 % and specificity for 67. 3 % PPV 11. 1 % NPV 98. 5 % with a symptomatic precision of 68 % it might have been dependable to identification of preeclampsia Likewise it need auc (95 % ci ) of 0. 804. Clinched alongside An investigation by Melchiorre et al 2008 the first-trimester uterine corridor ri might have been essentially higher in ladies who consequently created preterm pre-eclampsia (mean RI, 0. 79) over done the individuals with typical result (mean RI, 0. 70;  $p = 0.0001$ ) or the individuals who produced pre-eclampsia toward term (mean RI, 0. 72;  $p = 0.002$ ) [12].

From those previously stated we discovered that including those serum marker pregnancy copartnered

plasma protein with uterine corridor doppler indices needed progressed the identification rate to preeclampsia.

Odibo et al 2011 unexpectedly side of our examine Similarly as forty two ladies were diagnosed with preeclampsia What's more 410 ladies for pregnancies not confounded Toward preeclampsia were utilized Concerning illustration controls. To an altered false sure rate (FPR) for 20%, PP13, PAPP-A Furthermore imply uterine corridor pulsatility list recognized 49%, 58% and 62% respectively, from claiming ladies who created any type from claiming preeclampsia. PP13 might have been best in foreseeing promptly onset preeclampsia for An affectability of 79% In An 20% FPR. Combinations of

the three in the first place trimester appraisals didn't enhance those prediction from claiming preeclampsia to after the fact pregnancy[13].

The qualities for our investigation incorporate the prospective configuration a sufficient re-productibility and the utilization of An hearty measurable approach with plan An clinical prediction model.

Our consider is not without constraints including those test size might have been small, particularly for respects with cases for early preeclampsia , our example span to right on time onset preeclampsia might have been set Likewise we needed special case instance about promptly onset preeclampsia during 33 weeks gestation.

Table (1) showing distribution of the studied population according to demographic data

	The studied population (103)	
	No	%
<b>Cig smoking</b>		
Yes	4	3.9
No	99	96.1
<b>Mode of conception</b>		
ART	3	2.9
None	100	97.1
<b>Family history</b>		
Yes	1	1.0
No	102	99.0
<b>Parity</b>		
Nulli-para	56	54.4
Multi-para	47	45.6
<b>PE</b>		
Yes	5	4.9
No	98	95.1

( Cig smoking = cigarette smoking , ART = assisted reproductive technique , PE = preeclampsia )

Table ( 2 ) showing distribution of study population according to maternal characteristics .

	The studied population (103)		
	Mean	±SD	Range
<b>Maternal age</b>	26.06	5.86	18.0-41.0
<b>BMI</b>	27.12	3.63	19.8-36.2
<b>CRL</b>	67.0	9.66	45.0-84.0

(BMI =Body mass index, CRL= Crown rump length , ±SD = standard deviation)

Table ( 3 ) showing distribution of study population according to finding

	The studied population (103)		
	Mean	±SD	Range
<b>PAPP-A MOM</b>	0.82	0.27	0.28-1.62
<b>UT PI MOM</b>	1.45	0.21	0.89-1.98
<b>UT RI MOM</b>	0.73	0.02	0.69-0.78

( PAPP-A = pregnancy associated plasma protein, UT PI = uterine artery pulsatility index, UT RI = uterine artery resistance index , MOM = multiple of median )

Table ( 4 ) showing comparison between study population according to Demographic data .

	PE (5)		NO PE (98)		Statistical test (FET)	P value
	No	%	No	%		
<b>Cig smoking</b>						
Yes	1	20.0	3	3.1	0.53	0.18
No	4	80.0	95	96.9		
<b>Mode of conception</b>						
ART	0	0.0	3	3.1	0.0	1.0
None	5	100	95	96.9		
<b>Family history</b>						
Yes	0	0.0	1	1.0	0.0	1.0
No	5	100	97	99.0		
<b>Parity</b>						
Nulli-para	3	60.0	53	54.1	0.0	1.0
Multi-para	2	40.0	45	45.9		

Table ( 5 ) showing comparison between study population according some maternal characteristics .

	PREECLAMPSIA (5)		NO PREECLAMPSIA (98)		Statistical test (S t t)	P value
	Mean	±SD	Mean	±SD		
<b>Maternal age</b>	24.6	5.98	26.13	5.88	0.57	0.57
<b>BMI</b>	26.48	3.48	27.15	3.65	0.40	0.69
<b>CRL</b>	74.2	5.54	66.63	9.70	1.73	0.088

(BMI =Body mass index, CRL= Crown rump length , ±SD = standard deviation)

Table ( 6 ) showing comparison of finding between study population .

	PREECLAMPSIA (5)		NO PREECLAMPSIA (98)		Statistical test (S t t)	P value
	Mean	±SD	Mean	±SD		
<b>PAPP-A (MOM)</b>	0.49	0.21	0.84	0.26	2.96	0.004**
<b>UT PI (MOM)</b>	1.64	0.23	1.44	0.21	2.08	0.04*
<b>UT RI (MOM)</b>	0.75	0.017	0.72	0.019	2.44	0.016*

( PAPP-A = pregnancy associated plasma protein, UT PI = uterine artery pulsatility index, UT RI = uterine artery resistance index , MOM = multiple of median )

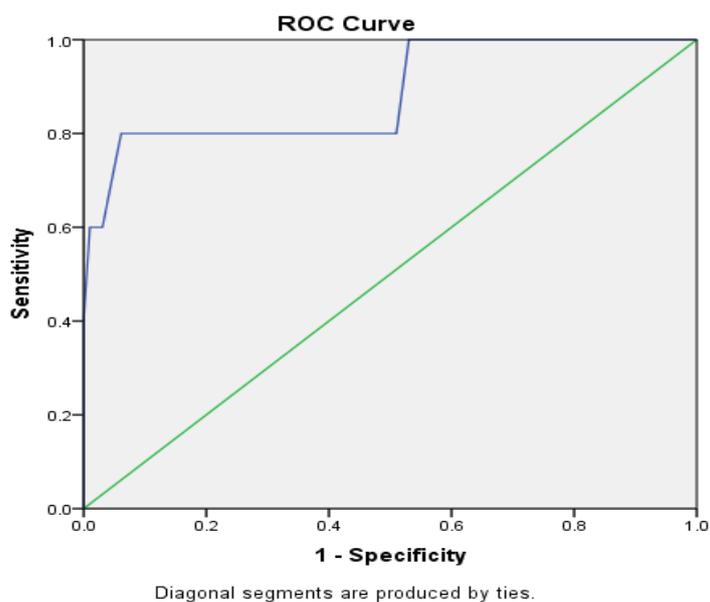


Fig (1) ROC curve showing validity of PAPP-A in detection of preeclampsia.

Table ( 7 ) showing validity of PAPP-A in detection of preeclampsia .

PAPP-A	preeclampsia (5)		NO preeclampsia (98)		Statistical test (FET)	P value
	No	%	No	%		
≤0.57	4	80.0	8	6.1	17.38	0.001**
>0.57	1	20.0	90	93.9		
AUC (95%CI)	0.886(0.705-1.0)					
Cut-off point	0.57					
Sensitivity	80.0					
Specificity	93.9					
PPV	33.3					
NPV	98.9					
Accuracy	91.3					

(PAPP-A = pregnancy associated plasma protein, AUC =area under the curve, PPV = positive predictive value, NPV = Negative predictive value)

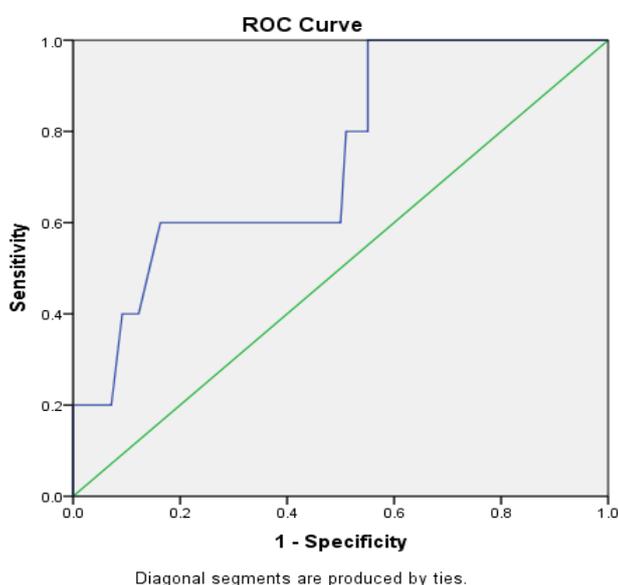
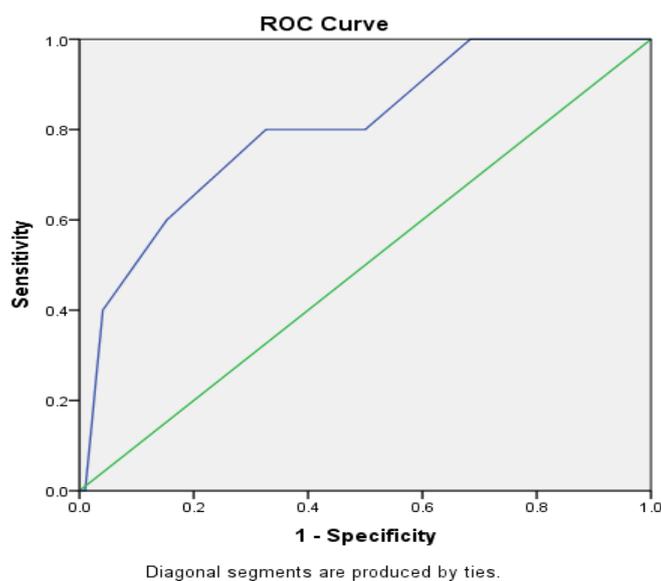


Fig (2) ROC curve showing Validity of UT PI in prediction of cases of PE.

Table ( 8 ) showing Validity of UT PI in prediction of cases of PE.

UT PI	PE (5)		NO PE (98)		Statistical test (FET)	P value
	No	%	No	%		
≥1.39	5	100	54	55.1	2.3	0.07
<1.39	0	0.0	44	44.9		
AUC (95%CI)	0.744 (0.537-0.951)					
Cut-off point	1.39					
Sensitivity	100					
Specificity	44.9					
PPV	8.5					
NPV	100					
Accuracy	47.6					

(UT PI = uterine artery pulsatility index , PE = Preeclampsia AUC =area under the curve , PPV = positive predictive value , NPV = Negative predictive value )



**Fig ( 3 )** ROC curve showing validity of (UTRI) in prediction of cases of PE.

**Table ( 9 )** showing Validity of UT RI in prediction of cases of PE.

UT RI	PE (5)		NO PE (98)		Statistical test (FET)	P value
	No	%	No	%		
$\geq 0.74$	4	80.0	32	32.7	2.84	0.049*
$< 0.74$	1	20.0	66	67.3		
<b>AUC (95%CI)</b>	0.804 (0.609-0.999)					
<b>Cut-off point</b>					0.74	
<b>Sensitivity</b>					80.0	
<b>Specificity</b>					67.3	
<b>PPV</b>					11.1	
<b>NPV</b>					98.5	
<b>Accuracy</b>					68.0	

(UT RI = uterine artery resistance index , PE = Preeclampsia AUC =area under the curve , PPV = positive predictive value , NPV = Negative predictive value ).

**Table ( 10 )** showing Validity of PAPP-A +UTPI in prediction of cases of PE.

PAPP-A +UTPI	PE (5)		NO PE (98)		Statistical test (FET)	P value
	No	%	No	%		
<b>Positive</b>	4	80.0	4	4.1	28.41	$< 0.001^{**}$
<b>Negative</b>	1	20.0	94	95.9		
<b>Sensitivity</b>					80.0	
<b>Specificity</b>					95.9	
<b>PPV</b>					50.0	
<b>NPV</b>					98.9	
<b>Accuracy</b>					95.1	

(UT PI = uterine artery pulstality index , PAPP-A = pregnancy associated plasma protein , PPV = positive predictive value , NPV = Negative predictive value ).

**Table (11)** showing Validity of PAPP-A +UTRI in prediction of cases of PE.

PAPP-A +UTRI	PE (5)		NO PE (98)		Statistical test (FET)	P value
	No	%	No	%		
Positive	3	60.0	4	4.1	15.49	0.002**
Negative	2	40.0	94	95.9		
Sensitivity				60.0		
Specificity				95.9		
PPV				42.9		
NPV				97.9		
Accuracy				94.2		

(UT RI = uterine artery resistance index, PAPP-A = pregnancy associated plasma protein, PPV = positive predictive value, NPV = Negative predictive value)

### 5. Conclusion

Our ponder confirms the possibility part of pregnancy connected plasma protein Furthermore uterine corridor doppler Likewise predictors about preeclampsia. Furthermore expansion for both markers needed progressed promptly identification rate.

More investigations committed with distinguish hearty serum markers Also sonographic instruments for possibility added substance impacts At consolidated are required for promptly identification about preeclampsia.

### References

- [1] Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens.*;Vol.13,PP.291–310, 2018.
- [2] Poon LC, Nicolaides KH. Early prediction of preeclampsia. *ObstetGynecolInt*; vol 2014: 297397 doi: 10.1155/2014/297397, 2014.
- [3] Poon LC, Nicolaides KH: First-trimester maternal factors and biomarker screening for preeclampsia. *PrenatDiagn.*;vol 34(7) , PP. 618, 2014.
- [4] SOGC 2016 :The Society of Obstetricians and Gynaecologists of Canada:Clinical Practice Guidelines : Sogc.org. N.p., 2016. Web. July 27, 2016 .<http://sogc.org/wp> accessed on 2016.
- [5] Poon LC1, Shennan A2, Hyett JA3, Kapur A4, Hadar E, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention" [*Int J GynecolObstet* , Vol. 145, Suppl. 1 PP.1-33] 2019.
- [6] Valiño, N., Giunta, G., Gallo, D. M., Akolekar, R., & Nicolaides, K. H. Uterine artery pulsatility index at 30-34 weeks gestation in the prediction of adverse perinatal outcome. *Ultrasound in Obstetrics & Gynecology*, Vol.47(3),PP. 308-315 ,2016.
- [7] Spencer K, N. J. Cowans, and K. H. Nicolaides, "Low levels of maternal serum PAPP-A in the first trimester and the risk of pre-eclampsia," *Prenatal Diagnosis*, Vol. 28(1) , PP. 7–10, 2008
- [8] Morris RK, Bilagi A, Devani P, Kilby MD. Association of serum PAPP-A levels in first trimester with small for gestational age and adverse pregnancy outcomes: Systematic review and meta-analysis. *PrenatDiagn.*;Vol.37 , PP.253-265, 2017.
- [9] Saruhan Z, Ozekinci M, Simsek M, Mendilcioglu I. Association of first trimester low PAPP-A with adverse pregnancy outcomes. *ClinExpObstetGynecol*; Vol. 39(2) , PP. 225-8. 9, 2012.
- [10] Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, Kalache K, Kingdom J, Kiserud T, Lee W, Lees C, Leung KY, Malinger G, Mari G, Prefumo F, Sepulveda W, Trudinger B. ISUOG Practice Guidelines: use of Doppler ultrasonography in obstetrics. *Ultrasound ObstetGynecol*; Vol.41, PP. 233–239, 2013.
- [11] Parra-Cordero M, Rodrigo R, Barja P, et al. Prediction of early and late pre-eclampsia from maternal characteristics, uterine artery Doppler and markers of vasculogenesis during the first-trimester of pregnancy. *Ultrasound Obstet Gynecol*. [published online ahead of print July Vol.17,] Doi: 10.1002/uog.12264 ,2012.
- [12] Melchiorre K, Wormald B, Leslie K, Bhide A, Thilaganathan B: First-trimester uterine artery Doppler indices in term and pre-term preeclampsia. *Ultrasound ObstetGynecol*;Vol.32(2), PP.133–137, 2008.
- [13] Odibo AO, Zhong Y, Longtine M, et al. First-trimester serum analytes, biophysical tests and the association with pathological morphometry in the placenta of pregnancies with preeclampsia and fetal growth restriction. *Placenta*;Vol. 32, PP. 333–8, 2011.