Research Article

iMedPub Journals
http://www.imedpub.com/

Reproductive Immunology: Open Access
ISSN 2476-1974

2016
Vol.1 No.3:15

DOI: 10.21767/ 2476-1974.100015

First Trimester Screening for Preeclampsia and Intrauterine Growth Restriction Using Uterine Artery Doppler and Maternal Serum Placental Growth Factor and Pregnancy Associated Plasma Protein- A

Dina Gamal Eldeen Y Elkholi[1*], Mohamed Abd Elgeleel Hefeda[2] and Halah Mohamed Nagy[3]

[1]Assistant Professor of Obstetrics and Gynecology, Faculty of Medicine, Tanta University, Tanta, Egypt

[2]Assistant Professor of Diagnostic Radiology, Faculty of Medicine, Tanta University, Tanta, Egypt

[3]Professor of Clinical Pathology, Faculty of Medicine, Tanta University, Tanta, Egypt

[*]**Corresponding author:** Dina Gamal Eldeen Y Elkholi, Faculty of Medicine, Assistant Professor of Obstetrics and Gynecology, Tanta University, Tanta, Egypt, Tel: 020/0403314936; E-mail: gyeldeenelkholi@yahoo.com

Received date: May 17, 2016; **Accepted date:** June 16, 2016; **Published date:** June 20, 2016

Citation: Eldeen Y Elkholi DG, Hefeda MAE, Nagy HM (2016) First Trimester Screening for Preeclampsia and Intrauterine Growth Restriction Using Uterine Artery Doppler and Maternal Serum Placental Growth Factor and Pregnancy Associated Plasma Protein- A. Reproductive Immunol Open Acc 1:15. doi: 10.21767/ 2476-1974.100015

Abstract

Objective: To assess the accuracy of first-trimester uterine artery Doppler indices combined with maternal serum placental growth factor (PlGF) and pregnancy associated plasma protein- A (PAPP-A) in the prediction of pre-eclampsia (PE) and intrauterine growth restriction (IUGR) in low risk pregnancy.

Design: Prospective observational study

Patients and methods: A total of 266 low risk singleton pregnant women at12-14 weeks' gestation were recruited and completed the study. Uterine artery (UtA) color Doppler study was estimated on the two sides, the mean pulsatility index (PI) was calculated and dicrotic diastolic notches were recorded. Estimation of maternal serum PlGF and PAPP-A were performed on the same day. The cut-off of Ut Ar PI was 2.35, the cut-off of PlGF was 12pg/ml and the cut off of PAPP-A was 0.42 MoM. The patients were followed up to detect PE and IUGR. PE developed in 14 cases (5.26 %), 2 cases early-onset 2 cases and late-onset 12 cases and IUGR in 19 cases (7.14 %), early-onset 3 cases and late-onset 16 cases. The sensitivity, specificity, positive and negative value (PPV and NPV) and accuracy were calculated. The higher sensitivity and PPV and accuracy for prediction of PE and IUGR were found when first trimester UtA PI and PlGF were combined. The addition of PAPR-A did not improve the accuracy.

Conclusion: The ideal first trimester markers for prediction of PE and IUGR in low risk pregnant women may be a combination of UtA PI and maternal serum PlGF.

Keywords: Preeclampsia; Intrauterine growth restriction; Uterine artery pulsatility index; Placental growth factor; Pregnancy-associated plasma protein-A

Introduction

Preeclampsia (PE)/eclampsia are the second commonest cause of direct maternal deaths in developed countries. Perinatal mortality in PE and IUGR is 6% and 10% respectively. Modern maternal care relies on prediction of adverse pregnancy outcomes such PE and IUGR early in pregnancy, there by starting early management including a high level of pregnancy monitoring to minimize the risk of expected pregnancy complications [1] both PE and IUGR share the same pathogenesis that is shallow implantation of the placenta that stems from the mother's immune system responding to the placenta as if it were a foreign invader. This theory suggests that a lack of immunological tolerance in pregnancy results in an auto-immune response to the antigens of the fetus and its placenta [2]. Consequently, PE and IUGR have the same markers for their prediction. As a predictive marker for development of PE and IUGR, uterine artery (UtA) Doppler waveform has been used extensively in the second trimester. Study of first trimester UtA Doppler waveform has been recently used as a better predictive marker for PE and IUGR. This allows early use of aspirin as a protective measure against these adverse pregnancy outcomes [3]. The sensitivity and positive predictive values of the PI of UtA as a predictor marker for PE and IUGR for low risk pregnancy is low, around 40%. Combining first trimester UtA PI with variable biochemical markers has been resorted to achieve a detection rate of PE and IUGR approaching 90% [4]. The success rate of this combination is variable. The aim of this study is to assess the success rate of combined UtA PI with PlGF and PAPP-A for predicting the development of PE and IUGR in low risk pregnancy.

Patients and Methods

A total of 300 women were recruited from the outpatient clinic of Obstetrics, Tanta University Hospitals, during the period June 2013 to December 2015.

Inclusion criteria

Primigravida, and singleton pregnancy at 12-14 weeks. Attending regularly the ante natal clinic and delivered at department of Obstetrics, Tanta University Hospitals.

Exclusion criteria

Multiple pregnancies: Women with medical disorders as diabetes mellitus, chronic hypertension, chronic renal, liver, thyroid or autoimmune diseases. Women with congenital or acquired gynaecological lesions. Women pregnant after treatment of infertility, Fetal congenital abnormality, increased nuchal translucency thickness or markers of chromosomal aberration Forty-four women were lost to follow up and 266 women completed the study. The study was approved by the ethics committee of Tanta University Hospital. All women included in the study signed a formal consent. All participants were subjected to detailed history taking and complete medical examination.

A transabdominal ultrasound, including color Doppler study of the uterine arteries, was performed for all pregnant women at 12-14 week's gestation. All women were followed up to detect the development of PE and IUGR by serial clinical examinations, measurement of blood pressure and detection of proteins in urine in addition to trans abdominal Doppler of UtAs and ultra sound scanning especially fetal biometry, estimated fetal weight and placental morphology. PE was diagnosed when systolic blood pressure was ≥ 140 mm Hg and/ or diastolic blood pressure ≥ 90 mm Hg and proteinuria of ≥ 300 mg in 24 hours or two readings of at least 2+ on dipstick analysis of midstream or catheter specimen in absence of urinary tract infection.

Color Doppler study of the uterine artery

Transabdominal ultrasonography examination with a probe (3.5 MHz) of (Seimen, Omnia, Medison 9900, and Germany) equipped with pulsed color Doppler. Gestational age was confirmed by crown-rump length and fetal viability was assured. The UtA PI was estimated and early diastolic notches were reported if present. Transabdominally, a midsagittal section of the uterus was obtained and the cervical canal was identified. The empty maternal bladder is preferable. The probe was moved laterally until the paracervical vascular plexus was seen.

Color Doppler was turned on and the uterine artery was identified as it turns cranially to make its ascent to the uterine body. Measurements were taken at this point, before the uterine artery branches into the arcuate arteries. Sample gate was set at 2 mm to cover the whole vessel, angle of insonation not more than 30° and the peak systolic velocity should >50 cm to ensure that the arcuate artery were not scanned instead of the UtA. When three similar consecutive waveforms had been obtained the Ut A PI was measured. The mean PI of the two UtAs was used for analysis. On the same day of Doppler study blood sample was obtained from all women allowed to stand in room temperature for 30 minutes then centrifuged at 3000 rpm for 10 minutes and the serum stored at -70°C until analysis.

Assay

All serum samples were assayed for PlGF and PAPP-A. PlGF was measured using commercial enzyme-linked immunosorbent assays (ELISA). PAPP-A was measured using DRG PAPP-A ELISA kit which is a solid phase enzyme linked immunosorbent assay based on the sandwich principle. Both PlGF and PAPP-A were assayed by Quantike ELISA kits from R&D systems Inc. Minneapolis, MN, USA. Cases expected to develop PE or IUGR were provided with special antenatal care to discover these complication as early as possible. Discovered PE and IUGR were managed by routine management for these cases. All delivered in the Department of Obstetrics and Gynecology, Tanta University.

Statistical analysis

Data were statistically described in terms and mean ± standard deviation (±SD). For comparing categorical data, chi Square(X2) test was performed. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut-off value for the studied diagnostic markers. P value less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical package for the Social Science: SPSS Inc, Chicago, IL for Microsoft windows (2006).

Results

The cut-off values of UtA PI, maternal serum PlGF, and PAPP-A in the first-trimester of 266 low risk pregnant women for prediction of PE and IUGR were 2.35, 12 pg/ml and 0.45 MoM respectively. UtA, PI was truly positive for PE in 6 cases and falsely negative in 8 cases. Consequently the sensitivity of UtA PI for prediction PE was 45.8%, specificity 84.5%, positive predictive value (PPV) 13.8%, and negative predictive value (NPV) 92.8%. UtA PI was truly positive for IUGR in 9 cases and falsely negative in 10 cases. Consequently the sensitivity of UtA PI for prediction of IUGR was 47.36%, specificity 85.42%, PPV 20% and NPV 95.4%. Maternal serum PlGF was truly positive in 12 cases of IUGR and falsely negative in 7 cases. Consequently its sensitivity for prediction of IUGR was 63.15%, specificity 80.06%, PPV 30.76% and NPV 96.9%

Combined UtA PI and PlGF for prediction of PE: 13 cases were true positive and 1 case false negative consequently combined UtAPI and PlGF had sensitivity for prediction of PE 92.85%, specificity 99.60%, PPV 92.85% and NPV 99.60%. Combined UtA PI and PlGF for prediction of IUGR:18 cases were truly positive and one case falsely negative. Consequently sensitivity was 94.73%, specificity 91.49%, PPV 46.15% and NPV 99.95% Clinical characteristics, average UtAs PI and maternal serum PlGF of women with PE {14 cases (5.26%), 2 (14.28%) early-onset and 12 (85.71%) late-onset} and women without PE (252 cases) are depicted in Table 1. Gestational at delivery, birth weight were significantly lower in women with PE compared to women without PE UtAs PI was significantly higher in women with PE compared to women without PE. Maternal serum PlGF was

This article is available from: http://dx.doi.org/10.21767/ 2476-1974.100015

significantly lower in women who developed PE compared to women who did not develop PE.

Clinical Characteristics, average Ut As PI and maternal serum PlGF in women who developed with IUGR {19 cases (7.14%), 3(15.78%) early-onset and 16 (84.21%) late-onset} and women who did not develop IUGR (247 cases) are depicted in Table 2. Gestational age at delivery and birth weight were significantly lower in women with IUGR compared to women without IUGR. Ut As PI was significantly higher in women who developed IUGR compared to women who did not develop IUGR. Maternal serum PlGF was significantly lower in women who developed IUGR compared to women who did not develop IUGR

Tables 3 and 4 predict the accuracy of Ut API cutoff point of >2.35 and PlGF cutoff point<12 pg/ml for prediction of PE and IUGR in low risk pregnancies. Sensitivity, positive predictive value and overall accuracy were significantly higher on combing Ut AsPI with maternal serum PlGF compared to UtA PI or PlGF alone. Specificity and negative predictive value were higher (but not significant) on combining UtA PI with PlGF compared to UtAPI or PlGF alone as they were already high (≥ 85% when each one was used alone for prediction of either PE or IUGR.

Table 1: Clinical characteristics, Doppler results, maternal serum PlGF and PAPP-A in women who developed preeclampsia and women who did not develop preeclampsia. BMI: Body Mass Index; CRL: Crown-Ramp Length; PI: Pulsatility Index; PlGF: Placental Growth Hormone; PAPP-A: Pregnancy Associated Plasma Protein –A.

	Women with PE n=14	Women without PE n =252	t/P	P
Age in years	25 ± 1.6	26 ± 2.12	1.736	0.084
BMI (Kg/m2)	24.4 ± 2.22	23.8 ± 3.88	0.573	0.567
CRL (mm)	70.0 ± 3.0	68.0 ± 3.0	0.930	0.535
Gestational age at delivery (weeks)	35.61 ± 5.37	38.44 ± 6.47	1.665	0.110
Presence of uterine artery diastolic notch (n %)	8(57.14)	10.8(42.8)	1.101	0.294
Average uterine artery PI	2.66 ± 0.04	2.10 ± 0.03	66.716	0.001
Serum PlGF (pg/ml)	9.8 ± 0.6	26.4 ± 1.4	66.924	0.001
Serum PAPP-A(MoM)	0.361 ± 0.04	0.643 ± 0.02	67.531	0.001

Table 2: Clinical characteristics, Doppler results, maternal serum PlGF and PAPP-A in women who developed IUGR and women who did not develop IUGR. BMI: Body Mass Index; CRL: Crown-Ramp Length; PI: Pulsatility Index; PlGF: Placental Growth Hormone; PAPP-A: Pregnancy Associated Plasma Protein –A.

	Women with IUGR n=19	Women without IUGR n =247	Pt	P
Age in years	26.3 ± 1.85	26.78 ± 3.78	0.548	0.584
BMI (Kg/m2)	23.53 ± 2.47	23.8 ± 3.88	1.719	0.087
CRL (mm)	65.0 ± 6.0	63.8 ± 3.0	1.531	0.127
Gestational age at delivery (weeks)	34.82 ± 1.24	38.21 ± 3.11	4.887	0.001
Presence of uterine artery diastolic notch (n %)	11(57.9)	93 (37.65)	3.036	0.081
Average uterine artery PI	2.58 ± 0.04	2.21 ± 0.22	7.309	0.001
Serum PlGF (pg/ml)	8.2 ± 0.6	27.6 ± 1.8	1.445	0.001
Serum PAPP-A (MoM)	0.47 ± 0.003	0.64 ± 0.03	1.532	0.001

Table 3: Sensitivity, specificity, PPV, NPV and accuracy of Ut A PI, PlGF, PAPAA, UtA PI+ PlGF and UtA PI+PlGF+PAPPA for prediction of PE. PPV: Positive Predictive Value; NPV: Negative Predictive Value; Ut A: Uterine Artery; PI: Pulsatility Index; PlGF: Placental Growth Factor; PAPP-A: Pregnancy Associated Plasma Protein –APE: Pre-Eclampsia

Cutoff points	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
UtA PI (>2.35)	42.8	84.52	13.5	97.73	82.33
PlGF (<12 pg/ml)	64.28	91.26	33.33	97.87	89.84
PAPPA (<0.45 MOM)	50	92.94	28	97.13	91.72
UtA PI (>2.35)+PlGF (<12pg/pg)	92.85	87.6	28.88	99.54	87.59
UtAPI(>2.35)+PlGF(<12pg/ml)+PAPP-A(<0.45MoM)	92.85	87.3	28.88	99.54	87.59

Table 4: Sensitivity, specificity, PPV, NPV and accuracy of UtA PI, PlGF, PAPP-A, UtAPI+PlGF and UtA PI+PlGF+PAPP-A for prediction of IUGR. PPV: Positive Predictive Value; NPV: Negative Predictive Value; UtA: Uterine Artery; PI: Pulsatility Index; PlGF: Placental Growth Factor; PAPP-A: Pregnancy Associated Plasma Protein-A; IUGR: Intrauterine Growth Restriction.

Cutoff points	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
UtA PI (>2.35)	47.36	85.42	20	59.47	82.7
PlGF (<12 pg/ml)	63.15	92.82	50	96.91	90.22
PAPPA (<0.45 MOM)	42.1	93.11	32	95.43	89.47
UtA PI (>2.35)+PlGF (<12pg/pg)	94.73	89.06	40	99.54	89.47
UtA PI (>2.35)+PlGF(<12pg/ml)+ PAPP-A(<0.45MoM)	94.73	89.06	40	99.54	89.47

Discussion

In normal pregnancy the spiral arteries in the placental bed are invaded by trophoblast, which becomes incorporated in the vessel wall and replaces the endothelium, muscular and elastic layers and neural tissues [5]. These physiological changes convert the spiral arteries from narrow muscular vessels to wide non-muscular channels independent of maternal vasomotor control. In placental dysfunction there is impaired trophoblastic invasion of spiral arteries and this impairment is most marked in PE and IUGR [6,7]. Indirect evidence of impaired placental perfusion in pregnancies destined to develop PE and IUGR has been provided by Doppler studies of the uterine arteries which showed increased PI during both the second and also in the first trimester of pregnancy [8].

Successful trophoblastic invasion and progressive dissolution of the muscular media of the spiral arteries result in lower vascular resistance in the first trimester and abolition of elastic properties by the second trimester in normal pregnancy these effects are mirrored by lower uterine artery Doppler indices and resolution of diastolic notches, respectively, making such Doppler studies surrogate markers for placental vascular development [9,10].

Angiogenesis is critical for trophoblastic invasion into decidual spiral arteries. Potent angiogenic growth factors namely vascular endothelial growth factor (VEGF) and PlGF are likely responsible for normal trophoblastic proliferation, migration and invasion and low levels of VEGF and PlGF or antagonists to VEGF or PlGF are plausible mediators of PE and IUGR. (1) VEGF levels are undetectable early in pregnancy accordingly estimation of PlGF is considered an index of placental function and when low a biomarker for PE and IUGR [11].

Pathogenesis of PE and IUGR may involve an imbalance of angiogenic molecules, VEGF and PlGF and measurements of PlGF in combination with soluble Fms-like tyrosine kinase-1(sFlt-1), an antiangiogenic molecule, may distinguish women who develop PE from women who develop other complications of pregnancy [12].

There is mounting evidence that preeclampsia involves an imbalance between angiogenic and antiangiogenic factors, induced or exacerbated by placental ischemia, which results in maternal endothelial dysfunction. For example, increased serum levels of sFlt-1 would lead to an antiangiogenic status by decreasing bioavailability of the free VEGF and PlGF. The consequent disruption of VEGF-PlGF signalling would result in endothelial damage and the clinical onset of PE [13].

Chaiworapongsa et al. found that elevated sFlt-1correlated with the severity and early onset of PE. However, Robinson et al. and Kim et al. observed no differences between mild and severe PE and early-onset and late-onset PE in terms of serum sFlt-1 but found the PE-related decrease in serum PlGF to be more pronounced in severe and early-onset PE [14-16]

A study of Thadhani et al. found that there was no statistical difference between maternal serum sFLt-1 levels in the first trimester in PE and IUGR and normal controls. In contrast to maternal serum sFlt-1, maternal serum PlGF levels did differ significantly compared with controls and thus subsequent risk for PE and IUGR can be obtained with and without inclusion of sFLt-1 in the models [17]. They also found the risk for PE and IUGR was significantly increased for every log unit decrease in maternal serum PlGF levels in the first trimester.

The ideal biomarker for PE and IUGR should be easily measured, simple, rapid, non-invasive, inexpensive, easy to perform, and should not expose the patient to discomfort or risk. The technology should be widely available and the results reproducible and reliable with a good sensitivity and specificity. Ideally it should provide an opportunity for intervention to prevent development of the disease or at least result in better maternal and/or fetal outcomes, should predict mild versus severe PE and IUGR, should delineate risk well early in pregnancy, best in the first trimester, and should serve as plausible mediator in its pathogenesis [18].

The present study suggested that PI of UtAs and maternal serum PlGF in the first trimester may be ideal markers for prediction of PE and IUGR as it had an accuracy of more than 87 and 89% respectively Tables 3 and 4. Elzen et al. (1995) examined 352 women at 12-13 weeks of gestation and found that groups with uterine artery PI in the higher quartile had an increased risk of subsequently developing PE [19].

In 2005, Gomez et al. published a prospective trial in prediction of PE, IUGR. PI greater than the 95th percentile was used at the cut-off value they identify 24% of pregnancies complicated by PE and IUGR [20]. Crovetto et al. conducted a large prospective study including 9462 women who underwent first-trimester screening. The authors reported that 11-13 weeks UT A. Doppler was included in the beak model for prediction of PE was a high detection rate [21], Abd El moety et al. studied first trimester UtA PI for prediction of PE and IUGR, at a cut- off point of 2.37, sensitivity was 100% [22].

This article is available from: http://dx.doi.org/10.21767/ 2476-1974.100015

The study of Melchiore et al. showed that there were no significant differences in first –trimester mean UtA PI in prevalence of bilateral notching between women who had a normal pregnancy outcome and those who developed PE [23]. In 2009 Melchrorre et al. carried out a prospective observational study and found that a mean UtA RI greater than 90th percentile in first trimester had a sensitivity of 25% for IUGR with specificity of 91.4% [24]. Martin et al. at 11-14 weeks gestations using the 95th percentile of mean PI as the screening threshold, the sensitivity and specificity for PE detection were 27% and 95.4% compared with 11.7% and 95.6% for IUGR [25]. Another study found the sensitivity and PPV of UtA PI, for prediction of PE, were low 27-81.3% and 3.1-11.3% respectively [26]. Dugoff et al. found, at 10-14 weeks'gestation, UtA PI above the 95th percentile had a sensitivity of 16.6% and specificity of 95% in prediction of PE and IUGR and no significant association between notching (unilateral or bilateral) and development of these pregnancy complications [27].

The sensitivity and specificity of first trimester UtAPI in predicting of PE in eight studies was 25.4% and 93.3% respectively and for IUGR 15.4% and 93.3% respectively [28]. Consequent to these studies, it is plausible that the addition of maternal serum biomarkers of placental development may further improve prediction either by increasing sensitivity or by lowering the false positive rate.

PlGF is an angiogenic growth factor related to VEGF. Both are produced by the trophoblast. VEGF and PlGF are likely responsible for normal trophoblast proliferations, migration and invasion of the spiral arteries and their conversion to wide uteroplacental vessels. Consequently VEGF and PLGF are ideal biomarkers that may increase the sensitivity and positive predictive value of UtA PI for prediction of PE and IUGR [11,29].

Although some investigators have suggested that levels of PlGF have not altered among women subsequently developed PE and IUGR, others have reported just the opposite as PlGF levels decrease in cases destined to have PE and IUGR, from the first trimester of pregnancy. Levels of VEGF are undetectable in the first trimester of pregnancy [11,30].

Kasdaglis et al. proved that many maternal variables such as race, smoking or caffeine intake were not found to have a relationship with PlGF levels [31]. Levine et al. found that the balance of angiogenic factors plays an important role in invasion of extravillous trophoblast into the decidual spiral arteries and transforming them into uteroplacental vessels and therefore a relationship with placental Doppler parameters is expected. This may support the use of combined Ut API and maternal serum PlGF in the first trimester for prediction of PE and IUGR [32].

In this study the sensitivity and PPV of UtA PI for prediction of PE and IUGR were 42.8%, 47.36%, 3.5% and 20.0% respectively. Combining PlGF with UtA PI raised the sensitivity and PPV for prediction of PE and IUGR to 92.85%, 94.75%, 28.88% and 40.0% respectively. The differences were statistically significant ($p<0.05$). PAPP-A is a syncytiotrophoblast-derived metalloproteinase, which enhances the mitogenic function of the insulin-like growth factors by cleaving the complex formed between such growth factors and their binding proteins. Insulin-like growth factor system is believed to play an important role in placental growth and development; it is not surprising that low maternal serum of PAPP-A in the first trimester, in absence of chromosomal abnormalities, can predict PE and IUGR [33]. However measurement of PAPP-A is not an effective standalone screening tool for prediction of PE and IUGR because less than 20% of the affected cases present serum levels below the fifth percentile [33].

In 2014, Hynh et al. concluded that data were sparse and often conflicting but reviewing recent literature revealed some evidence of an association between low PAPP-A levels in the first trimester and adverse pregnancy outcomes including PE and IUGR. In this study, sensitivity and PPV of PAPPA-A (cut- off value of 0.45 MoM) for prediction of PE and IUGR were 50.1%, 42.10%, 28.0% and 32.0% respectively which were lower than the sensitivity and PPV of PlGF. More-over combining of PAPP-A with UtA PI and PlGF for prediction of PE and IUGR did not improve the sensitivity, specificity, PPV and NPV or accuracy (Table 4) [34].

Conclusion

The ideal first trimester markers for prediction of PE and IUGR in low risk pregnant women may be a combination of UtA PI and maternal serum PlGF.

Acknowledgement

We are very grateful to Prof Dr Ibraheem Kabbash, Professor of community medicine and medical statistics, Faculty of Medicine, Tanta University for performing the statistical analysis of this article.

References

1. Kane SC, Costa DS, Brennecke S (2014) First trimester biomarkers in the production of later pregnancy complications. Biomed Res Int 2014: 213-218.
2. Hunt JS, Petroff MG, McIntire RH, Ober C (2005) HLA-G and immune tolerance in pregnancy. The FASEB J 19: 684-693.
3. Everett TR, Lees CC (2012) beyond the placental bed: placental and systemic determinants of the uterine artery Doppler waveform. Placenta 33: 893-901.
4. Wallace AE, Host AJ, Whitley GS, Cartwright JE (2013) Decidua natural killer cell interactions with trophoblasts is impaired in pregnancies at increased risk of preeclampsia. Am J Pathol 183: 1953-1861.
5. Alves JAG, Silva BYDC, Souse PCPD, Maia SB, Costa FDS (2013) Reference range of uterine artery Doppler parameters between the 11th and 14th pregnancy weeks in a population sample from North east Brazil. Rev Bras Ginecol Obstet 32: 128-132.
6. Lefebvre J, Demers S, Bujold E (2012) Comparison of two different sites of measurement for transabdominal uterine artery Doppler velocimetry at 11-13 weeks. Ultrasound Obstet Gynecol 40: 288-292.
7. Ridding G, Schluter PJ, Hyett JA, Mclennan AC (2014) uterine artery pulsatility index assessment at 11-13 weeks' gestation. Fetal Diagn Ther 36: 299-304.

8. Guidance: Hypertension in Pregnancy: The Management of Hypertensive Disorders During pregnancy (2010) National Institute for Health and Clinical Excellence.

9. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, et al. (2014) Maternal adaptations to pregnancy. In Williams Obstetrics Cunningham FG et al (eds) McGraw-Hill: New York pp 167-200.

10. Papageorghiou AT, Yu C, Erasmus I, Cuckle H, Nicolaides K (2005) Assessment of risk for the development of preeclampsia by maternal characters' and uterine artery Doppler. BJOG 112: 167-200.

11. Taylor RN, Grim Wood J, Taylor RS, McMaster M T, Fisher SJ, et al. (2003) Longitudinal serum concentrations of placental growth factor evidence for abnormal placental angiogenesis in pathologic pregnancy 2002; Am J Obstet Gynecol 188: 177-182.

12. Maynard SE, Min JY, Merchan J, Lim KH, Li J, et al. (2003) Excess placental soluble Fms-like tyrosine kinase 1(SFlt-1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 88: 2348-2351.

13. Widmer M, Villar J, Benigni E (2007) Mapping the theories of preeclampsia and the role of angiogenic factors:a systemic review. Obstet Gynecol 109: 734-741.

14. Chaiworapongsa T, Romero R, Espinoza J (2004) Evidence supporting a role for blockade of vascular endothelial growth factor system in the pathophysiology of preeclampsia. Am J Obstet Gynecol 190: 1541-1550.

15. Robinson CJ, Jhnson DD, Chang EY (2006) Evaluation of placental growth factor and soluble fms-like tyrosine kinase-1receptor levels in mild and severe preeclampsia. Am J Obstet Gynecol 195: 255-259.

16. KimYN, Lee DS, Jeong DH (2009) The relationshipof the level of circulating antiangiogenic factors to clinical manifestations of preeclampsia. Prenat Diagn 29: 464-470.

17. Thadhani R, Mutter WP, Wolf M, Levine RJ, Taylor VR, et al. (2004) First trimester placental growth factor and soluble fms-like tyrosine kinase I and risks for preeclampsia. J Clin Endocrinol Metab 89: 770-775.

18. Roberts JM, Redman DW (2001) Pathogenesis and genesis and genetics of preeclampsia, Lancet 357: 53-56.

19. van den Elzen HJ, Cohen-Overbeek TE, Grobbee DE, Quartero RW, Wladimiroff JW (1995) Early uterine artery Doppler velocimetry and the outcome of pregnancy in women age 35 years Ultrasound Obstet Gynecol 5: 328-33.

20. Gomeze O, Martinez JM, Figueras F (2005) Uterine artery Doppler at 11-14 weeks of gestation to screen for hypertensive disorders and associated complications in an unselected population. Ultrasound of obstetrics and Gynecology 26: 490-494.

21. Crovetto F, Fiqueras F, Triunfo S (2015) First trimester screening for early and late preeclampsia based on maternal characteristics, biophysical parameters and angiogenic factors. Prenat Diagn 35: 183-191.

22. Abel Moety G, Almohamedy M, Sherif N, Raslana A, Mohamed T, et al. (2015) Could first-trimester assessment of placental functions predict preeclampsia and intrauterine growth restriction? A prospective cohort study. J Matern Fetal Neonatal Med pp 1-5.

23. Melchiore K, Wormald B, Leslie K (2008) First-trimester uterine artery Doppler indices in term and preterm pre-eclampsia. . Ultrasound Obstet Gynecol 32: 133-137.

24. Melchiore K, Leslie K, Prefumo F (2009) First trimester uterine artery Doppler in the prediction of small-for gestational age pregnancy and intrauterine growth restriction. Ultrasound Obstet Gynecol 33: 524-529.

25. Martin AM, Bindra R, Curcio P (2001) Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11-14 weeks of gestation. Ultrasound Obstet Gynecol 18: 583-586.

26. Bahado-Singh RO, Jodicke C (2010) Uterine artery Doppler in first-trimester pregnancy screening. Clin Obstet Gynecol 53: 879-887.

27. Dugoff L, Lynch AM, Cioffi-Ragan D (2009) First trimester uterine artery Doppler abnormalities predict subsequent intrauterine growth restriction. Am J Obstet Gynecol 33: 524-529.

28. Kasdaglis T, Aberdeen G, Baschat AA (2010) Placental Growth factor in the first trimester: relationship with maternal factors and placental Doppler studies. Ultrasound Obstet Gynecol 35: 280-285.

29. Ong CY, Liao AW, Cacho Am, Spencer K, Nicolaides KH (2001) First-trimester maternal serum levels of placental growth factor as predictor of preeclampsia and fetal growth restriction. Obstet Gynecol 98: 1218-1220.

30. Tidwell SC, Ho HN, Chiu WH, Shau WY, Chow SN, et al. (2001) Decreased serum placental growth factor in early second trimester and preeclampsia. Am J Obstet Gynecol 97: 898-904.

31. Kasdaglis T, Aberdeen G, Turan O, Kopelman J, Atlas R, et al. (2010) Placental growth factor in the first trimester: relationship with maternal factors and placental Doppler studies. Ultrasound Obstet Gynecol 35: 280-285.

32. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, et al. (2004) Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 350: 672-683.

33. Staboulidou I, Galindo A, Maiz N, Karagiannis G, Nicolaides KH (2009) First-trimester uterine artery Doppler and serum pregnancy-associated plasma protein-A in preeclampsia and chromosomal abnormalities. Fetal Diagn Ther 25: 336-339.

34. Huynh L, Kingdom J, Akhtar S (2014) Low pregnancy-associated plasma protein A in the first trimester. Can Fam Physician 60: 899-903.

This article is available from: http://dx.doi.org/10.21767/ 2476-1974.100015