

Trans abdominal Uterine Artery Doppler Between 11th To 14th Week of Gestation for the Prediction Of outcome In High-Risk Pregnancies

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Abstract: Background: Uterine Artery Doppler is promising. An ultrasound screening programme in high risk pregnant women, especially women with preeclampsia, would offer clinicians the opportunity to pre-empt the disease before it manifests clinically. **Aim of the Work:** Is to assess the value of transabdominal uterine artery Doppler ultrasound between 11-14 weeks of gestation for the prediction of outcome in pregnancies at high risk for preeclampsia. **Patients and Methods:** An observational study proposed to 100 women referred to antenatal clinic of Bab El-Sheriya hospital for high-risk pregnancies. **Results:** Abnormal uterine artery Doppler has a low positive predictive value, on the other hand its absence predict quit well the absence of preeclampsia (NPV=100%) and fetal growth restriction (NPV=100%). **Conclusion:** Normal uterine arteries Doppler ultrasound in the form of absence of bilateral notching and resistance index (RI)<0.80 between 11-14 weeks of gestation is strongly related to normal pregnancy outcome in women at high risk for preeclampsia. **Recommendations:** Normal uterine artery Doppler waveforms in the first trimester identify women who are suitable for routine antenatal care, hence the importance of uterine artery Doppler between 11-14 weeks of gestation, especially in high risk pregnancies. It is a single, easy and cheap test.

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Key words: abdominal Uterine Artery Doppler, gestation, preeclampsia, ultrasound screening programme

1. Introduction

Preeclampsia occurs in about 3% of pregnancies, with a risk of recurrence ranging from 7.5% to 65% (Sibai et al., 1991).

An increased risk of preeclampsia has also been reported in the presence of chronic conditions such as: chronic hypertension, renal diseases, diabetes, autoimmune diseases, and inherited thrombophilias (Makkonen et al., 2000).

In uncomplicated pregnancies the spiral arteries undergo a series of changes that convert them from small diameter high-resistance vessels into low-resistance channels, while defective trophoblastic invasion is associated with subsequent development of preeclampsia and fetal growth restriction, which are major causes of perinatal and maternal mortality (Brosens et al., 1997).

There is evidence that uterine artery Doppler can be used as a tool for the assessment of trophoblast invasion in the first trimester, as the proportion of decidual vessels with endovascular trophoblast invasion is significantly higher in pregnancies with low uterine artery resistance when compared with high-resistance ones (Prefumo et al., 2004).

Early identification of pregnancies at risk to develop severe complications such as preeclampsia is one of the main objectives of perinatal medicine.

Although the underlying mechanism of these complications is still poorly understood, there are increasing evidences of a relationship between impaired placentation and the subsequent development of preeclampsia (Pijnenborg et al., 1994).

Doppler ultrasonography, a non invasive method for studying the uteroplacental circulation, provides the capability to qualitatively evaluate blood flow in small branches of the uterine arteries. In normal pregnancies, impedance to flow in the uterinearteries decrease with gestation. However, in cases of impairment of trophoblastic invasion, Doppler studies showed increased impedance to flow in the uterine arteries as they failed to develop into low resistance vessels (Dugoff et al., 2005).

Hafner et al., (2006) reported that placental volume and uterine artery Doppler have similar sensitivities for predicting preeclampsia, although uterine artery Doppler is marginally more sensitive for prediction of preeclampsia.

Schuchter et al., (2001) demonstrated that an increased uterine artery pulsatility index (PI) and a decreased placental volume at 11-14 weeks of gestation, is associated with the subsequent development of fetal growth restriction and pregnancy induced hypertension.

Aim of the Work:

The aim of this study to assess the value of transabdominal uterine artery Doppler ultrasound between 11-14 weeks of gestation for the prediction of outcome in pregnancies at high risk for preeclampsia.

2. Subjects and Methods:

This observational study proposed to 100 women referred to antenatal clinic of Bab El-Sheriya hospital for high risk pregnancies.

Inclusion criteria:

- 1- Singleton pregnancy.
- 2- Gestational age between 11-14 weeks confirmed by ultrasound.
- 3- Increased risk of developing preeclampsia given by previous early onset preeclampsia, previous HELLP syndrome (hemolysis, elevated liver enzymes, low platelet) or eclampsia, presence of chronic disease such as: chronic hypertension, renal disease, autoimmune diseases or inherited thrombophilia, and a history of early fetal growth restriction in the previous pregnancy, unexplained intrauterine death, or placental abruption not associated with abdominal trauma.

Exclusion criteria:

Patients with multiple pregnancy, gestational age above 14 weeks at the first evaluation, and fetal structural or chromosomal abnormalities excluded from the study.

Full consent was taken from each patient, then all patients included were subjected to the following;

- 1- Full history taking.
- 2- General examination.
- 3- Doppler ultrasound of uterine artery was performed using a 3.5-5MHz curvilinear transabdominal probe, and the size of the sampling gate was set to 2mm. Patients were examined in semi recumbent position. A mid sagittal section of the uterus was obtained and the cervical canal was identified. The probe moved laterally until the paracervical vascular plexus was seen. Color Doppler was turned on and the uterine artery was identified as it turned cranially to make its ascent to the uterine body. Measurements were taken at this point, before the uterine artery branched into the arcuate arteries. The pulsed Doppler gate was placed over the vessel and the signal was updated until at least three consecutive flow velocity waveforms of good quality were obtained. The presence of diastolic notching and resistance index (RI) were investigated. Abnormal uterine Doppler identified by the presence of bilateral notching or by mean resistance index (RI) >0.8 at 11-14 weeks of gestation.

Adverse gestational outcomes evaluated in this study were preeclampsia (blood pressure $>140/90$ mmHg and proteinuria >0.3 g/24h after 20 weeks of pregnancy), fetal growth restriction, placental abruption and intrauterine death.

Statistical analysis was done using Chi-square test, and a p-Value less than 0.05 considered statistically significant.

3. Results

Our study included 100 pregnant women at high risk for preeclampsia where transabdominal Doppler ultrasound of the uterine artery at 11th to 14th weeks of pregnancy was performed to them to investigate the presence of diastolic notching and measure resistance index. These women were followed-up prospectively to evaluate adverse outcomes and to correlate its appearance with early Doppler measurements.

Table (1): Indications for referral for the 100 women enrolled in the study.

Indication	n (%)
History of preeclampsia	32(32%)
History of fetal growth restriction	9(9%)
History of intrauterine death	4(4%)
History of placental abruption	5(5%)
Chronic hypertension	35(35%)
Renal disease	12(12%)
Autoimmune disease	2(2%)
Inherited thrombophilia	1(1%)

117 patients met all the criteria of the study and were included in the study, however 17 of these missed during follow up and were excluded because pregnancy outcome data were not available.

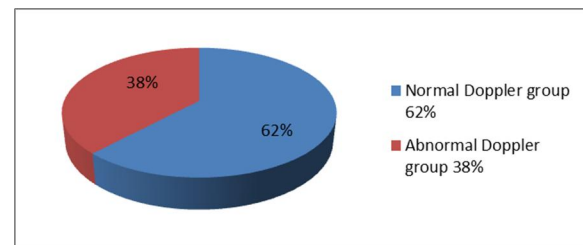


Fig. (2): Percentage of women with normal and abnormal uterine artery waveform among the studied group.

Among 100 women, 38(38%) had abnormal uterine artery Doppler and 62(62%) had normal uterine artery Doppler.

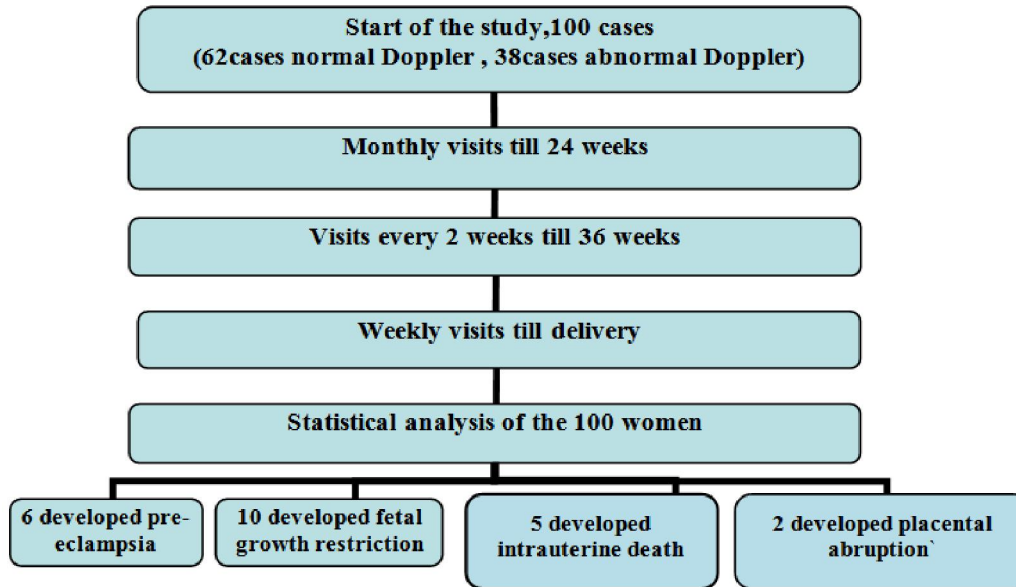


Table (2): Prevalence of adverse gestational outcomes among the 100 women enrolled in the study and among the normal and abnormal Doppler groups.

Adverse gestational outcomes	Prevalence (n=100)	Normal Doppler (n=62)	Abnormal Doppler (n=38)
Preeclampsia	6 (6%)	0	6
Fetal growth restriction	10 (10%)	0	10
Intrauterine death	5 (5%)	0	5
Placental abruption	2 (2%)	2	0

Adverse gestational outcomes evaluated were preeclampsia in 6 cases, fetal growth restriction in 10 cases, intrauterine death in 5 cases and placental abruption in 2 cases. All cases of preeclampsia, fetal growth restriction and intrauterine death were among the abnormal Doppler group while the two cases of placental abruption were among the abnormal Doppler group.

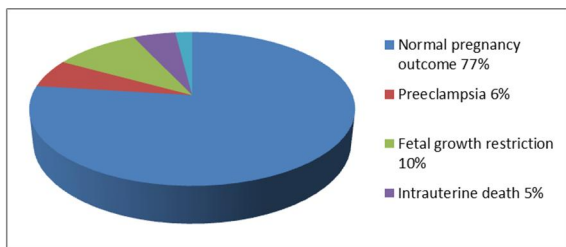


Fig. (3): Prevalence of adverse gestational outcomes among the 100 women enrolled in the study.

Adverse gestational outcomes evaluated were preeclampsia in 6 cases, fetal growth restriction in 10 cases, intrauterine death in 5 cases and placental abruption in 2 cases.

Table (3): General data of the total population of the studied group (n=100).

Variable	Mean±SD
Age	23.6±5
Weight	67.9±7.8
Height	158.9±7
BMI	27±3

This table shows the general data of the studied patients: age, weight, height and body mass index (BMI).

Table (4): Comparison between the studied groups as regard the general data.

Variable	Normal Doppler (n=62)	Abnormal Doppler (n=38)	P value
Age	27.9±5	24±6	>0.05NS
Weight	68±9	69±8	>0.05NS
Height	160±5	158±6	>0.05NS
BMI	26.7±4.4	27.5±2.5	>0.05NS

This table shows that there is no significant (NS) differences between both studied groups as regard general data.

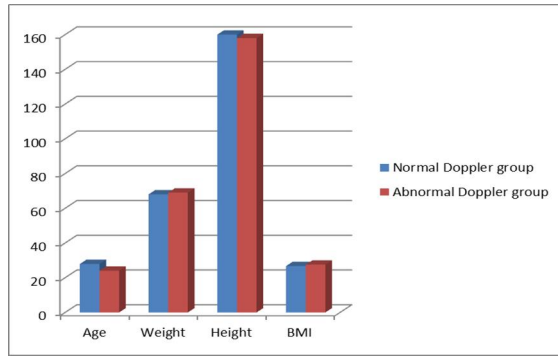


Fig. (4): Comparison between the studied groups as regard the general data.

From the grid chart, it is obvious that the difference is negligible between the studied groups as regard the general data.

Table (5): Laboratory data of the total population of the studied group (n=100).

Variable	Mean±SD
HB	10.9±1.03
Platelets	257.4±32
Urea	24.85±4
Creatinine	0.67±0.03

From the table, the average hemoglobin of the total cases was 10.9gm/dL and the average platelets count was 257.4 thousand/mm³. Moreover, the average blood urea was 24.8mg/dL and the average serum creatinine was 0.67mg/dL.

Table (6): Comparison between the studied groups as regard the laboratory data.

Variable	Normal Doppler (n=62)	Abnormal Doppler (n=38)	P value
Hb	10.8±1.03	11±0.7	>0.05NS
Platelets	272.8±32	242±31	>0.05NS
Urea	25.7±4	24±3.5	>0.05NS
Creatinine	0.7±0.03	0.65±0.06	>0.05NS

From the table it is obvious that there is no significant (NS) differences between normal Doppler cases and cases who had abnormal Doppler concerning the laboratory data.

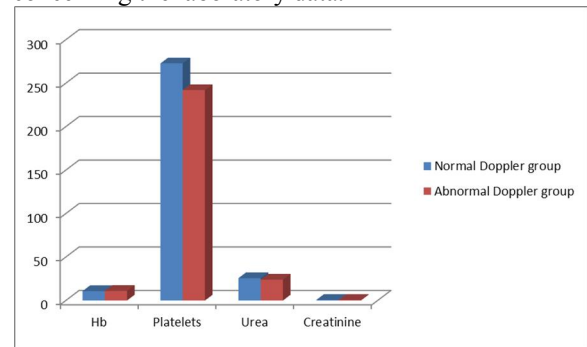


Fig. (5): Comparison between the studied groups as regard the laboratory data.

The grid chart shows that there is very little differences as regard the laboratory data of both groups.

Table (7): Correlation between adverse gestational outcomes with uterine artery Doppler at 11th to 14th weeks of gestation.

Adverse gestational outcomes	Normal Doppler (n=62)	Abnormal Doppler (n=38)	P-Value
Preeclampsia	0	6	0.005
Fetal growth restriction	0	10	0.0003
Intrauterine death	0	5	0.02
Placental abruption	2	0	0.32NS

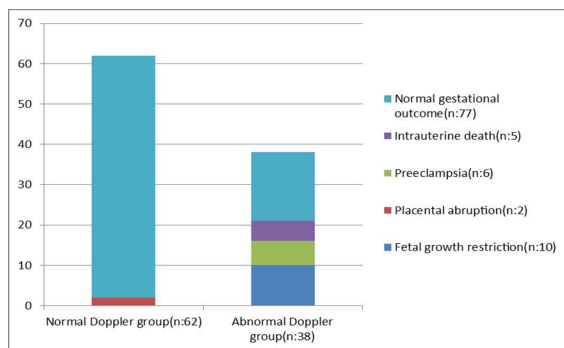


Fig. (6): Prevalence of adverse gestational outcomes among the normal and abnormal Doppler groups.

This table shows that in women at high risk for preeclampsia, normal impedance to flow in uterine arteries between 11-14 weeks of gestation is strongly related to normal pregnancy outcome, as no patients with normal uterine artery flow had preeclampsia, fetal growth restriction or intrauterine death. Significant p-Value is observed in adverse gestational outcomes as preeclampsia, fetal growth restriction and intrauterine death, while it is not significant in placental abruption.

This figure shows that in women at high risk for preeclampsia, normal impedance to flow in uterine arteries between 11-14 weeks of gestation is strongly related to normal gestational outcome, as no patients

with normal uterine artery flow had preeclampsia,

fetal growth restriction or intrauterine death.

Table (8): Predictive value of abnormal uterine artery waveform configuration at 11th to 14th weeks of gestation.

Adverse outcomes	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Preeclampsia	100%	65.9%	15.7%	100%
Fetal growth restriction	100%	68.8%	26.3%	100%
Intrauterine death	100%	65.2%	13.1%	100%

This table shows the sensitivity, the specificity, the positive predictive value (PPV) and the negative predictive value (NPV) of abnormal uterine artery waveform configuration at 11th to 14th weeks of gestation. Abnormal uterine artery Doppler has a low positive predictive value, on the other hand it's absence predict quite well the absence of preeclampsia (NPV=100%) and fetal growth restriction (NPV=100%).

4. Discussion

The development of pre-eclampsia and fetal growth restriction is thought to be a consequence of impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels into wide non-muscular channels, the physiological process of trophoblastic invasion is reflected in the observation from Doppler ultrasound studies that impedance to flow in the uterine arteries decreases with gestation between 6 and 24 weeks and remains constant thereafter (**Kingdom et al., 2000**).

Physiological transformation of placental vessels is usually complete by 24 weeks of gestation. It can be observed that uterine artery vascular impedance decreases until 24 weeks as a reflection of vessel transformation, and in normal pregnancy uterine artery vascular impedance remains largely unchanged for the remainder of the pregnancy (**Papageorgiou et al., 2005**).

In pregnancies complicated by pre-eclampsia and/or intrauterine growth restriction, impedance to flow in the uterine arteries is increased. Studies in women with hypertensive disease of pregnancy have reported that, in those with increased impedance (increased resistance index or the presence of an early diastolic notch), compared to hypertensive women with normal flow velocity waveforms, there is a higher incidence of pre-eclampsia, intrauterine growth restriction, emergency Cesarean delivery, placental abruption, shorter duration of pregnancy and poorer neonatal outcome (**Prefumo et al., 2004**).

In the current study 100 women at high risk for preeclampsia with singleton pregnancy and gestational age between 11-14 weeks were included, full consent was taken from each patient, then all patients included were subjected to the following;

4- Full history taking.

5- General examination.

6- Doppler ultrasound of uterine artery was performed using a 3.5-5MHz curvilinear transabdominal probe, and the size of the sampling gate was set to 2mm. Patients were examined in semi recumbent position. A mid sagittal section of the uterus was obtained and the cervical canal was identified. The probe moved laterally until the paracervical vascular plexus was seen. Color Doppler was turned on and the uterine artery was identified as it turned cranially to make its ascent to the uterine body. Measurements were taken at this point, before the uterine artery branched into the arcuate arteries. The pulsed Doppler gate was placed over the vessel and the signal was updated until at least three consecutive flow velocity waveforms of good quality were obtained. The presence of diastolic notching and resistance index (RI) were investigated. Abnormal uterine Doppler identified by the presence of bilateral notching or by mean resistance index (RI) >0.8 at 11-14 weeks of gestation.

Follow-up of the cases:

- Monthly visit till the end of the second trimester.

- Then, fortnightly till the end of the 36th week.

- Then, weekly till delivery.

The following were done in each visit:

- Blood pressure was measured to assess development of pre-eclampsia (elevation of blood pressure >140/90 in two successive occasions at least 6hrs apart after complete physical and mental rest with positive albuminuria >300mg/Litre with or without edema).

- The blood pressure was measured in the sitting position for all patients with the lower arm at heart level. The cases should be in complete physical and mental rest during blood pressure measurement.

- Urine sample was taken in each visit to detect albuminuria.

- Examination of the lower limb to detect edema and its level if present by pressing the thumb against the tibia in the leg edema and pinching for higher edema.

- Abdominal examination to assess fundal level and symphysiofundal height.

- Abdominal ultrasound by the same machine mentioned (abdominal probe with a frequency 3.5MHz) to check fetal viability and to estimate its biometry to detect fetal death or growth restriction.

- Fetal death is determined by absent fetal heart beats, and fetal growth restriction is determined when the fetal biometry is less than 5th percentile for its corresponding gestational age on growth curves.

Adverse gestational outcomes evaluated in this study were preeclampsia (blood pressure >140/90mmHg and proteinuria > 0.3g/24h after 20 weeks of pregnancy), fetal growth restriction, placental abruption and intrauterine death. Statistical analysis was done using Chi-square test, and a p-Value less than 0.05 considered statistically significant.

Our study shows that in women at high risk for preeclampsia, normal impedance to flow in uterine arteries between 11-14 weeks of gestation is strongly related to normal pregnancy outcome, as no patients with normal uterine artery flow had preeclampsia, fetal growth restriction or intrauterine death.

Transabdominal Doppler ultrasonography is less invasive than transvaginal technique and is an effective and reproducible method of measuring uterine artery pulsatility index (PI) or resistance index (RI) in the first trimester (**Martin et al., 2001**) (**Hollis et al., 2001**).

Quantitatively, the RI appears to be the most repeatable and reproducible measurement between 10-14 weeks of gestation, and also a qualitative assessment of the inter-observer agreement (**Hollis et al., 2001**).

Bilateral notching is present in about 50% of patients in the first trimester, therefore it has a low positive predictive value, on the other hand its absence predicts quite well the absence preeclampsia and fetal growth restriction. By recognizing normal uterine artery Doppler waveform at 11-14 weeks of gestation, it is possible to identify a low-risk population suitable for community antenatal care (**Vainio N et al., 2005**).

Existing data coming from screening studies suggest that increased impedance to flow in uterine arteries between 11 and 14 weeks identifies 27% of women who subsequently develop preeclampsia. Sensitivity of first trimester uterine artery Doppler for preeclampsia and fetal growth restriction requiring delivery before 32 weeks is higher being 60% and 28% respectively, but the high false positive rate and the low positive predictive value remain the main limitation (**Martin et al., 2001**). Only a few studies have evaluated first trimester uterine artery Doppler in high-risk pregnancies and all used transvaginal ultrasound (**Vainio et al., 2005**).

Our study evaluate the correlation between uterine artery Doppler at 11-14 weeks of gestation studied with transabdominal approach and gestational outcome in high-risk patients. Normal impedance to flow in uterine arteries conferred a high reduction in the risk of developing preeclampsia: no woman with normal uterine artery waveform in the first trimester developed preeclampsia. Our results obtained with transabdominal approach are comparable to those obtained transvaginally by Vainio et al., who showed that absence of bilateral notching, assessed with transvaginal ultrasound Doppler at 12-14 weeks of gestation, had a 97% negative predictive value for preeclampsia and fetal growth restriction in a high-risk population (**Vainio et al., 2005**).

Patients with abnormal uterine artery Doppler waveform configurations are a high-risk group that might benefit from prophylactic interventions. In low risk population, the sensitivity of uterine artery Doppler for prediction of preeclampsia and fetal growth restriction is lower when the test is carried out at 11-14 weeks of gestation rather than 22-24 weeks. However, the potential advantage of earlier screening is that prophylactic intervention may be more effective (**Hollis et al., 2001** **Vainio et al., 2002**). Although low dose aspirin treatment significantly reduces the incidence of preeclampsia in selected populations (**Duley L et al., 2007** **Campbell S 2005**), this is more likely to be effective when started in the first trimester, before the secondary wave of trophoblast invasion has begun.

The results of this study were in agreement with the study done by **Fratelli et al., (2008)**, who evaluate the correlation between uterine artery Doppler at 11-14 weeks studied with a transabdominal approach and gestational outcome in high risk patients. Impedance to flow in uterine arteries was increased in 86% of the women who subsequently developed complications requiring delivery before 34 weeks of gestation. Normal impedance to flow in uterine arteries conferred a high reduction in the risk of preeclampsia: no woman with normal uterine artery waveform in the first trimester developed preeclampsia and only one required delivery before 34 weeks of gestation. The results obtained with a transabdominal approach are comparable to those obtained transvaginally by **Vainio N et al. (2005)**, who showed that absence of bilateral notching, assessed with transvaginal ultrasound Doppler at 12-14 weeks of gestation, had a 97% negative predictive value for preeclampsia and fetal growth restriction in a high risk population.

The results of this study were in agreement with other studies, that showed a one-stage color Doppler screening program at 23 weeks identified most women who subsequently developed serious

complications of impaired placentation associated with delivery before 34 weeks (**Albaiges et al., 2000**), (**Lees et al., 2001**), (**Papageorghiou et al., 2004**), (**Ricardo et al., 2008**), (**Cnossen et al., 2008**), (**Katie et al., 2009**).

In the study done by **Ricardo et al. (2008)** Doppler examination of the uterine arteries was carried out in 1057 singleton pregnancies at 22-24 week. The mean uterine artery PI was 1.03 and the 95th percentile was 1.55. In 54 cases (5.1%) the mean PI was > 1.55 (screen positive). In the study population there were 48 cases of preeclampsia (5.1%), 72 fetal growth restrictions (7.5%) and 7 intrauterine deaths (0.7%). The screen-positive group showed an incidence of 47.1% of combined adverse results. The relative risks after a positive screening test were 7.3 (CI 4.2–12.6) for pre-eclampsia, 3.9 (CI 2.3 – 6.6) for fetal growth restriction and 4.5 (CI 3.2–6.4) for overall placental insufficiency. So they concluded that, Uterine artery Doppler at 22–24 weeks identifies women at higher risk for the development of subsequent complications of placental insufficiency. This test could be used in combination with other markers to stratify the level of care offered in the third trimester of pregnancy.

Cnossen et al. (2008) reported that, Uterine artery Doppler ultrasonography provided a more accurate prediction when performed in the second trimester than in the first-trimester. An increased pulsatility index with notching was the best predictor of pre-eclampsia (positive likelihood ratio 21.0 among high-risk patients and 7.5 among low-risk patients). It was also the best predictor of overall (positive likelihood ratio 9.1) and severe (positive likelihood ratio 14.6) intrauterine growth restriction among low-risk patients. So they concluded abnormal uterine artery waveforms are a better predictor of pre-eclampsia than of intrauterine growth restriction. A pulsatility index, alone or combined with notching, is the most predictive Doppler index. These indices should be used in clinical practice. Future research should also concentrate on combining uterine artery Doppler ultrasonography with other tests.

Few studies have examined the value of uterine artery screening in the first trimester, **Martin et al. (2001)** reported that, the sensitivities for pre-eclampsia requiring delivery before 36, 34 and 32 weeks were 40, 50 and 60% respectively, and for FGR they were 22, 24 and 28% respectively. The results of the study were compared to second trimester screening performed on a similar population and although the sensitivities were found to be lower in first versus second trimester screening, the authors concluded that the potential advantage of earlier identification of a high-risk group might make prophylactic interventions more effective.

Some Studies combining uterine artery Doppler with maternal serum markers have demonstrated that measurement of first-trimester maternal serum pregnancy-associated plasma protein A and free beta human chorionic gonadotrophin improve sensitivities of second-trimester Doppler. Maternal serum placental protein 13 remains a promising method for early screening, although a recent study suggests lower sensitivities than initially reported. **Papageorghiou and Campbell, (2006)** reported that, uterine artery Doppler screening identifies women at high risk for developing adverse pregnancy outcomes. Detection rates may be increased and false positive rates reduced by combination with maternal characteristics or serum markers.

Conclusion

In conclusion, our results indicate that normal uterine arteries Doppler ultrasound in the form of absence of bilateral notching and resistance index (RI)<0.80 between 11-14 weeks of gestation is strongly related to normal pregnancy outcome in women at high risk for preeclampsia.

Recommendations

Normal uterine artery Doppler wave forms in the first trimester identify women who are suitable for routine antenatal care, hence the importance of uterine artery Doppler between 11-14 weeks of gestation, especially in high risk pregnancies. It is a single, easy and cheap test. Therefore, it should be implemented on a wider scale when Doppler facilities and expertise are available in maternity centers.

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