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RESEARCH ARTICLE

FIRST TRIMESTRIC BIO-CHEMICAL ANALYSIS OF MATERNAL SERUM HOMOCYSTEINE AND UTERINE ARTERY DOPPLER AS A NEW MODALITY FOR EARLY PREDICTION OF PERINATAL OUTCOME

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ABSTRACT

Background: Routine prenatal care focuses on the detection of women at increased risk, aiming for appropriate intervention. appropriate combinations of some markers can serve as an indicator for early prediction of any adverse pregnancy outcome.

Patients and methods: This is a prospective cohort study that was conducted at Obstetrics and Gynecology department, Al-Azhar University Hospital (New-Damietta). About 200 singletons, low risk pregnant women were included in the study. Both ultrasound examinations and bio-chemical analysis of serum homocysteine were performed at 11-14 weeks of gestation.

Results: Total homocysteine ranged from 2.5 to 11 µmol/l and there was statistically significant decrease of total homocysteine levels in non-complicated group when compared to complicated group. There was statistically significant difference between different scores as regard to total homocysteine (the lowest level was observed in zero score (5.20±0.80) and the highest in score three (7.62±2.21). There was significant moderate proportional correlation between ultrasound score and total homocysteine. Combining both ultrasound score (any of scores 1, 2, 3 or 4) with hyper-homocysteinemia revealed that, 165 cases were negative for this combination and 35 cases were positive. Predictive power of hyper-homocysteinemia alone was 75.0%; while abnormal ultrasound alone had predictive power of 0.67 and finally both abnormal ultrasound with hyper-homocysteinemia had a predictive power of 100.0%

Conclusion: The combination of homocysteine levelwith uterine artery doppler in the first trimester can be used as an early indicator in predicting adverse perinatal outcome.

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INTRODUCTION

First trimestric studying of the uteroplacental circulation through doppler velocimetry is an important modality that provides insight look and can be used as an assessment tool for assessing resistance to blood flow in this circulation so, it can be usedas a screening test to identify women at high risk for developing adverse pregnancy outcome. Intrauterine growth restriction (IUGR) is considered disease of theories. Numerous theories on the ethiopathogenesis of IUGR are based on alterations of placentation, a complex process initiated in the first trimester of pregnancy, which could compromise the normal development of the pregnancy. During thisperiod, a correct vascular adaptation betweenmaternal andfetal circulations is necessary, and this supposes some histological and functional changes (Lopez-Quesada *et al*., 2004).

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Abnormal placentation appears to play a role in the pathogenesis of preeclampsia and may serve as a common pathologic link with IUGR. Hyper-homocysteinemiahas been implicated as an independent risk factor for occlusive vascular diseases (Hankey *et al*., 1999). Therefore, the increased obstetric risk in hyper-homocysteinemiccases could be attributed to vasculardamage deriving from alterations of the placental vessels, withconsequent infarction and placental insufficiency. Also, hyper-homocysteinemiaare associated with serious pregnancy complications, including preeclampsia, abrupto-placentaand neural tube defects. Furthermore, an elevated plasma homocysteine concentration is regarded as a risk factor for atherosclerosis and venous thrombosis (Goddijn-Wessel *et al*., 1996). The etiology through which hyper-homocysteinemia is attributed to increased risks of pregnancy complications is unknown. One of these theories are Low dietary folate intakes and low circulating folate concentrations during pregnancy One metabolic effect of folate deficiency is an elevated plasma homocysteine concentration. It is not yet

known whetherhyper-homocysteinemiais harmful by itself through vascular damage,folate deficiency or defective methylation and DNA synthesis (Scholl TO *et al*., 2000).

Aim of the work

To evaluate the predictive value of combining both uterine doppler velocimetry and maternal plasma homocysteine levels at 11 to 14 weeks of gestation as an early predictor of adverse perinatal outcome.

PATIENTS AND METHODS

This is a prospective cohort study that was conducted at Obstetrics and Gynecology department, Al-Azhar University Hospital (New-Damietta). About 200 singletons, low risk pregnant women aged between 20 and 30 years were included in the study. All pregnant women receive 400 mcg of folic acid. The ultrasound examinations were performed at 11-14 weeks of gestation. Also, bio-chemical analysis of maternal plasma homocysteine was done at the same time. An 8-ml maternal blood sample was collected on the day the uterine artery (UA) doppler examination was performed. The sample was centrifuged at 4000 cycles/min for 5 min to separate the serum. The sera were stored at -30oC until the time for the analysis of homocysteine level. Plasma homocysteine level was determined by solid phase competitive chemiluminescent enzyme immunoassay (DPC IMMULITE 2500 analyzer, China). Hyper-homocysteinemia is defined as homo-cysteine levels at > 7.46 µmol/l.

Exclusion criteria

Females with one or more of the following were excluded from the study:

1) Diabetes mellitus;
2) Chronic hypertension;
3) Cardiovascular or renal disease;
4) Aspirin or anticoagulant drug intake;
5) Bleeding disorders.

All patients were subjected to full history taking (maternal age, gravidity, parity, body mass index), clinical examination and laboratory investigations (CBC, kidney and liver function tests, blood grouping and Rhesus factor identification). Patients were followed until delivery and any obstetric complications (pre-eclampsia, gestational hypertension, IUGR, placental abruption, intrauterine fetal death, preterm birth) encountered were recorded. Levels of homocysteine and Doppler scores were compared between pregnant women with and without obstetric complications. Statistical analysis: Comparison of maternal plasma homocysteine with different doppler scores was carried out using the one-way analysis of variances. The significance between two groups was evaluated by independent samples (t) test for numerical data and chi square test for categorical variables. Spearman correlation analysis was performed for correlations between two variables.

RESULTS

The present study included 200 pregnant females; 146 of them (73.0%) completed their pregnancy without complications, while 54 cases (27.0%) had complications. Prematurity was the most common complication, presented in 33 cases out of 54 cases (61.1%), and followed by pre-eclampsia in 16 cases (29.6%) and both conditions in 5 cases (9.3%). Female age ranged from 20 to 30 years and there was no statistically significant difference between non-complicated and complicated groups as regard to age (the mean age was 25.50±2.97 and 26.25±3.67 years respectively). Body weight ranged from 63 to 84 kg; the height ranged from 1.61 to 1.74m; while BMI ranged from 22.95 to 28.39 kg/m^2; and there was no statistically significant difference between complicated and non-complicated groups (Table 1). As regard to parity; 101 cases (50.5%) were primipara and 99 cases (49.5%) were multipara and there was no statistically significant difference between non-complicated and complicated cases as regard to parity (e.g., primipara represented 48.6% and 55.6% of non-complicated and complicated groups respectively). In addition, gestational age ranged from 33 to 40 weeks of gestation and there was statistically significant increase of gestational age in non-complicated group when compared to complicated group (37.93±0.79 vs 35.59±1.23 weeks respectively). Furthermore, fetal weight ranged from 1700 to 3350 gm; and there was statistically significant increase of fetal weight in non-complicated when compared to complicated groups (3157.87±87.28 vs 2868.14±214.63g respectively) (table 1).

As regard, uterine notch; uterine notch was absent in 145 cases out of 200 cases (72.5%); unilateral in 37 cases (18.5%) and bilateral in 18 cases (9.0%); and there was statistically significant increase of bilateral notch in complicated group when compared to non-complicated group (20.4% vs 4.8% respectively). In addition, pulsatility index of uterine artery ranged from 0.87 to 1.60 on the right side and from 0.80 to 1.50 on the left side; and the mean PI ranged from 0.85 to 1.55; and there was significant decrease of uterine artery PI in non-complicated group when compared to complicated group on the right and left sides.

Furthermore, ultrasound score was zero in 76 cases (38.0%); one in 66 cases (33.0%); two in 32 cases (16.0%); three in 16 cases (7.8%) and four in 10 cases (5.0%), and there was statistically significant increase of higher score in complicated cases when compared to non-complicated cases (Table 2). Total homocysteine levels ranged from 2.5 to 11 µmol/l and there was statistically significant decrease of total homocysteine levels in non-complicated when compared to complicated group (5.51± 1.28 vs 7.93±1.75 respectively) (Table 2). Regarding relation between total homocysteine levels and ultrasound scores, there was statistically significant difference between different scores as regard to total homocysteine levels (the lowest level was observed in zero score (5.20±0.80) and the highest in score three (7.62±2.21). In addition, there was significant moderate proportional correlation between ultrasound score and total homocysteine levels (i.e., with increased ultrasound score, there is significant increase in homocysteine levels) (Table 3).

As regard to relation between ultrasound score and complications, there was no complication in zero score; while there was significant increase of both prematurity and preeclampsia in score three and four when compared to lower scores (Table 3). As regard to relation between fetal body weight and ultrasound score, there was significant difference between different scores (the lowest weight was in score four (2863.0±179.01 g) and the highest in score zero (3179.07±76.54g). In addition, there was inverse (negative), moderate and statistically significant correlation between

ultrasound score and fetal body weight (Table 3). Combining both ultrasound score (any of scores 1, 2, 3 or 4) with hyper-homocysteinemia revealed that, 165 cases were negative for this combination and 35 cases were positive (i.e., 35 cases had ultrasound score extending from 1 to 4; and at the same time hyper-homocysteinemia). Regarding relation between abnormal ultrasound with hyper-homocysteinemia and complications, all positive cases (35 cases) had complications; these complications were in the form of prematurity in 23 cases, preeclampsia in 8 cases and both in 4 cases; and there was statistically significant difference between negative and positive cases as regard to complications and type of complications. In negative cases, 19 cases (11.5%) had complications; complications were prematurity in 10 cases, preeclampsia in 8 cases and both in 1 case (Table). As regard to predictive power of hyper-homocysteinemia alone, it was 75.0%; while abnormal ultrasound alone had predictive power of 0.67 and finally both abnormal ultrasound with hyper-homocysteinemia had a predictive power of 100.0%

DISCUSSION

Fetal morbidity and mortality were mainly due to pre-eclampsia and fetal growth restriction (Reidy and Russell, 2011; Steegers *et al*., 2010). Early onsets of these conditions are associated with increased risk of complications (Crispi *et al*., 2008). Early-onset preeclampsia is associated with a 20-fold higher rate of maternal mortality than is late-onset disease and is one of the key contributors to early fetal growth restriction (von Dadelszen *et al*., 2009). Women with early-onset pre-eclampsia require admission for treatment and one-third experience complications that may need intensive care (Churchill and Duley, 2002; Tyson *et al*., 2008). Early identification of women at risk is very important aim of antenatal care. Clinical risk assessment for pre-eclampsia is carried out in the first trimester for early identification of women who may benefit from preventative treatment, such as aspirin (National Institute for Health and Clinical Excellence, 2010; Milne *et al*., 2009).

Table 1. Comparison between complicated and non-complicated groups as regard to female characteristics, gestational age and fetal weight

		Not complicated	Complicated	Test	P value
Age (mean±SD)		25.59±2.50	26.16±2.70	1.39	0.16(ns)
Weight (mean±SD)		67.65±4.56	67.55±4.11	0.13	0.20(Ns)
Height (mean±SD)		1.655±0.027	1.653±0.023	0.56	0.35(ns)
BMI(mean±SD)		24.656±0.969	24.698±0.953	0.27	0.15(n)
Parity	Primipara	71(48.6%)	30(55.6%)	0.75	0.38(ns)
(n,%)	Multipara	75(51.4%)	24(44.4%)		
Gestational age (mean±SD)		37.93±0.79	35.59±1.23	15.73	<0.001*
Fetal weight (mean±SD)		3157.87±87.28	2868.14±214.63	13.59	<0.001*

Table 2. Comparison between complicated and non-complicated groups as regard to ultrasound findings and homocysteine levels

		Not complicated	Complicated	Test	P value
	None	114(78.1%)	31(57.4%)		
Uterine notch	Unilateral	25(17.1%)	12(22.2%)	13.50	0.001*
	Bilateral	7(4.8%)	11(20.4%)		
Right UA PI		1.08±0.12	1.17±0.20	3.73	<0.001*
Left UA PI		1.09±0.12	1.28±0.08	10.62	<0.001*
Mean PI		1.09±0.11	1.23±0.10	8.01	<0.001*
	Zero	76(52.1%)	0(0.0%)		
	One	50(34.2%)	16(29.6%)		
Ultrasound	Two	19(13.0%)	13(24.1%)	94.58	<0.001*
Score	Three	1(0.7%)	15(27.8%)		
	Four	0(0.0%)	10(18.5%)		
Homocysteine level		5.51±1.28	7.93±1.75	10.65	<0.001*

Table 3. Comparison between different ultrasound scores as regard to total homocysteine levels

		Zero	One	Two	Three	Four	Statistics		
							F	p	r
Homocysteine		5.20±0.80	6.56±2.08	6.49±1.45	7.62±2.21	7.51±1.75	13.35	0.002*	0.42*
Complications	None	76(100.0%)	50(75.8%)	19(59.4%)	1(6.3%)	0(0.0%)			
	Prematurity	0(0.0%)	7(10.6%)	8(25.0%)	12(75.0%)	6(60.0%)			
	Pre-eclampsia	0(0.0%)	7(10.6%)	3(9.4%)	2(12.5%)	4(40.0%)	110.36	<0.001*	
	Both	0(0.0%)	2(3.0%)	2(6.3%)	1(6.3%)	0(0.0%)			
Fetal body weight		3179.07± 76.54	3065.15± 208.34	3042.18± 184.50	2877.50± 145.44	2863.00± 179.01	19.14	<0.001*	0.51*

Table 4. Percentage of complications in cases with abnormal ultrasound with hyper-homocysteinemia

		Negative (165)		Positive (35)		Statistics	
		n	%	n	%	X^2	p
Complications	None	146	88.5%	0	0.0%	114.70	<0.001*
	Complicated	19	11.5%	35	100.0%		
Type of complications	None	146	88.5%	0	0.0%	118.47	
	Prematurity	10	6.1%	23	65.7%		
	Preeclampsia	8	4.8%	8	22.9%		<0.001*
	Both	1	0.6%	4	11.4%		

Doppler of the uterine artery can pick up these abnormalities. However, it is currently not part of this assessment. Individual studies, owing to a lack of power, have failed to produce guidance on first-trimester screening with uterine artery Doppler for adverse pregnancy outcome (Bujold *et al*., 2010; Cnossen *et al*., 2008). Routine prenatal care focuses on the detection of women at increased risk, aiming at careful monitoring and appropriate intervention. Although these problems become manifest in the second half of pregnancy and a lot of research have been employed accordingly, there is evidence that they are associated with events taking place in the first trimester of pregnancy (Abdel Moety *et al*., 2016). Hyper-homocysteinemia was found to be associated with comorbidities such as placental abruption, pre-eclampsia, IUGR, preterm birth or intrauterine fetal death in several studies (Dekker *et al*., 1995). Vitamin B12, B6 and folate play a role in the metabolism of homocysteine (Cotter *et al*., 2001). The aim of the present work was to analyze the relationship of maternal plasma homocysteine together with the first trimester uterine artery Doppler velocimetry on pregnancy outcome. We also aimed to find out whether the addition of homocysteine measurement to uterine artery Doppler screening improves the prediction of adverse pregnancy outcome. This study was conducted at the Department of the Obstetrics and Gynecology at Al-Azhar University Hospital (Damietta) and Damietta General Hospital. A total of 200 singletons, low risk pregnant women aged between 20 and 30 years were included in the study. All pregnant women took 400 mcg of folic acid. The ultrasound examinations were performed at 11 to 14 weeks of gestation. The blood for bio-chemical analysis was collected at the same time the ultra-sonographic measurement performed. In this study, we have shown that maternal serum homocysteine level increases in 11 to 14 weeks of gestations that are complicated with pre-eclampsia and preterm birth. The addition of homocysteine determination to uterine artery Doppler in the first trimester adds advantage in predicting adverse perinatal outcome. There is no optimal method for early identification of pregnancies that are going to be complicated with conditions like pre-eclampsia or preterm birth. However, it was reported that, screening uterine artery flow velocity waveforms with Doppler seems to be an easy, inexpensive and noninvasive method of identifying pregnancies at risk of developing complications.

A characteristic uterine artery Doppler velocity pattern with decreased diastolic flow and a diastolic notch has been described in complicated pregnancies with adverse perinatal outcome (Akbas *et al*., 2014). Some studies have examined the value of uterine artery screening in the first trimester. The existing data suggested that increased impedance to flow in the uterine arteries identifies about 25% of those who subsequently develop pre-eclampsia. As for second trimester screening, abnormal Doppler findings are better at predicting more severe diseases; the sensitivity for pre-eclampsia increases with increasing prematurity, and the same appears to be true for IUGR (Jamal *et al*., 2013). Harrington *et al*. (1997), in their Doppler study performed at 12 to 16 weeks of gestation, demonstrated that increased impedance in early pregnancy is also associated with IUGR, pregnancy-induced hypertension and preterm birth. To reduce the false positive rate of Doppler velocimetry in predicting poor pregnancy outcome, some authors have proposed the addition of other parameters associated with placental functioning (Florio *et al*., 2003). Coining with this theory, in the present work, we analyzed the addition of homocysteine. It is well known that, hyper-homocysteinemia is a risk factor for endothelial dysfunction and vascular diseases such as atherosclerosis and occlusive vascular disease (Vollset *et al*., 2000). In addition, hyper-homocysteinemia has also been shown to be associated with several pregnancy complications like recurrent pregnancy loss, placental abruption, intrauterine fetal demise, pre-eclampsia and IUGR (Kaymaz *et al*., 2011). In the present work, we used a uterine artery scoring system (PI was used instead of RI) defined by López-Quesada *et al*. (2004). Elevated PI is considered to be an independent risk factor for poor obstetric outcome. PI values greater than 1.5 were defined as elevated. Doppler score was calculated as 0 being the smallest value if both uterine arteries' PI were less than 1.5 and had no bilateral diastolic notch. The score was calculated as 4 being the highest value if both uterine arteries' PI were greater than 1.5 and had bilateral diastolic notch. They proposed the addition of plasma homocysteine to uterine artery Doppler study performed at 24 to 25 weeks of gestation. They found no significant difference between plasma homocysteine, folate and vitamin B12 levels within the five Doppler score groups and they found no correlation between hyper-homocysteinemia and the existence of obstetric complications at 24 to 25 weeks of gestation. These results are in contradiction to that of the present study. However, by adding of hyper-homocysteinemia to uterine artery scores, they found that the sensitivity in predicting obstetric complications increased from 66.7 to 77.8%. These results are in agreement with the present study as adding hyper-homocysteinemia to uterine artery Doppler findings increased sensitivity of uterine artery Doppler in prediction of pregnancy complications from 57% to 70%. Different factors are responsible for contradiction in the first part of their results as the sample size, the time of Doppler and homocysteine assessment. In Kaymaz *et al*. (2011) study, at 11 to 14 weeks of gestation, they also found no correlation between hyper-homocysteinemia and the occurrence of obstetric complications. However, they found mean homocysteine levels to be significantly higher in different Doppler scores as presented in the current study. They added, as the Doppler scores increased, so did the mean plasma homocysteine levels. These results agree with that of the present study. Mascarenhas *et al*. (2014) performed a cohort study compromising 100 antenatal women between 8-12 weeks of gestation. They found that, serum homocysteine level in late first trimester (8-12 weeks) of pregnancy are significantly associated with prior pregnancy losses, particularly in the second and third trimesters and with prior hypertensive disorders of pregnancy. They added that increased serum homocysteine levels were also significantly associated with hypertensive disorders of pregnancy, pregnancy loss, oligohydramnios, meconium stained amniotic fluid and low birth weight.

Guven *et al*. (2007) performed a two-stage screening strategy by measuring uterine artery Doppler velocimetry at 20 to 22 and 24 to 26 weeks of gestation and searched for their possible association with mid-trimester maternal plasma homocysteine levels. They found no difference in the homocysteine levels between pregnant women with abnormal Doppler findings and controls in both visits. They measured uterine artery RI instead of calculating Doppler scores as we did and defined abnormal blood flow as an average RI >0.58 and/or bilateral early diastolic notch and concluded that combining mid-trimester maternal plasma homocysteine with uterine artery Doppler velocimetry was not a useful approach. These results are contradicted to that of the present work and it may be explained by the different time at registration of Doppler indices and

measurement of plasma homocysteine levels. In the present work, the predictive power of Doppler indices reached 57% and this had clinical implications especially in patients with preeclampsia. Initiation of aspirin treatment is recommended, at the earliest, at 12 weeks of gestation in women with risk factors (National Institute for Health and Clinical Excellence, 2010). The meta-analysis by Bujold *et al*. (2010) showed that commencement of aspirin before 16 weeks of pregnancy halves the risk of pre-eclampsia, with no significant effect if commenced after that period.

Studies that commenced aspirin before 16 weeks in this meta-analysis included women who were at moderate or high risk for pre-eclampsia. However, an individual patient data meta-analysis did not identify any significant subgroup effect for aspirin commenced before or after 20 weeks of pregnancy (Askie *et al*., 2007). It is likely that early administration of aspirin reduces the risks by improving placentation, with a beneficial effect particularly on the risks of early- compared with late-onset pre-eclampsia (Velauthar *et al*., 2014). A meta-analysis of five randomized trials demonstrated that commencement of low-dose aspirin before 16 weeks of pregnancy significantly reduces the risk of early-onset pre-eclampsia, with no effect on term pre-eclampsia. These findings reinforce the need for early identification of women at risk for pre-eclampsia (Roberge *et al*., 2012). Current recommendations (for commencing prophylactic aspirin for prevention of pre-eclampsia) target women with one clinical high-risk factor or two moderate-risk factors. Uterine artery Doppler in the first trimester will enable clinicians to identify women at risk of developing pre-eclampsia and fetal growth restriction and its complications, and initiate preventive measures such as aspirin and regular fetal monitoring to minimize adverse outcomes. There is no significant difference in the screening performance of uterine artery Doppler with the use of either lower or mean pulsatility indices (Napolitano *et al*., 2011).

An interesting finding of the present study is the higher predictively of hyper-homocysteinemia for pregnancy complications. It was better than Doppler ultrasound (70% vs 57% respectively). The addition of homocysteine to Doppler indices yielded a predictive power like that of hyper-homocysteinemia alone; and these results reflected the importance of homocysteine determination in the first trimester in predicting adverse pregnancy outcome. However, these results must be taken with caution; as the complications registered in the present work was confined to preeclampsia and preterm birth. Future studies are required to validate the present results. Previous studies performed around 16 weeks' gestation for the prediction of pre-eclampsia by investigating only maternal homocysteine concentration in asymptomatic women have reported conflicting variable results. Sorensen *et al*. (1999) reported that nulliparous women with elevated homocysteine levels experienced a 9.7-fold increased risk of pre-eclampsia as compared with multiparous women without homocysteine elevation. Moreover, Cotter *et al*. (2001) have shown that elevated plasma homocysteine levels in early pregnancy can increase the risk of developing severe pre-eclampsia by almost threefold. In contrast, Hietala and colleagues (2001) found similar mean homocysteine levels at 16 weeks between the women who developed pre-eclampsia and those who remained normotensive, but this study included women with mild pre-eclampsia. However, in another study performed on 406 singleton pregnancies without previous risk factors, and investigating second-trimester maternal serum homocysteine levels and uterine artery Doppler combination for prediction of pre-eclampsia and isolated intrauterine growth restriction, sensitivities of 61.3 and 54% for pre-eclampsia and isolated IUGR were demonstrated (Onalan *et al*., 2006). Although this study confirms the potential role of this combined method in predicting pre-eclampsia and IUGR, the results are not in accordance with previous studies (Yu *et al*., 2005; Lopez-Quesada *et al*., 2004).

In a population of 683 women, Yu *et al*. (2005) showed that maternal plasma homocysteine concentration at 22–24 weeks is not elevated in women who subsequently develop pre-eclampsia, even in cases defined as at high risk, by abnormal uterine artery Doppler velocimetry. Additionally, Lopez-Quesada *et al*. (2004) demonstrated no significant differences in plasma homocysteine concentrations of 94 pregnant women with respect to abnormal Doppler findings and the existence of obstetric complications. Moreover, the addition of homocysteine determination to uterine Doppler evaluation at 24 weeks of gestation did not improve its predictive value. Finally, the current study has the limitations of having a relatively small number of subjects. The moderate positive correlation we found between the Doppler scores and occurrence of any pregnancy complication may be more powerful if analyzed with a greater number of subjects. However, the potential advantages of early screening of pregnancy complications may allow prophylactic interventions as soon as possible. Thus, it is necessary to identify women at risk at early stages of pregnancies. Developing new screening strategies to predict pregnancy complications by combination of Doppler parameters with other biochemical markers is an advantage for early detection of pregnancies at risk and these methods are further required in future studies.

Conclusion

First trimestric screening (11-14-week gestation) of both maternal plasma homocysteine level and uterine artery doppler study gives an early prediction of any adverse perinatal outcome.

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