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Carotid Artery Intima–Media Thickness and Resistance and Pulsatility Indices of Uterine and Renal Arteries in Pre-eclampsia: A Quantitative Analysis by Color Doppler Ultrasonography

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The recent development of high-resolution ultrasonography has provided the best opportunity to measure intima-media thickness and also arterial wall thickness in the peripheral arteries in pregnant women especially those with pre-eclampsia. The present study aimed to determine resistance index (RI) and pulsatility index (PI) of uterine and renal arteries, as well as common carotid intima-media thickness (IMT) in pregnant women with pre-eclampsia using color Doppler ultrasonography and also to compare these parameters with healthy pregnant women. This case-control study was conducted on 50 consecutive Iranian women suffering from pre-eclampsia, selected from the patients referring to prenatal clinic for routine pregnancy check-up from April 2013 to March 2014. Also, 50 age- and gestational week-matched normotensive pregnant women were included as the control group. IMT of common carotid artery as well as RI and PI indices of uterine and renal artery were measured by color Doppler ultrasound. Comparing uterine RI in women with pre-eclampsia and healthy normotensive pregnant women showed higher RI in the former group (0.50 ± 0.07 versus 0.45 ± 0.09, p = 0.002). Also, uterine PI in women with pre-eclampsia was higher than the healthy group (0.84 ± 0.19 versus 0.71 ± 0.17, p = 0.005). The RI index of renal artery was 0.56 ± 0.08 in pre-eclampsia group and 0.55 ± 0.07 in healthy group with no statistically significant difference (p = 0.480). There was also no difference in PI index of renal artery between pre-eclampsia group and normotensive group (0.93 ± 0.23 versus 0.94 ± 0.19, p = 0.930). Comparing IMT of common carotid artery in pre-eclampsia group and control group showed significantly higher IMT in the former group (0.49 ± 0.06 versus 0.44 ± 0.07, p < 0.001). Increased common carotid IMT and also RI and PI indices of uterine artery are common findings in women with pre-eclampsia that can help to predict early and late pre-eclampsia and poor cardiovascular outcome. Changes in RI and PI renal artery may not be expected in pre-eclampsia that should be further assessed in future studies.

Keywords: Carotid Intima-Media Thickness; Pre-Eclampsia; Ultrasonography, Doppler, Color.

Pre-eclampsia is one of the most common complications during pregnancy with serious harmful effects on both fetus and mother. Despite its high prevalence, its pathogenesis and the best ways for its prevention remain unclear[1-3]. Not only pre-eclampsia can directly increase the risk for hemodynamic instability leading life-threatening events, but it has also been identified as an independent major risk factor for cardiovascular disorders, including ischemic heart disease and ischemic stroke even years after delivery[4-7]. The main pathophysiologic effects of pre-eclampsia on vascular bed are based on hypertension-based endothelial dysfunction leading three pathways of 1) inflammation and foam cells formation that

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cause atherosclerosis and increased carotid intima-media thickness; 2) large vessels remodeling leading to arterial stiffness and increased cardiac after-load; and 3) angiogenesis impairment and micro-vessels rarefaction leading to elevated peripheral arterial resistance[8-12]. In total, the occurrence of early onset pre-eclampsia is frequently associated with increased risk for cardiac and peripheral arterial remodeling and vascular stiffness[13].

The recent studies have exclusively focused on the changes in carotid intima-media thickness during pregnancy. It has been well demonstrated that some abnormal reversible changes in arterial wall thickness within pregnancy and early after delivery that can be improved in postpartum depends on some baseline demographic factors, such as the serum level of estradiol, age at pregnancy, high body mass index, and high blood pressure early in the pregnancy [14]. However, in women who suffer pre-eclampsia, thickening of arterial intima layer, thinning of media layer especially in peripheral arteries, such as carotid artery, as well as renal and uterine arteries that commonly occur may deteriorate early and long-term outcomes of pregnancy[15].

The recent development of high resolution ultrasonography has provided the best opportunity to measure regional intima-media thickness in peripheral arteries and also to assess arterial wall thickness[16, 17]. However, a few studies are available in favor of this new modality to assess peripheral arterial changes in pregnant women with pre-eclampsia. The present study aimed to determine resistance index (RI) and pulsatility index (PI) of uterine and renal arteries as well as common carotid intima-media thickness (IMT) in pregnant women with pre-eclampsia using color Doppler ultrasonography and also to compare these parameters with healthy pregnant women.

MATERIALS AND METHODS

Study population

This case-control study was conducted on 50 consecutive Iranian women suffering from pre-eclampsia with a gestational age of 18 to 22 weeks, who were selected from the patients referring to prenatal clinic of Valiasr Hospital for routine check-up from April 2013 to March 2014. Also, 50 age- and gestational week-matched normotensive pregnant women were included as the control group. All included women were nulliparous, had singleton pregnancies, and also had no underlying risk factors for peripheral arterial abnormalities such as smoking, diabetes, chronic hypertension, cardiovascular disorders, hyperlipidemia, in-vitro fertilization or history of pre-eclampsia. The pre-eclampsia was diagnosed according to the guidelines of the International Society for the Study of Hypertension in Pregnancy, as a systolic blood pressure higher than 140 mmHg and/or diastolic blood pressure higher than 90 mmHg with microscopic proteinuria of 300 mg/24 hours; or macroscopic proteinuria of e"1^{+} on two random urine samples, collected at least 6 hours apart.

Study measurements

All participants underwent common carotid artery measurements with the color Doppler ultrasound to measure common carotid IMT. Also, the Doppler indices, generated automatically from the ultrasonography, included PI and RI of uterine and renal arteries. In this regard, RI was defined as the difference between peak systolic velocity and end diastolic velocity divided by peak systolic velocity. PI was also defined as the difference between peak systolic velocity and end diastolic velocity divided by time averaged velocity.

Ethical considerations

The study complied with the Declaration of Helsinki and the research protocol was approved by the Ethics Committee at the … University. The design and objectives of the study were explained to all patients and they enter the study willingly. All participants and their partners signed informed consent before recruitment into the study. The additional costs of the research were provided from the research financial plan and was not imposed on participants. The names and private information of patients were kept confidential and were analyzed anonymously.

Statistical analysis

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using T test or Mann-Whitney U test, whenever the data did not appear to have normal distribution or when the assumption of

equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using chi-square test. For the statistical analysis, the statistical software SPSS version 21.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

RESULTS

Comparing uterine RI in women with pre-eclampsia and healthy normotensive pregnant women showed higher RI in the former group (0.50 ± 0.07 versus 0.45 ± 0.09, p = 0.002). Also, uterine PI in women with pre-eclampsia was higher than the healthy group (0.84 ± 0.19 versus 0.71 ± 0.17, p = 0.005). The RI index of renal artery was 0.56 ± 0.08 in pre-eclampsia group and 0.55 ± 0.07 in healthy group with no statistically significant difference (p = 0.480). There was also no difference in PI index of renal artery between pre-eclampsia group and normotensive group (0.93 ± 0.23 versus 0.94 ± 0.19, p = 0.930). Comparison of IMT of common carotid artery in pre-eclampsia group and control group showed significantly higher IMT in the former group (0.49 ± 0.06 versus 0.44 ± 0.07, p < 0.001).

DISCUSSION

Ultrasonographic assessment of common carotid IMT and also resistance and pulsatility indices of uterine artery in our study showed higher rates in women with pre-eclampsia, when compared to normotensive groups. However, the measured resistance and pulsatility indices of renal artery remained unchanged in pre-eclampsia group. In fact, pathologic changes in both common carotid and uterine artery, such as arterial stiffness, could be considered as major factors for predicting poor prognosis in patients with pre-eclampsia. According to this fact that the changes in arterial stiffness and remodeling may cause long-term persistent hemodynamic changes, the changes in ultrasonographic arterial parameters may predict long-term prognosis in women with pre-eclampsia.

Carotid artery IMT has been well established in atherosclerosis-related pathogenesis of myocardial infarction and stroke[18]. Recent studies have proposed IMT in a variety of diseases, such as breast cancer[19], intra-uterine growth retard (IUGR)[20], and diabetes mellitus type 2[21]. Regarding increase in carotid IMT following pre-eclampsia, similar results have been reported in a few available studies. Yuan et al have compared 23 pregnant women with pre-eclampsia with a control group and have shown more prevalent carotid arterial hypertrophy and remodeling in carotid arteries of pre-eclamptic women, compared to normotensive pregnant women. They have proposed that the difference might be explainable by afterload difference. However the relative carotid arterial wall thickness showed no significant difference between the groups [22]. In a study by Akhter et al, pre-eclampsia was significantly associated with a higher mean common carotid artery IMT and higher intima-media thickness ratio than healthy women, both early and one-year later after pregnancy[23]. In another study by Yuan et al, carotid arterial IMT, internal diameter, pulse wave velocity and arterial wall tension were significantly greater in pre-eclamptic group even after adjusting for body mass index and carotid arterial pressure[24]. Blaauw et al also compared the ultrasonographic findings of IMT in 22 pregnant women with early-onset pre-

Table 1. Comparing color Doppler indices in pre-eclampsia group and healthy pregnant group

Index	Pre-eclampsia group(N = 50)	Healthy group(N = 50)	p-value
RI (uterine artery)	0.50 ± 0.07	0.45 ± 0.09	0.002
PI (uterine artery)	0.84 ± 0.19	0.71 ± 0.17	0.005
RI (renal artery)	0.56 ± 0.08	0.55 ± 0.07	0.480
PI (renal artery)	0.93 ± 0.23	0.94 ± 0.19	0.930
IMT (common carotid)	0.49 ± 0.06	0.44 ± 0.07	< 0.001

eclampsia with 22 matched controls and showed an increased IMT of the common femoral and carotid artery compared with the normal pregnancy group even after adjusting confounders[25]. They have associated IMT as a marker of endothelial dysfunction which might pursue accelerated atherosclerosis in women with former pre-eclampsia. But they have proposed that whether these changes are a consequence of functional or structural cardiovascular changes remain unclear[25]. In total, because carotid arterial stiffness and its increased IMT correlated significantly with cardiac diastolic functioning parameters and blood pressures[22], these parameters can effectively help to predict early and late cardiovascular events in women with pre-eclampsia.

With respect to the pathologic effects of pre-eclampsia on parameters of uterine artery, the previous similar studies revealed consistent results to our survey. In a quantitative investigation of hemodynamic adaptation to pregnancy using uterine artery Doppler ultrasonography, higher RI was found in the pre-eclamptic patients of third trimester[26]. They have accordingly suggested RI index as an appropriate diagnostic and prognostic marker of complicated pregnancy. In another study by Verlohren et al, patients with early-onset pre-eclampsia had an increased prevalence of high uterine artery mean RI that was also negatively associated with birth weight and have suggested uterine artery RI as the best available screening tool for pre-eclampsia and have consequently proposed the placental origin of pre-eclampsia[27]. Myatt also evaluated the association of uterine artery Doppler measurements with pre-eclampsia in 2,188 low-risk nulliparous women and indicated higher RI and PI of uterine artery in pre-eclamptic group than in healthy group, but they have proposed that uterine artery Doppler performed at 21st gestational week is not a sensitive method for diagnosis of pre-eclampsia, as they have reported that RI or PI above the 75th percentile has a sensitivity of 43% and specificity of 67% for predicting preeclampsia[28]. Papageorghiou and colleagues have examined 8,335 singleton pregnancies and have suggested uterine artery Doppler ultrasound a proper diagnostic tool for severe pre-eclampsia and fetal growth restriction[29]. A review study has indicated that uterine artery Doppler sonography is a more accurate method, when performed in the second trimester, compared to first trimester; however, they have concluded poor predictive characteristics for most Doppler indices, which varied with patient risk and outcome severity[30]. This review study have demonstrated increased pulsatility index with notching as the best predictor of pre-eclampsia.Thus, measuring RI and PI indices predict pre-eclampsia consequences, which has a significant importance, because the performance of uterine artery Doppler in predicting pre-eclampsia had remained uncertain and the recent findings demonstrate its high efficacy to assess severity of this event in pregnant women.

Despite clear effects of pregnancy-induced hypertension on resistance rate of uterine artery, the effects of hypertension on intra-renal resistance remained questioned. We could not show significant changes in RI and PI indices of renal artery by ultrasonography in pre-eclampsia group. Bahseret al could show increased intra-renal RI in women with pre-eclampsia versus healthy pregnant women and the overall prevalence of increased RI was estimated to be 84% [31]. Similar finding was reported by Kublickas et al on increasing RI in renal artery of pre-eclamptic group[32]. However, similar to our result, in a study by Thaler et al, the renal artery RI was not significantly different between the hypertensive group and the normal group (RI = 0.605 +/- 0.04) [33]. More interestingly, in their study, the value of RI was also similar in all hypertensive patient categories including pre-eclampsia, pregnancy-induced hypertension and chronic hypertension. According to our findings, it seems that measuring RI and PI index of renal artery could not predict abnormal changes in renal function, especially nephropathy in women with pre-eclampsia. In fact, the renal RI and PI measurements were not correlated with the severity of hypertensive disorders in pre-eclamptic women.

The strengths of the present study include a statistically significant sample size, as some studies have investigated a sample size of smaller than 30 [18, 21]. Beside the resistance index (RI) and pulsatility index have also been evaluated, beside IMT, in order to determine a more accurate relationship between cardiovascular dysfunction and pre-eclampsia. Nevertheless, the present study had some limitations, including patients referring

to one center. Multi-centric studies with a larger sample size would add to the results of the present study.

CONCLUSION

In conclusion, alteration in common carotid IMT as well as increased values of uterine artery PI and RI is common findings in pre-eclamptic women; however pre-eclampsia may not affect RI and PI indices of renal artery. Thus, by assessing severity of increasing common carotid IMT and also RI and PI of uterine artery, the possibility of assessing poor outcome in pre-eclamptic women may be provided.

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