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Review article

Using ultrasound and Doppler ultrasound to assess vascular changes in pre-eclampsia and eclampsia: a systematic review



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ABSTRACT

Objectives: This systematic review aimed to evaluate whether Doppler ultrasound of the ophthalmic artery and uterine artery, and ultrasound of flow-mediated dilation of the brachial artery, can be used to effectively assess vascular function in pregnant women without disease or other complications with pre-eclampsia and eclampsia to establish the most appropriate method for evaluating these diseases.

Methods: Two databases were searched for relevant articles: the National Library of Medicine (PubMed) and the Virtual Health Library. Articles published between 1989 and 2014 about Doppler ultrasound of the ophthalmic artery were retrieved; all articles published from 2000 to 2014 about using ultrasound to assess flow-mediated dilation of the brachial artery were retrieved; and for Doppler ultrasound of the uterine artery, only articles published between January 2013 and March 2014 were retrieved because the literature in this area is extensive. **Results:** A total of 260 articles were retrieved; 32 were eligible for inclusion. There were 16 articles on using Doppler ultrasound to evaluate the ophthalmic artery and eight about using it to assess the uterine artery, and eight articles evaluated the use of ultrasound to assess flow-mediated dilation of the brachial artery.

Conclusions: Doppler ultrasound is useful in diagnosing pre-eclampsia and eclampsia in pregnant women; the use of this technique makes early intervention feasible, and thereby improves prognosis; and it reduces the morbidity and mortality of pregnant women and their newborns.

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Uso de ultrassom Doppler e ultrassom na avaliação das alterações vasculares na pré-eclampsia e eclampsia: Uma revisão sistemática

R E S U M O

Palavras chave:

Artéria oftálmica
Dilatação fluxo-mediada
Artéria uterina
Sonografia Doppler
Pré-eclampsia
Eclampsia

Objetivos: Essa revisão sistemática teve como objetivo avaliar se o ultrassom Doppler das artérias oftálmica e uterina e o ultrassom de dilatação fluxo-mediada da artéria braquial podem ser utilizados para uma avaliação efetiva da função vascular em mulheres grávidas com pré-eclampsia e eclampsia e sem outras doenças ou complicações, para estabelecer o método mais apropriado para avaliação dessas doenças.

Métodos: Pesquisa em dois bancos de dados—National Library of Medicine (PubMed) e Virtual Health Library—em busca de artigos relevantes. Foram recuperados artigos publicados entre 1989 e 2014 sobre ultrassom Doppler da artéria oftálmica; todos os artigos publicados de 2000 até 2014 sobre o uso do ultrassom para a avaliação da dilatação fluxo-mediada da artéria braquial; e apenas artigos publicados entre janeiro de 2013 e março de 2014 sobre ultrassom Doppler da artéria uterina, diante da grande riqueza da literatura nessa área.

Resultados: No total, foram recuperados 260 artigos; 32 se qualificaram para inclusão: 16 artigos sobre uso do ultrassom Doppler para avaliar a artéria oftálmica, oito artigos sobre o uso dessa técnica para avaliar a artéria uterina e, finalmente, oito artigos sobre o uso do ultrassom para avaliar a dilatação fluxo-mediada da artéria braquial.

Conclusões: O ultrassom Doppler tem utilidade no diagnóstico da pré-eclâmpsia e da eclâmpsia em mulheres grávidas; o uso dessa técnica possibilita uma intervenção precoce e, com isso, melhora o prognóstico; e ainda diminui a morbidade e a mortalidade de grávidas e de seus neonatos.

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Introduction

Pre-eclampsia (PE) has been a major cause of maternal and perinatal morbidity and mortality worldwide.¹ Although the condition can be treated, PE can be fatal. Ten percent of women experience high blood pressure during pregnancy, and PE cause complications in 2–8% of pregnancies. In general, 10–15% of direct maternal deaths are associated with PE and eclampsia.^{2,3}

More than half a million women worldwide die each year from pregnancy-related causes. PE is common and is a major cause of maternal death both in developed and developing countries.⁴ However, in developing countries, mortality from PE can reach 99%, as it does in some countries in Africa. PE also causes high rates of perinatal and neonatal death. Two Millennium Development Goals—4 and 5—specifically aim to reduce child and maternal mortality.⁵

PE affects 2–8% of all pregnancies, although treatment is generally effective. However, 10–15% of direct maternal deaths are associated with PE and eclampsia.^{2,3} PE causes complications in the liver, kidneys, brain and the circulatory system. For the newborn, the risks include intrauterine growth retardation (IUGR) and prematurity.²

PE has been called the “disease of theories” because of its enigmatic pathophysiology. Screening for PE and restricted intra uterine growth (IUGR) has been a major clinical and research issue since the disease was first reported in the 19th century.¹ Since then, clinical studies have shown that early detection and treatment of PE and eclampsia reduce maternal and fetal morbidity and mortality.^{1,4} However, preventing PE

and eclampsia remain major problems in maternal and child health.³

Ultrasound of the brachial artery, and Doppler ultrasound of the ophthalmic artery and uterine artery are propaedeutic, non-invasive methods that contribute to the understanding of the pathophysiology of PE and eclampsia.^{6–9} The present study is a systematic review of the literature that evaluates the effectiveness of these tests in assessing vascular function in normal pregnant women and in women with PE and eclampsia to establish the most appropriate methods for the evaluating these diseases.

Methods

For this systematic review, a search protocol not registered in databases of systematic reviews was prepared. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were used.¹⁰ In this protocol all of the following were predefined and limited: the topic of interest, inclusion criteria, search strategies and selection of studies, the quality evaluation form used to record the data for analysis and to present results, and interpretation of study results.

Inclusion criteria varied in accordance with the artery being studied. Articles about Doppler ultrasound of the ophthalmic artery published between 1989 and 2014 were retrieved. All articles published between 2000 and 2014 about using ultrasound to assess flow-mediated dilation of the brachial artery were retrieved. For Doppler ultrasound of the uterine artery, only articles published between January 2013 and March 2014 were retrieved because the literature in this area is extensive.

Articles in English and Portuguese were included. Observational and experimental studies conducted in pregnant women without disease or other complications with PE and eclampsia were included if the ophthalmic artery and uterine artery had been assessed by Doppler ultrasound, and flow-mediated dilation of the brachial artery flow had been assessed by ultrasound. Articles that did not fully meet the criteria were excluded.

Two researchers independently conducted an active search for articles. When there was doubt or disagreement among the researchers, a third researcher acted as a mediator.

The databases of the National Library of Medicine (PubMed) and the Virtual Health Library were searched. The following descriptors for the ophthalmic artery were used: *ophthalmic artery AND Doppler OR Doppler color ultrasonography OR Doppler sonography AND pregnancy AND preeclampsia/eclampsia OR pre-eclampsia OR toxemia of pregnancy*. For the brachial artery, the descriptors used were: *brachial artery AND pregnancy AND flow-mediated dilation*. For the uterine artery, the descriptors used were: *Doppler OR Doppler color ultrasonography OR Doppler sonography AND uterine artery AND pregnancy OR preeclampsia/eclampsia OR pre-eclampsia OR toxemia of pregnancy*.

To increase the specificity of the searches, the filters *humans* and *adults* were used.

Results

Fig. 1 and Tables 1–3 show the results. A total of 260 articles were retrieved, of which 32 were eligible for inclusion in the review. There were 16 articles on using Doppler ultrasound to evaluate the ophthalmic artery and eight about using it to assess the uterine artery, and eight articles evaluated using ultrasound to assess flow-mediated dilation of the brachial artery (Fig. 1).

Table 1 shows the studies included in the review of the ophthalmic artery. Patients with PE showed a decreased pulsatility index and resistance index with vasodilation and cerebral blood flow.^{6,9,11,12}

Table 2 summarizes the studies of using ultrasound to evaluate the brachial artery. Flow-mediated dilation of the brachial artery was lower in pregnant women with pre-eclampsia.

Table 3 summarizes the studies using Doppler ultrasound to assess the uterine artery. All of these studies were cross-sectional. The pulsatility index for this artery was increased in women with PE and eclampsia. Some studies evaluated the correlation between findings on Doppler ultrasound and maternal outcome (PE) and the association with biochemical markers and maternal factors. Other studies were conducted in pregnant women during the first trimester, with the intent of detecting changes before the symptoms of PE were apparent. Another group of studies was performed during the second trimester of pregnancy; a period during which there may already be signs of PE.

Discussion

Ophthalmic artery

Patients with PE showed a decreased pulsatility index and decreased resistance index, with cerebral vasodilation and

increased blood flow.^{6,9,11,12} Such changes were present even in patients with PE and photophobia (Table 1).¹³ Nakatsuka et al.¹⁴ observed the same decreases in the pulsatility index and resistance index in pregnant women and in those who used vasodilator drugs (Table 1). Barbosa et al.¹⁷ demonstrated that immediately prior to eclampsia the resistance index proved to be an important biomarker at the cut-off of 0.56 (Table 1).

During the second trimester, the combined Doppler assessment of the uterine artery, the ophthalmic artery and ultrasound assessment of flow-mediated dilation of the brachial artery helped differentiate the degree and severity of PE (Table 1).⁸

Brandão, Cabral and Leite^{7,18} observed that impairment in the placentation process and endothelial dysfunction preceded PE, and that disruption to the blood flow in the central nervous system occurred after the onset of illness (Table 1).

The variables used by Matias et al.³⁸ to assess the ophthalmic artery using Doppler ultrasound were accurate in the differential diagnosis of hypertensive disorders as well as in assessing the severity and progression of disease (Table 1).

Gurgel et al.²¹ tested during the first trimester the efficacy of using the pulsatility index of the uterine artery and the first diastolic peak of the ophthalmic artery to detect PE. They observed that the combination of the factors with maternal uterine artery Doppler or ophthalmic arteries can predict 78% of cases of early-onset PE, a TFP of 10%. Maternal changes preceding PE are not limited to the uteroplacental vascular bed (Table 1).¹⁸

Brachial artery

Flow-mediated dilation of the brachial artery is higher in pregnant women without complications than in non-pregnant women, and it has a positive correlation with gestational age up to 32 weeks of gestation (Table 2).²² Savidou et al.²³ observed that in some pregnant women who develop PE, maternal serum placental growth factor (PlGF) and soluble endoglin (sEng) are altered. However, these changes do not correlate directly with maternal endothelial dysfunction (Table 2).

Brodzski et al.²⁴ concluded that healthy normotensive pregnant women with bilateral uterine artery resistance showed impaired endothelial function, but no difference was found in vascular mechanical properties (Table 2). Chambers et al.²⁵ found that vascular function was also impaired in non-pregnant women who had PE or hypertension during a previous pregnancy.

Kamat et al.²⁷ reported that in patients at risk of developing PE, flow-mediated dilation is smaller, and that women with flow-mediated dilation greater than 30% have zero risk of developing PE. This measurement should be performed between 18 and 24 weeks of pregnancy, and can be considered a sensitive early predictor for evaluating patients at risk for PE (Table 2).

Filho et al.²⁸ reported that their findings suggested that superimposed PE was associated with poorer endothelial function (Table 2).

Table 1 – Studies assessing use of Doppler ultrasound of ophthalmic artery in normal pregnant women and pregnant women with pre-eclampsia (PE).

Author/year	Study design	Sample	Degree of evidence	Variables	Results
Belfort et al. ¹¹	Case-control	8 PE		RIOA = ↓ PIOA = ↓	Magnesium sulfate produces vasodilation
Hata et al. ¹²	Cross-sectional study	20 N 7 PL 3 PG	B	PIOA = 2.75 ± 0.66 PIOA = 1.58 ± 0.66 PIOA = $1.86-2.44$	PI lowest value in mild pre-eclampsia
Hata et al. ⁹	Cross-sectional study	9 PEL 6 PEG	B	PIOA = 1.47 ± 0.30 PIOA = 1.17 ± 0.08	PI lowest value in severe pre-eclampsia
Ohno et al. ¹³	Cross-sectional study	20 with ophthalmological manifestations 11 sem ophthalmologic manifestations	B	PIOA = 0.71 ± 0.17 PIOA = 0.97 ± 0.20	PI lower in patients with ophthalmologic manifestations
Nakatsuka et al. ¹⁴	Case-control	10 PEG	A	PIOA = 1.67 ± 0.47 RIOA = 0.74 ± 0.6 PROA = 0.83 ± 0.09	Vasodilator effect of NO
Ohno et al. ¹⁵	Case-control	1 PE puerperal	A		Prostaglandin E1 vasodilator effect
[5pt] Takata et al. ⁸	Cross-sectional study	25 PEL 27 PEG	B	PIOA = 1.66 ± 0.25 PIOA = 1.61 ± 0.40	
Ayaz et al. ¹⁶	Cross-sectional study	27 PEL/M 3 SP	B	PI = 0.91 ± 0.10 PIOA = 1.49 PIOA = 1.52 PIOA = 1.36	PI increased in severe PE
Diniz et al. ⁶	Cross-sectional study	20 MP 20 SP	B	PIOA = 1.16 ± 0.25 PIOA = 1.00 ± 0.29	PI severe decreases in PE
Barbosa et al. ¹⁷	Cross-sectional study	112 imminent eclampsia	B	RIOA < 0.56	RI is a relevant biomarker in imminent eclampsia
Brandão et al. ⁷	Cross-sectional study	59 PN 15 PE	B	RIOA = 0.70 ± 0.03 PIUA = 0.84 ± 0.12 DILA = 8.42 ± 3.15 RIOA = 0.68 ± 0.03 PIUA = 1.20 ± 0.16 DILA = 3.60 ± 2.38	RI did not change in this gestational period
Brandão et al. ¹⁸	Cross-sectional study	25 PN 26 PE early 30 PE late	B	RIOA = 0.74 ± 0.03 DILA = 14.12 ± 6.14 RIOA = 0.63 ± 0.02 DILA = 7.62 ± 5.42 IRAO = 0.65 ± 0.02 DILA = 5.83 ± 4.12	Endothelial dysfunction and hyperperfusion Central nervous system PE early and late
Matias et al. ¹⁹	Cross-sectional study	274 pregnant women with risk factors for PE		PIOA = 2.17 ± 0.53 RIOA = 0.81 ± 0.81 PROA = 0.53 ± 0.12	Values greater than the normal patients
de Oliveira et al. ²⁰	Cross-sectional study	30 MP 30 SP	B	RIOA = 0.73 ± 0.06 PIOA = 1.63 ± 0.35 PROA = 0.65 ± 0.10 RIOA = 0.63 ± 0.09 PIOA = 1.13 ± 0.31 PROA = 0.89 ± 0.12	Central hyperperfusion in SP

Table 1 – (Continued)

Author/year	Study design	Sample	Degree of evidence	Variables	Results
Gurgel et al. ²¹	Cross-sectional study	22 PE early 9 PE late	B	PIUA = 1.85 ± 0.3 PIOA = 2.11 ± 0.6 PIUA = 1.60 ± 0.5 PIOA = 1.92 ± 0.6	Evaluates the maternal circulation before vascular changes settle
Belfort et al. ¹¹	Case-control	8 PE	A	RIOA = ↓ PIOA = ↓	Magnesium sulfate produces vasodilation

RI, resistance index; RIOA, resistance index of the ophthalmic artery; PI, pulsatility index; PIOA, pulsatility index of the ophthalmic artery; PIUA, pulsatility index of the uterine artery; PE, pre-eclampsia; MP, mild pre-eclampsia; SP, severe pre-eclampsia; PROA, peak ratio of the ophthalmic artery.

Flow-mediated dilation less than 4.5% may be used to estimate the risk of PE. Its decrease is directly related to morbidity in PE (Table 2).²⁹

Uterine artery

According to Jamal et al.,³⁰ Doppler ultrasound used to assess the uterine artery during the second trimester is a useful screening method for identifying a high-risk pregnancy.

The authors attributed this to the severity of the disease, as indicated in other theories (Table 3). Lai et al.³¹ used this test for patients with a prior maternal history of PE together with blood pressure measurements, and found that there was an improvement in the sensitivity of the assessment (Table 3). Gallo et al.³² found that in normal pregnancy associated with PE, maternal characteristics and the pulsatility index are associated with the severity of disease (Table 2).

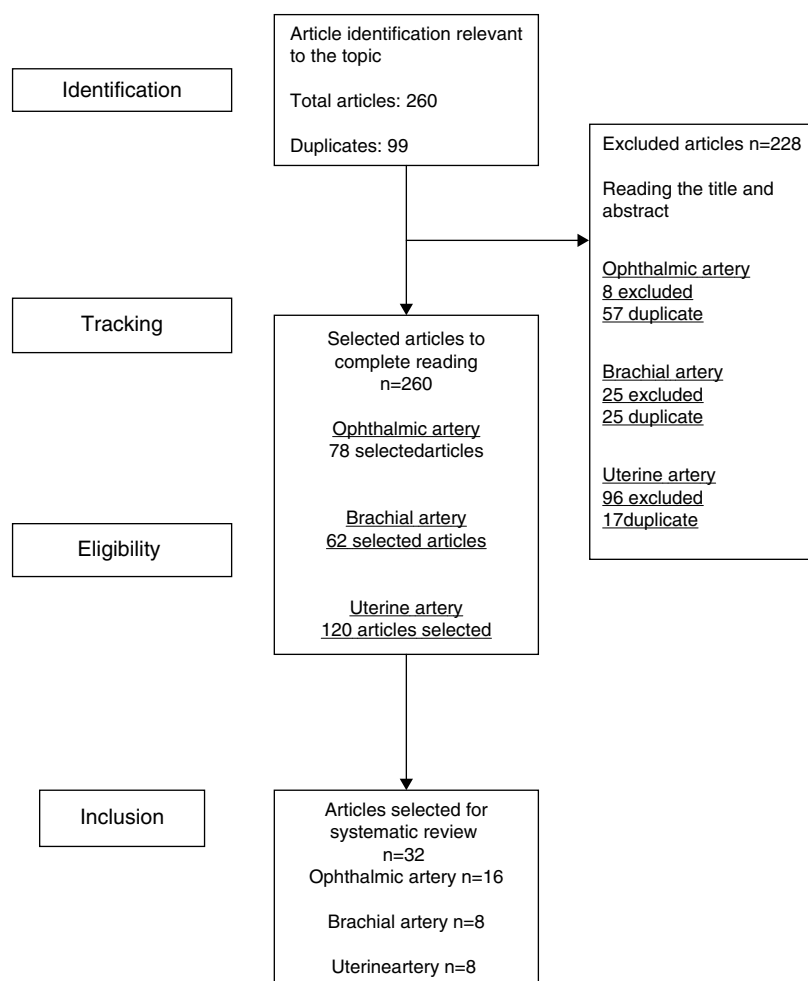


Fig. 1 – Flow diagram of identification and selection of studies included in the systematic review.

Table 2 – Studies using ultrasound to assess flow-mediated dilation of brachial artery in non-pregnant women, normal pregnant women and pregnant women with pre-eclampsia (PE).

Author/year	Study design	Sample	Degree of evidence	FMD		
				NP	NW	PE
Savvidou et al. ²²	Cross-sectional study	NP = 19 NW = 157	B	6.4 ± 2.4%	8.84 ± 3.18%	
Savvidou et al. ²³	Cross-sectional study	P = 83	B		8.2 ± 2.8 UA without notches 7.6 ± 4.5 UA with notches	3.8 ± 3.2 sem CIUR 2.6 ± 2.3 com CIUR
Brodzski et al. ²⁴	Cross-sectional study	P = 57	B		13.7% UA without notches 6.3% UA with notches	
Chambers et al. ²⁵	Cross-sectional study	NW = 48 PE = 113	A	With PE in a previous pregnancy = 3.36 mm without PE in previous Pregnancies = 3.29 mm	FMD lower in the group that had PE in a previous pregnancy	
Henriques et al. ²⁶	Cross-sectional study	PE = 60	B		PE in women with previous pregnancy have a higher frequency of FMD changed	
Kamat et al. ²⁷	Cross-sectional study	NW = 81	B			Cut-off = 8.7%, S = 88% E = 93%
Filho et al. ²⁸	Cross-sectional study	PE = 14 SPE = 13	B			SPE = 6.0% (1.9–10.3) PE = 13.6% (4.4–17.1)
Vieira et al. ²⁹	Cross-sectional study	PE = 64	B			PE = 11.8% (5.4–16.6%) CPE = 7.4% (2.2–13.3%) CCPE = 2.8% (0.0–7.2)

FMD, flow-mediated dilation; P, pregnant women; NW, non-pregnant women; NP, normal pregnant women; PE, pre-eclampsia; IUGR, intrauterine growth retardation; SPE, superimposed pre-eclampsia; CPE, complicated pre-eclampsia; PECC, pre-eclampsia with a combination of complications (HELLP: H, hemolysis; EL, elevated liver enzymes; LP, low platelets, eclampsia, stillbirth); EPE, early pre-eclampsia; LPE, late pre-eclampsia; HA, gestational hypertension; UA, uterine artery.

Table 3 – Studies assessing use of Doppler ultrasound of uterine artery in normal pregnant women and in pregnant women with pre-eclampsia (PE).

Author/year	Sample	PI	Bilateral notches (%)	Degree of evidence	Study design	Results
Jamal et al. ³⁰	435 N = 390 GC = 45	N = 0.99 (+0.32) GC = 1.27 (+0.55)	N = 18 (4.6%) GC = 9 (20%)	B	Cross-sectional study	S = 33% S = 66%
Lai et al. ³¹	4.294	0.71 Percentile90 = 1.02 Percentile95 = 1.16		B	Cross-sectional study	Second trimester maternal characteristics of the Doppler = UA can effectively identify patients at high risk of developing PE
Gallo et al. ³²	50.490	PE < 34 sem=0.996 PE > 34 < 38 = 1.377 PE > 38 = 1.509		B	Cross-sectional study	PI normal pregnancy is associated with maternal characteristics In PE the PI is associated with disease severity
Gomes-Arriagaet al. ³³	92	PE c/IUGR = 2.11 ± 0.43 PE s/IUGR = 1.89 ± 0.66		B	Cross-sectional study	EPE = PI and sFlt-1/PlGF abnormal LPE = PI normal in 50% of cases A sFlt-1/PlGF shows high specificity and low sensitivity to confirm PE
Scazzocchio et al. ³⁴	5759	N = 1.67 (0.53–1.25) EPE = 1.68 (1.54–1.84) LPE = 2.23 (1.75–3)		B	Cross-sectional study	First trimester – PAPP-A/b-HCG/PA/Doppler da UA is useful for predicting risk of PE in low-risk patients
Arcangelli et al. ³⁵	382	PE cut-off = 1.79 EPE cut-off = 1.9		B	Cross-sectional study	Second trimester – Doppler da UA is not efficient in anticipating risk of PE in patients with low risk
Parra-Cordeiro et al. ³⁶	5367	Controls PI = 1.02 (0.83–1.31) EPE PI = 1.39 (1.14–1.76) PE PI = 1.14 (0.97–1.43)	B	Cross-sectional study	Características maternas, associadas a AU da Doppler e PlGF pode prever 1/2 das gestações que serão complicadas pela PEP	
Prajapati et al. ³⁷	200	N = 0.7 PE = 0.9		B	Cross-sectional study	Uterine Doppler in the 2nd quarter is a useful screening test associated with HCM and PAM greatly enhances the power of the test.

N, normal pregnant women; GC, pregnancy complicated by pre-eclampsia; IUGR, premature labor, placenta previa, fetal death; EPE, early pre-eclampsia; LPE, late pre-eclampsia; MCH, maternal medical history; MBP, mean blood pressure.

An abnormal average pulsatility index and an abnormal ratio of soluble fms-like tyrosine kinase to placental growth factor are common in early PE (Table 3).³³

Scazzocchio et al.³⁴ observed that during the first trimester a combined test assessing maternal factors, Doppler ultrasound of the uterine artery, mean arterial pressure and plasma protein A is useful for predicting PE in low-risk pregnancies (Table 3).

In the first trimester, the combination of maternal characteristics and uterine artery Doppler and placental growth factor, can predict about half of pregnancies complicated by early PE (Table 3).³⁶

However, during the second trimester, uterine artery Doppler ultrasound in low-risk pregnant women does not effectively identify women who are at risk of complications (Table 3).³⁵ Nonetheless, it is a useful screening method for identifying high-risk pregnancies. Moreover, the usefulness of Doppler ultrasound of the uterine artery improves when it is combined with a previous maternal history of PE and measurement of mean arterial blood pressure (Table 3).³⁷

Ultrasound of the uterine artery, used with assessments of orbital circulation and flow-mediated dilation of the brachial artery, help differentiate the degree and severity of PE (Table 1).⁸

Conclusion

During the first trimester of pregnancy, when tests that assess maternal vascular function are used with knowledge of maternal history, patients who are at risk can be evaluated more effectively. During the second trimester of pregnancy in patients with already established disease, changes are seen on Doppler ultrasound of the uterine artery and ultrasound of flow-mediated dilation, since changes in the ophthalmic artery are seen by Doppler ultrasound after the onset of symptoms of PE.

Based on the findings of this systematic review, Doppler ultrasound of the ophthalmic artery and uterine artery, and ultrasound assessment of flow-mediated dilation of the brachial artery, can be useful in identifying patients at risk and monitoring disease progression, as well as for providing effective treatment.

Our findings show that these methods are useful, making early intervention feasible and thereby improving prognosis and reducing morbidity and mortality of pregnant women and their newborns faced with cases of PE and eclampsia.

Conflicts of interest

The authors declare no conflicts of interest.

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