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Centralização Cerebral Materna na Doença Hipertensiva Específica da Gestação

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Glaucimeire Marquez Franco

Centralização Cerebral Materna na Doença Hipertensiva Específica da Gestação

Tese de Doutorado apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Goiás para obtenção do Título de Doutor em Ciências da Saúde.

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SUMÁRIO

TABELAS, FIGURAS E QUADROS

SÍMBOLOS, SIGLAS E ABREVIATURAS

AO	Artéria Oftálmica
ACM	Artéria Cerebral Média
BMI	Body Mass Index
BVS	Biblioteca Virtual em Saúde
BA	Brachial Artery
CIUR	Crescimento Intrauterino Restrito
DFM	Dilatação Fluxo Mediada
E	Eclâmpsia
GE	Group Eclâmpsia
GN	Group Normal (Pregnant Women)
GPEG	Pregnant Women with Severe Preeclampsia
GPEL	Pregnant Women with Mild Preeclampsia
HELLP	Hemolysis, Elevated Enzymes Liver, Low Count Platelets
HMI	Hospital Materno Infantil
IG	Gestational Age
IMC	Índice de Massa Corpórea
IP	Índice de Pulsatilidade
IR	Índice de Resistência
MP	Preeclampsia mild
NHBPEP	National High Blood Pressure Education Program
NO	Òxido Nítrico
OA	Ophthalmic Artery

PA Pressão Arterial

PAM Pressão Arterial Média

PIGF Placental Growth Factor

PR Peak Ratio

PRES Síndrome de Encefalopatia Posterior Reversível

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PUC-GO Pontifícia Universidade Católica de Goiás

PVD Pico de Velocidade Diastólica

PVM Pico de Velocidade Média

PVS Pico de Velocidade Sistólica

ROC Receiver Operator Curve Characteristic

RPV Razão entre Picos de Velocidade

sENg Soluble Endogolin

sFlt-1 Soluble Fms-Like Receptor Tirosinase Quinase

SP Severepreeclampsia

S/D Relação Sístole-Diástole

TCLE Termo de Consentimento Livre Esclarecido

UA Uterine Artery

VLH Virtual Library on Health

VD Velocidade Diastólica

VEGF Fator de Crescimento do Endotélio Vascular

VS Velocidade Sistólica

RESUMO

Introdução: A pré-eclâmpsia é um importante problema em obstetrícia, com altos índices de morbidade perinatal e mortalidade em todo o mundo, principalmente nos países em desenvolvimento. **Objetivos:** Avaliar a ocorrência de centralização cerebral materna em gestantes portadoras de doença hipertensiva específica da gestação. Produzir um artigo de revisão sistemática sobre Doppler da artéria oftálmica e da artéria uterina e sobre a dilatação fluxo-mediada da artéria braquial. Elaborar um artigo original para avaliar a ocorrência da centralização cerebral materna em gestantes portadoras de doença hipertensiva específica da gestação. Estabelecer a curva de normalidade da relação do Doppler da artéria uterina com o Doppler da artéria oftálmica. Comparar a relação do Doppler da uterina com o Doppler da artéria oftálmica no grupo normal e patológico. Definir o ponto de corte, através da curva ROC, para diagnóstico de pacientes com doença hipertensiva específica da gestação. **Métodos:** A revisão sistemática da literatura envolveu 260 artigos indexados das bases de dados Medline via PubMed e Biblioteca Virtual em Saúde (BVS), publicados entre 1989 e 2014. Para o artigo original, foi realizado um estudo caso controle com 178 gestantes distribuídas em dois grupos: um grupo-controle de pacientes normais (PN), num total de 83 gestantes normotensas; e um grupo casos de 95 pacientes com doença hipertensiva específica da gestação. As variáveis estudadas foram: a velocidade sistólica (VS), a velocidade diastólica (VD), o índice de resistência, a relação sístole-diástole. Além dessas variáveis foram estudadas paridade, aborto, peso, altura, IMC, idade materna, idade gestacional. **Resultados:** Por meio da estratégia de busca, localizaram-se 260 artigos, dos quais foram elegíveis 32 artigos, sendo dezesseis artigos sobre a artéria oftálmica, oito artigos sobre a artéria braquial e oito artigos sobre a artéria uterina. Um total de 178 pacientes fez parte do estudo. A média de idade das pacientes do grupo de gestantes normais foi de 29,8±4,7 e das pacientes com doença hipertensiva específica da gestação, de 26,14±6,17. A média da idade gestacional das pacientes gestantes normais foi de 34,3±3,5 semanas e das pacientes com doença hipertensiva específica da gestação, de 32,40±3,37. A média do índice de massa corporal (IMC) das gestantes normais foi de 26,8±5,6 e das pacientes com doença hipertensiva específica da gestação, de 30,55±5,12. Foi realizada uma curva de normalidade da relação sístole-diástole com o respectivo ponto de corte. Desenvolveu-se uma curva ROC com o ponto de corte, considerando a velocidade sistólica, a velocidade diastólica, a relação sístole-diástole e o índice de resistência da artéria oftálmica, respectivamente. **Conclusão:** O Doppler da artéria oftálmica e da artéria uterina e a dilatação fluxo mediada podem ser úteis para identificar pacientes em risco. Observou-se que a ocorrência de centralização materna em gravidez de alto risco como a pré-eclâmpsia (PE) é real, visto que na curva de normalidade a média e o desvio padrão do Doppler da AU/AO da relação sístole-diástole foram de 0,43 ± 0,16. O ponto de corte mais sensível, verificado por meio da curva ROC, que define centralização cerebral materna nas pacientes com doença

hipertensiva específica da gestação, é de 0,57 para a S/D da UD/AO, com 78% de sensibilidade e 13% de falso positivo e 77% de especificidade.

Palavras chave: artéria oftálmica, dilatação fluxo mediada, artéria uterina, Doppler, pré-eclâmpsia, eclampsia.

ABSTRACT

Introduction: Preeclampsia and eclampsia are important causes of maternal and perinatal morbidity and mortality worldwide **Objectives**: To evaluate the maternal brain centralization in pregnant women with specific gestational hypertension. Produce a systematic review article on the ophthalmic artery Doppler and uterine artery and the flow-mediated dilation. Develop an original article in order to assess the possible occurrence of maternal brain centralization in pregnant women with specific gestational hypertension. Establish normal values of the ratio of uterine artery to the ophthalmic artery (mean and standard deviation). Compare the ratio of uterine with the ophthalmic artery in normal and pathological group. Set the cut-off point, using the ROC curve for specific diagnosis of patients with hypertensive disease of pregnancy. **Methods**: A systematic literature review involved 260 indexed articles from Medline via PubMed and Virtual Health Library (VHL), published between 1989 and 2014. For the original article, we performed a case-control study of 178 pregnant women divided into two groups: a control group of normal patients (PN), a total of 83 normotensive pregnant women; and one case group of 95 patients with specific gestational hypertension. The analyzed parameters which formed part of the variables studied were: systolic velocity (VS), diastolic velocity (RV), the resistance index, systole-diastole relationship. In addition to these variables were also studied epidemiological variables of pregnancy, parity, abortion, weight, height, BMI, maternal age, gestational age. **Results**: Through the search strategy, were located 260 articles, of which 33 articles were eligible, with fifteen articles on the ophthalmic artery, eight articles on the brachial artery and eight articles on uterine artery. A total of 178 patients took part in study. The average age of normal pregnant women group of patients was 29.8 ± 4.7 and patients with specific gestational hypertension, of 26.14 ± 6.17. The mean gestational age of normal pregnant patients was 34.3 ± 3.5 weeks and the patients with specific gestational hypertension, of 32.40 ± 3.37. The mean body mass index (BMI) of healthy patients was 26.8 ± 5.6 and patients with specific gestational hypertension, of 30.55 ± 5.12. A normality curve systole-diastole compared with the respective cutoff was performed. A ROC curve was developed, with the cutoff point, considering the systolic velocity, diastolic velocity, systolic-diastolic ratio and the resistance index of the ophthalmic artery, respectively. **Conclusion**: The Doppler uterine artery and ophthalmic artery flow-mediated dilatation can be useful to identify patients at risk for allowing the monitoring of disease progression and perform effective interventions. It is observed that the possibility of maternal centralization in high-risk pregnancy as the PE is real, whereas in the average normal values and the standard deviation of the Doppler AU / AO-systole-diastole ratio were 0.43 ± 0 16. The cutoff point more sensitive, verified by the ROC curve, which defines maternal brain centralization in patients with hypertensive disorders of pregnancy, is 0.57 for the S / D for UD / AO, with 78% sensitivity and 13 % false positive and 77% specificity.

Key words: Ophthalmic artery, flow-mediated dilatation, uterine artery, Doppler sonography, preeclampsia, eclampsia.

1 INTRODUÇÃO

A pré-eclâmpsia é um importante problema em obstetrícia, com altos índices de morbimortalidade perinatal em todo o mundo, principalmente nos países em desenvolvimento. Os Comitês Estaduais de Mortalidade Materna declararam que a maioria dessas mortes poderia ser evitada com medidas básicas de saúde pública (DULEY, 2009; ESCALANTE, 2011; WHO, 2013).

Na Cúpula do Milênio da Organização das Nações Unidas (ONU), das oito Metas de Desenvolvimento adotadas, uma delas é a redução da mortalidade materna em 75% até 2015 (DULEY, 2009; ESCALANTE, 2011; MORSE et al., 2011). Para alcançar essa meta, será preciso diminuir os índices da mortalidade materna em 15% ao ano. Contudo, no Brasil, em 2011 a mortalidade materna reduziu apenas 8,6% (ESCALANTE, 2011).

A partir desses conhecimentos, faz-se necessário o estudo da doença hipertensiva específica da gestação, com o objetivo de delinear estratégias que venham diminuir a sua morbimortalidade.

A pré-eclâmpsia é uma desordem multissistêmica de causa desconhecida (SIBAI; DEKKER; KUPFERMINC, 2005; BRANDÃO, A.H.F et al., 2010). Acredita-se que a pré-eclâmpsia, principalmente a precoce, ocorra em dois estágios. O primeiro estágio da doença acontece antes de vinte semanas de gestação e se dá por causa de uma placentação defeituosa. Nesse período ainda não há sinais e sintomas da doença. O segundo estágio é o das consequências dessa placentação defeituosa (SIBAI; DEKKER; KUPFERMINC, 2005; AMORIM; SOUZA, 2009; BRANDÃO, A.H.F et al., 2010; STEEGERS et al., 2010).

Existem várias teorias que tentam explicar a fisiopatologia da pré-eclâmpsia, dentre elas, destacam-se duas: A teoria da origem vascular da doença defende a premissa de que a pré-eclâmpsia é caracterizada por uma resposta vascular anormal à placentação defeituosa (primeiro estágio da doença, quando ainda não há sintomas da doença), o que levaria à isquemia, à má perfusão, ao estresse oxidativo e à doença vascular. A doença vascular caracteriza-se com o aumento sistêmico da resistência vascular, agregação de plaquetas aumentada, ativação do sistema de coagulação, e disfunção endotelial (segundo estágio da doença) (SIBAI; DEKKER; KUPFERMINC, 2005; CABRAL et al., 2009; ACOG, 2013).

A teoria imunogenética acredita que a pré-eclâmpsia seja uma má-adaptação imunológica materno-paterna, ou seja, uma reação aloimune materna desencadeada por uma rejeição do enxerto fetal. Esta teoria sugere o envolvimento de fatores imunogenéticos na fisiopatologia da pré-eclâmpsia (AMORIM; SOUZA, 2009). Aventa-se uma possível implicação do gene da síntese do óxido nítrico e do sistema *human leucocyte antigen* (HLA), e resultando em uma resposta imunológica materna anormal ao trofoblasto, determinando à má adaptação placentária (AMORIM; SOUZA, 2009; ACOG, 2013).

O estudo atual se justifica diante das controvérsias existentes na literatura sobre a fisiopatologia e modelo hemodinâmico da pré-eclâmpsia. Não há descrição na literatura sobre o estudo da relação Doppler das artérias uterinas com o Doppler da artéria oftálmica (AU\AO). A determinação desses novos padrões de fluxo pode promover novas perspectivas sobre a fisiopatologia, o diagnóstico e a gravidade da pré-eclâmpsia e eclâmpsia.

2 REVISÃO DA LITERATURA

2.1 Pré-eclâmpsia

2.1.1 Conceito

A pré-eclâmpsia é hipertensão de início recente e proteinúria (≥300 mg em 24 h) que surge após a 20ª semana de gestação ou, na ausência de proteinúria, hipertensão em conjunto com evidência de doença sistêmica (NBPH, 2000; ACOG, 2013; CHAIWORAPONGSA et al., 2014). Hipertensão é definida como uma pressão sanguínea sistólica de pelo menos 140 mm Hg e diastólica de pelo menos 90 mm Hg, medida, no mínimo duas vezes, em 4 a 6H de intervalo, e após 20ª semana de gestação em mulheres sabidamente normotensas previamente (SIBAI; DEKKER; KUPFERMINC, 2005; ACOG, 2013; CHAIWORAPONGSA et al., 2014).

Eclâmpsia é definida como a ocorrência de convulsões que não podem ser atribuídas a outras causas em uma mulher com pré-eclampsia (NBPH, 2000). No quadro 1 estão demonstradas as outras causas de convulsão.

Quadro 1. Eclâmpsia: diagnóstico diferencial

• **Acidente vascular cerebral**
Hemorragia intracerebral
Trombose arterial ou venosa
• **Doenças hipertensivas**
Encefalopatia hipertensiva
Feocromocitoma
• Lesão expansiva do sistema nervoso central
Tumor
Abscesso
• Distúrbios metabólicos
Hipoglicemia
Uremia
• Infecção
Meningites
Encefalites
• Púrpura trombocitopênica trombótica
• Epilepsia

Fonte: FEBRASGO – Manual de Orientação Gestação de Alto Risco-2011

Classificação

Segundo a Federação Brasileira de Ginecologia e Obstetrícia, a pré-eclâmpsia é classificada em leve e grave (BRANDÃO, A.H.F et al., 2010). Considera-se grave quando presente um ou mais dos seguintes critérios: pressão arterial ≥ 160 x 110 mmHg, proteinúria ≥ 2 g/24 horas (ou > 2+ em amostra de urina), creatinina sérica > 1,2 mg%, sintomas de eclâmpsia iminente, eclâmpsia (crise convulsiva), dor epigástrica ou no hipocôndrio direito, aumento de enzimas hepáticas (AST, ALT), plaquetopenia (< 100.000/mm3), anemia hemolítica microangiopática (NBPH, 2000; FEBRASGO, 2011).

Existe outra classificação mais recente da pré-eclâmpsia que se baseia no início das manifestações clínicas da doença (CHAIWORAPONGSA et al., 2014; HUPPERTZ, 2008).

Na pré-eclâmpsia precoce, as pacientes apresentam início da sintomatologia antes das 34 semanas. Na pré-eclâmpsia tardia, os sintomas iniciam-se após as 34 semanas (CHAIWORAPONGSA et al., 2014; HUPPERTZ, 2008).

A PE precoce associa-se principalmente à remodelação placentária incorreta, com evidências de lesões isquêmicas ao exame da placenta. Pacientes com PE precoce apresentam Doppler de artérias uterinas anormais, e é frequente a associação com crescimento intrauterino restrito (CIUR) e resultados maternos e fetais adversos. Pacientes com idade acima de 35 anos apresentam maior risco de desenvolvimento de PE precoce (CHAIWORAPONGSA et al., 2014; HUPPERTZ, 2008).

A PE tardia está mais associada a fatores constitucionais maternos, com índice de massa corporal (IMC) elevado. O Doppler de artérias uterinas é normal ou pouco alterado. O comprometimento do desenvolvimento fetal é menor, e o resultado perinatal é mais favorável (CHAIWORAPONGSA et al., 2014; HUPPERTZ, 2008).

Nos casos de pré-eclâmpsia é preciso identificar a gravidade deles, uma vez que o prognósticos materno e fetal dependem da conduta a ser estabelecida. Então, a presença de um ou mais dos critérios descritos no quadro 1 identifica um caso de pré-eclâmpsia como grave (CHAIWORAPONGSA et al., 2014; HUPPERTZ, 2008).

Quadro 1. Indicadores de pré-eclâmpsia grave

Pressão arterial ≥ 160 x 110 mmHg
Proteinúria ≥ 2 g/24 horas (ou > 2+ em amostra de urina)
Creatinina sérica > 1,2 mg%
Sintomas de eclâmpsia iminente
Eclâmpsia (crise convulsiva)
Dor epigástrica ou no hipocôndrio direito
Aumento de enzimas hepáticas (AST, ALT)
Plaquetopenia (< 100.000/mm3)
Anemia hemolítica microangiopática

Fonte: FEBRASGO – Manual de Orientação Gestação de Alto Risco-2011

2.2 Endotélio

A identificação de gestantes de alto risco para a PE requer um acompanhamento pré-natal mais especializado e rigoroso, para permitir intervenções mais precoces, se necessário, e assim conseguir prever e alterar a história natural da pré-eclâmpsia, o que pode melhorar os resultados maternos e perinatais relacionados a esta doença (CALIXTO et al., 2014).

A liberação endotelial de óxido nítrico tem sido proposta como o principal fator responsável pela diminuição da resistência vascular sistêmica observada durante a gravidez. Além disso, uma diminuição da produção ou um aumento da inativação do óxido nítrico tem sido ligada à disfunção endotelial, que caracteriza a pré-eclâmpsia (SAVVIDOU et al., 2000; TEIXEIRA, 2008; BÖGER et al., 2010; CUNHA FILHO et al., 2010; BRANDÃO; CABRAL; CABRAL, 2011).

Fatores derivados do endotélio são responsáveis por vários efeitos, tais como manter e regular o tônus vascular, a agregação de plaquetas e a proliferação de músculo liso nas imediações. Fatores derivados do endotélio incluem, principalmente, a endotelina-1 e o óxido nítrico, considerados vitais para manter e regular o tônus vascular por diferentes vias. As células endoteliais também liberam outros fatores, tais como o fator hiperpolarizante derivado do endotélio (EDHF), que provoca a hiperpolarização da membrana, abrindo canais de íons K (TEIXEIRA, 2008; BRANDÃO; CABRAL; CABRAL, 2011).

Óxido nítrico é essencial para a manutenção do tônus vascular das paredes dos vasos sanguíneos, desempenhando um papel importante na dilatação dos vasos sanguíneos e na prevenção de danos no endotélio, durante o aumento da pressão arterial ou de fluxo. O óxido nítrico atua em ambos os componentes celulares do sangue e do músculo liso vascular. Centra-se na enzima guanilatociclase, que quando ativada aumenta a concentração intracelular de GMP cíclico, que por sua vez ativa a proteína cinase G e induz o relaxamento do músculo liso vascular, inibindo a ativação e agregação das plaquetas. Além disso, o NO pode inibir a síntese e os efeitos hemodinâmicos da endotelina-1 (ET-1), um vasoconstritor potente peptídeo derivado do endotélio, que pode estimular a produção de NO (BRANDÃO; CABRAL; CABRAL, 2011).

A pré-eclâmpsia é a hipertensão na gravidez, também conhecida como hipertensão induzida pela gravidez. A pré-eclâmpsia geralmente se desenvolve após a vigésima semana de gestação. Os primeiros testes para detectar esta condição revelam a presença de proteínas na urina para além

da elevação da pressão sanguínea. A pré-eclampsia é originária da placenta e inicia-se com a invasão inadequada do citotrofoblasto e termina com o grau de disfunção endotelial materno. Produção de fatores antiangiogênicos placentários, especificamente solúvel fms relacionados tirosina-quinase 1 (sFlt-1) e endoglin solúvel, está desregulada na pré-eclâmpsia e envolvida em sua patogênese. Esses fatores antiangiogênicos placentários que são liberados na circulação materna agem bloqueando o endotélio materno, o que resulta em hipertensão, proteinúria, e as outras manifestações sistêmicas da pré-eclâmpsia. A melhor maneira de tratamento para a pré-eclâmpsia é uma cesariana ou indução do parto, se o bebê está suficientemente desenvolvido (geralmente 37 semanas ou mais recente). Tem sido relatado que os eritroblastos fetais e DNA livre que entrarem na circulação materna causam a pré-eclâmpsia em mulheres suscetíveis (ROMERO et al., 2008; TEIXEIRA, 2008; JÚNIOR; DE AGUIAR; CORRÊA, 2009; BRANDÃO; CABRAL; CABRAL, 2011).

A dilatação fluxo-mediada da artéria braquial é um método não invasivo e de fácil execução. Uma isquemia transitória provocada por uma pressão aplicada no membro superior leva à liberação de óxido nítrico pelo endotélio vascular, causando vasodilatação compensatória (SAVVIDOU et al., 2000). A quantidade de NO liberado no endotélio, quando lesado, não é capaz de provocar a vasodilatação, promovendo aumento no lúmen vascular em proporção menor que o esperado (BRANDÃO, A.H.F. et al., 2010).

A dilatação fluxo mediada (DILA) é um exame promissor e é considerada uma técnica confiável e reprodutível para a avaliação da função endotelial (MATSUBARA et al., 2010). Nas pacientes com pré-eclâmpsia, no

segundo trimestre de gestação ela já se encontra significativamente alterada. Alguns estudos demonstraram que a DILA pode ser utilizada como método preditor de PE, uma vez que em pacientes que desenvolveram PE já se mostrava significativamente reduzida mesmo antes das manifestações clínicas da doença (SIERRA-LAGUADO; GARCIA; LOPEZ-JARAMILLO, 2006).

O método consiste em avaliar a artéria braquial através da ultrassonografia com transdutor linear com a paciente em condições basais de repouso e durante uma hiperemia induzida por um esfingnomanômetro insuflado no antebraço (FIGURAS 1 e 2). A medida do exame é analisada através do porcentual de aumento do diâmetro da artéria braquial pós-oclusão (D2) em relação aos seus valores basais (D1) originando a fórmula seguinte:

$$\mathbf{DFM = (D2 – D1) / D1 \times 100\ \%}$$

FIGURA 1 – Ilustração da técnica de medida da dilatação fluxo-mediada da artéria braquial.

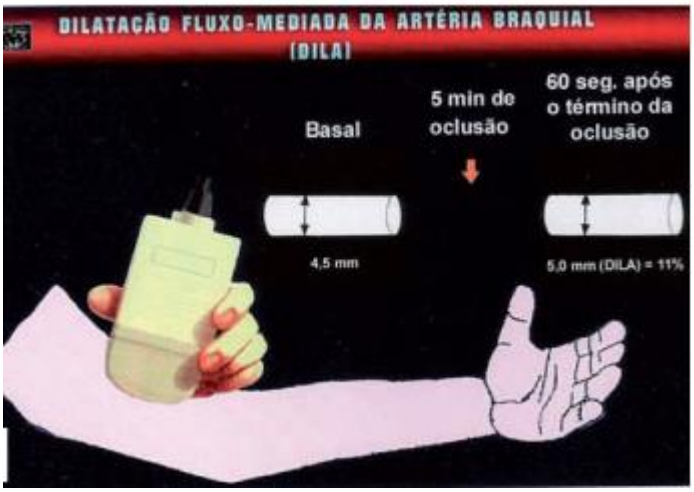
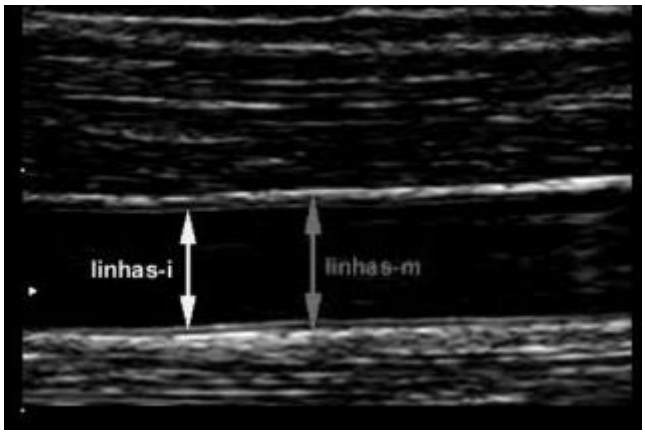


FIGURA 2 – Imagem ultrasonográfica da artéria braquial durante a medida da dilatação fluxo-mediada.



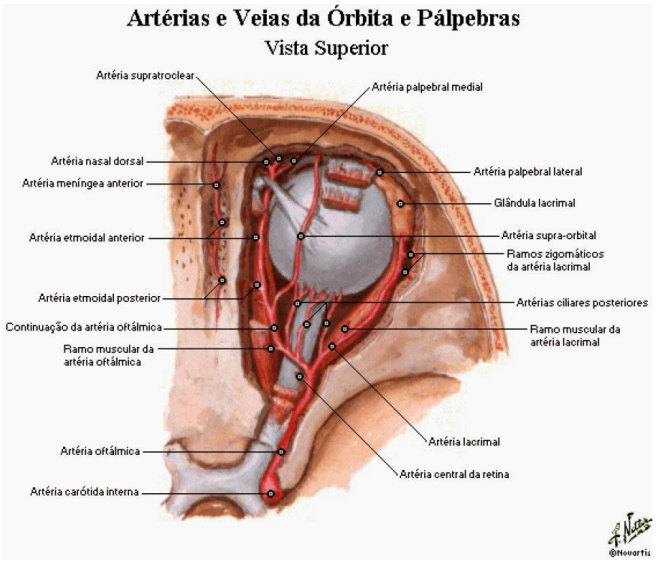
2.3 Artéria Oftálmica

Outro exame que se mostra promissor na avaliação da perfusão sanguínea e integridade do endotélio é o Doppler da artéria oftálmica. Desde os primeiros estudos da artéria oftálmica, observaram-se uma vasodilatação e um hiperfluxo nas pacientes com pré-eclâmpsia (HATA et al., 1992).

A artéria oftálmica é o principal vaso nutridor da circulação orbital. Ela é ramo direto da carótida interna, que é responsável por grande parte da irrigação cerebral. A artéria oftálmica origina-se na região temporal e posterior ao nervo óptico, dirigindo-se à região nasal, depois de cruzar anteriormente o nervo óptico, onde dá origem a grande parte dos seus ramos, que são a artéria central da retina, artérias ciliares posteriores, artéria lacrimal, artéria supratroclear e artéria supraorbital (Figura 3). A avaliação da artéria oftálmica através do Doppler consiste numa análise indireta da circulação intracraniana, em virtude das similaridades embriológicas,

anatômicas e funcionais entre os vasos intracranianos de pequeno calibre e as artérias orbitais (DINIZ et al., 2004).

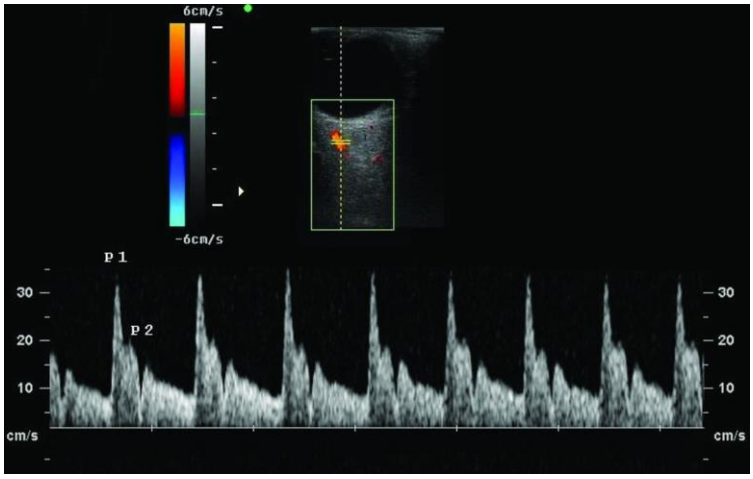
FIGURA 3- Imagem representativa da artéria oftálmica



O estudo Doppler da artéria oftálmica é uma técnica reprodutível e de fácil acesso, uma vez que não há obstáculos anatômicos, como ossos e gordura, na sonolucência do globo ocular, do ângulo quase vertical da artéria oftálmica para o transdutor e pela possibilidade de se obter informações sobre a microcirculação cerebral (DINIZ; MORON; SASS; et al., 2008).

O padrão espectral normal da artéria oftálmica é uma onda de padrão dicrótica, verificado pela presença de onda monofásica, com ascensão sistólica rápida e diástole com duas incisuras, proto e mesodiastólicas. Há pequena elevação na velocidade de fluxo após as incisuras, durante a diástole (DINIZ et al., 2004) (Figura 4).

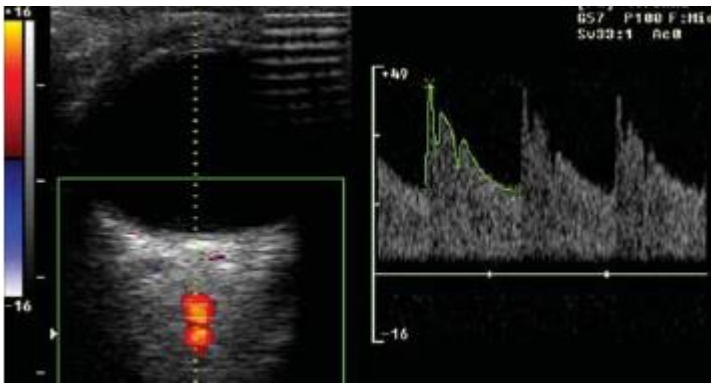
FIGURA 4- Imagem representativa da onda dopplerfluxométrica da artéria oftálmica de uma gestante normal.



As modificações hemodinâmicas no sistema nervoso central, observadas na pré-eclâmpsia, se refletem em alterações significativas nos formatos de onda do Doppler da artéria oftálmica, com aumento do fluxo diastólico após a incisura protodiastólica, o que não é observado nos casos de gestações normais (Figura 5). Possivelmente, a explicação fisiopatológica disso esteja no fato de a artéria oftálmica ser fisiologicamente mais dilatada, por causa de uma liberação basal contínua de óxido nítrico. Outra explicação tem a ver com as anastomoses das artérias oftálmicas com ramos da artéria carótida externa, diminuindo a resistência para compensar o vasoespasmo da artéria cerebral média. Outra teoria descrita baseia-se na hipótese de que o vasoespasmo na pré-eclâmpsia predominaria na microvasculatura, ocasionando isquemia local, e nesta situação, um mecanismo de compensação seria a dilatação da artéria de maior calibre, no caso, a artéria oftálmica. Seria um mecanismo semelhante ao que ocorre com os fetos hipóxicos, uma “centralização materna”, ou seja, um mecanismo compensatório para manter o fluxo nos órgãos vitais. Porém, em fase mais

avançada da pré-eclâmpsia grave, esta vasodilatação desaparece e ocorre vasoconstrição (BELFORT et al., 1999; AYAZ et al., 2003; CARNEIRO et al., 2008; DINIZ; MORON; DOS SANTOS; et al., 2008).

FIGURA 5- Imagem representativa da onda dopplerfluxométrica da artéria oftálmica de uma gestante com DHEG.



Nos estudos Doppler com artéria oftálmica os índices mais utilizados são o índice de pulsatilidade, o índice de resistência, a velocidade de pico sistólico, a velocidade de pico diastólico e a razão de pico. A razão de pico foi estudada pela primeira por Nakatsuka et al (2002).

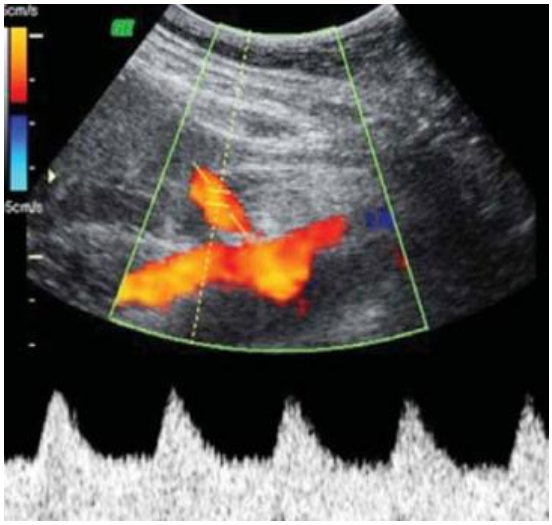
2.4 Dopplerfluxometria das artérias uterinas

Com o advento da dopplervelocimetria, a avaliação do fluxo útero-placentário tornou-se bem conhecido, com a avaliação qualitativa das artérias uterinas como método de rastreamento precoce e não invasivo, em gestações de alto risco. Desde os primeiros estudos, os autores já se referiam a esta metodologia como útil na avaliação das condições como pré-eclâmpsia e retardo do crescimento intrauterino (FITZERALD; DRUMM, 1977).

Na gravidez normal, a resistência no fluxo da artéria uterina diminui com o avanço da idade gestacional. A incapacidade de se conseguir uma

circulação de baixa resistência está associada com um risco subsequente de resultados adversos da gravidez (Figura 6). As últimas duas décadas têm mostrado o papel do Doppler das artérias uterinas na triagem de complicações da gravidez no primeiro e segundo trimestre da gestação com melhores sensibilidade e especificidade. Estudos mais recentes têm combinado Doppler da artéria uterina no primeiro trimestre com história materna e marcadores bioquímicos, e suas alterações entre o primeiro e segundo trimestre para melhorar a detecção. Alguns estudos foram realizados a fim de se investigar o valor do IP artéria da artéria uterina entre 30-33 semanas de gestação na predição de pré-eclâmpsia (LAI et al., 2013).

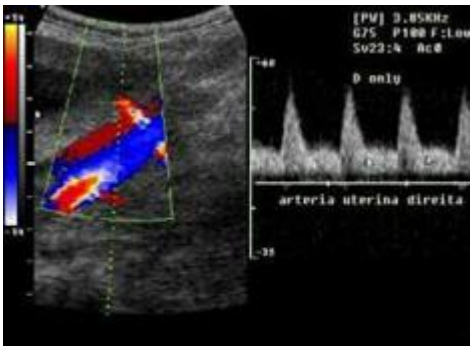
FIGURA 6- Imagem representativa da forma da onda dopplerfluxométrica da artéria uterina de uma gestante normal.



Estudos mostram que o Doppler das artérias uterinas no segundo trimestre apresenta uma associação entre o resultado adverso da gravidez e a maior média do índice de pulsatilidade da artéria uterina ou a prevalência de incisura diastólica. Alguns estudos mostram pouca sensibilidade do

Doppler de segundo trimestre para a predição de pré-eclâmpsia em uma população de nultíparas de baixo risco (MYATT et al., 2012). (Figura 7).

FIGURA 7- Imagem representativa da forma da onda dopplerfluxométrica da artéria uterina de uma gestante com DHEG.



Estudos anteriores relataram que o ultrassom Doppler realizado entre 11-14 semanas de gestação tem a melhor utilidade para predição do parto antes de 32 semanas de gestação. E se realizado no segundo trimestre, o ultrassom Doppler permitirá identificar as mulheres que desenvolvem pré-eclâmpsia ou CIUR, particularmente a pré-eclâmpsia grave ou pré-eclâmpsia que exige parto antes de 32 semanas de gestação .(PARRA et al., 2005). Estudos recentes, porém, mostram que o ultrassom Doppler das uterinas no primeiro trimestre, quando associado a outros marcadores maternos como características maternas, b-HCG, proteína plasmática-A, é útil para predizer pré-eclâmpsia em um pré-natal de baixo risco (SCAZZOCCHIO et al., 2013).

Doppler das artérias uterinas anormais é um bom preditor de pré-eclâmpsia precoce, mas não para a de início tardio. Artérias uterinas anormais ao Doppler estão associadas ao desenvolvimento anormal do trofoblasto (PAPAGEORGHIOU, 2008).

A pré-eclampsia é caracterizada como a invasão do trofoblasto e desenvolvimento da circulação uteroplacentária anormais, conduzindo à inflamação subsequente com disfunção endotelial materna. Há evidências crescentes de que pode haver diferentes fenótipos de pré-eclâmpsia e que, de fato, as pré-eclâmpsias precoce ou tardia a leve ou grave podem ter diferentes fisiopatologias subjacentes (ROBERTS; HUBEL, 2009).

Gravidezes que mais tarde desenvolveram pré-eclampsia precoce ou tardia se caracterizam por placentação prejudicada e um estado antiangiogénico durante o primeiro trimestre de gravidez. Os modelos de regressão, que incluem características maternas, Uta Doppler e PlGF, aparentemente podem prever cerca de metade das gestações que serão complicadas por pré-eclampsia precoce. Acredita-se que mais investigações em vários domínios são necessárias para auxiliar na criação de um teste de rastreio melhor e mais específico da população para a pré-eclâmpsia, durante o primeiro trimestre de gravidez (GOMEZ-ARRIAGA et al., 2013).

Em um artigo de revisão os autores relatam que as combinações de marcadores bioquímicos e ultrassonográficos melhoraram o desempenho de previsão de início de pré-eclâmpsia. E que do ponto de vista da medicina integrativa, são necessários grandes estudos de base populacional avaliando algoritmos que combinem múltiplos marcadores, para que a triagem seja finalmente implementada (GIGUERE et al., 2010).

3 3 OBJETIVOS

3.1 Objetivo Geral

Avaliar a ocorrência de centralização materna em gestantes portadoras de DHEG.

3.2 Objetivos Específicos

1º artigo:

- Produzir um artigo de revisão sistemática sobre Doppler da artéria oftálmica, Doppler da artéria uterina e dilatação fluxo-mediada.

2º artigo:

- Avaliar a ocorrência da centralização cerebral materna em gestantes portadoras de doença hipertensiva específica da gestação.

- Estabelecer a curva de normalidade da relação do Doppler da artéria uterina com o Doppler da artéria oftálmica (AU/AO).

- Comparar a relação do Doppler da artéria uterina com o Doppler da artéria oftálmica (AU/AO) do grupo normal e patológico.

- Estabelecer a curva ROC, para diagnóstico de pacientes com doença hipertensiva específica da gestação.

4 PUBLICAÇÕES

4.1 Artigo 1 – Ultrasound and Doppler Vascular Changes in the Preeclampsia and Eclampsia: Systematic Review

Autores

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Revista (Submetido)

Submission Confirmation

Submission Confirmation

The American Journal of Obstetrics & Gynecology (ajog@rrohio.com)

Adicionar aos contatos

24/02/2015

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"Using Ultrasound and Doppler Ultrasound to Assess Vascular Changes in Pre-eclampsia and Eclampsia: A Systematic Review"

Dear Prof. Glaucimeire Marquez Franco:

This acknowledges the receipt of your submission entitled, "Using Ultrasound and Doppler Ultrasound to Assess Vascular Changes in Pre-eclampsia and Eclampsia: A Systematic Review," to the American Journal of Obstetrics & Gynecology.

Please understand that if any item was omitted the submission will be considered incomplete and returned for resubmission.

Also, it is the responsibility of the corresponding author to ensure that:

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2) all appropriate Conflicts of Interest / Financial Disclosures for ALL authors has been included on the title page of the submission.

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Sincerely,

The Editors

Using Ultrasound and Doppler Ultrasound to Assess Vascular Changes in Pre-eclampsia and Eclampsia: A Systematic Review

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Conflict of interest: none

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 8 about using it to assess the uterine artery, and 8 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.

Keywords

Ophthalmic artery, flow-mediated dilation, uterine artery, Doppler sonography, pre-eclampsia, eclampsia

Introduction

Pre-eclampsia (PE) has been a major cause of maternal and perinatal morbidity and mortality worldwide [1]A. 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]DB.

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]D. 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]D.

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]D. 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]D.

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 nineteenth century [1]A. Since then, clinical studies have shown that early detection and treatment of PE and eclampsia reduce maternal and fetal morbidity and mortality [1, 4]AD. However, preventing PE and eclampsia remain major problems in maternal and child health [3]B.

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]B.

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

Figure 1 and Tables 1, 2 and 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 8 about using it to assess the uterine artery, and 8 articles evaluated using ultrasound to assess flow-mediated dilation of the brachial artery (Figure 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]B.

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]B. Such changes were present even in patients with PE and photophobia (Table 1) [13]B. 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).A. Barbosa *et al.* [15] demonstrated that immediately prior to eclampsia the resistance index proved to be an important biomarker at the cut-off of 0.56 (Table 1)B.

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]B.

Brandão, Cabral and Leite[7, 16] 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).B

The variables used by Matias*et al*. [17] 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) AB.

Gurgel*et al*. [18] 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]B.

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) [19]B. Savidou*et al*. [20] 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)B.

Brodski*et al.* (2008)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*. (2001) found that vascular function was also impaired in non-pregnant women who had PE or hypertension during a previous pregnancy.

Kamat*et al*. 2011 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)B.

Filho*et al*. (2010) reported that their findings suggested that superimposed PE was associated with poorer endothelial function (Table 2)B.

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) [21]B.

Uterine artery

According to Jamal *et al*.,[22] 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)B. Lai *et al.*[23] 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)B. Gallo *et al.*[24] found that in normal pregnancy associated with PE, maternal characteristics and the pulsatility index are associated with the severity of disease (Table 2)B.

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) [25]B.

Scazzocchio *et al.*[26] 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)B.

In the first trimester, the combination of maternal characteristics and uterine artery Doppler ecom the placental growth factor, can predict about half of pregnancies complicated by early PE (Table 3)[27]B.

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) [28]B. 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) [29]B.

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]B.

Discussion

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.

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

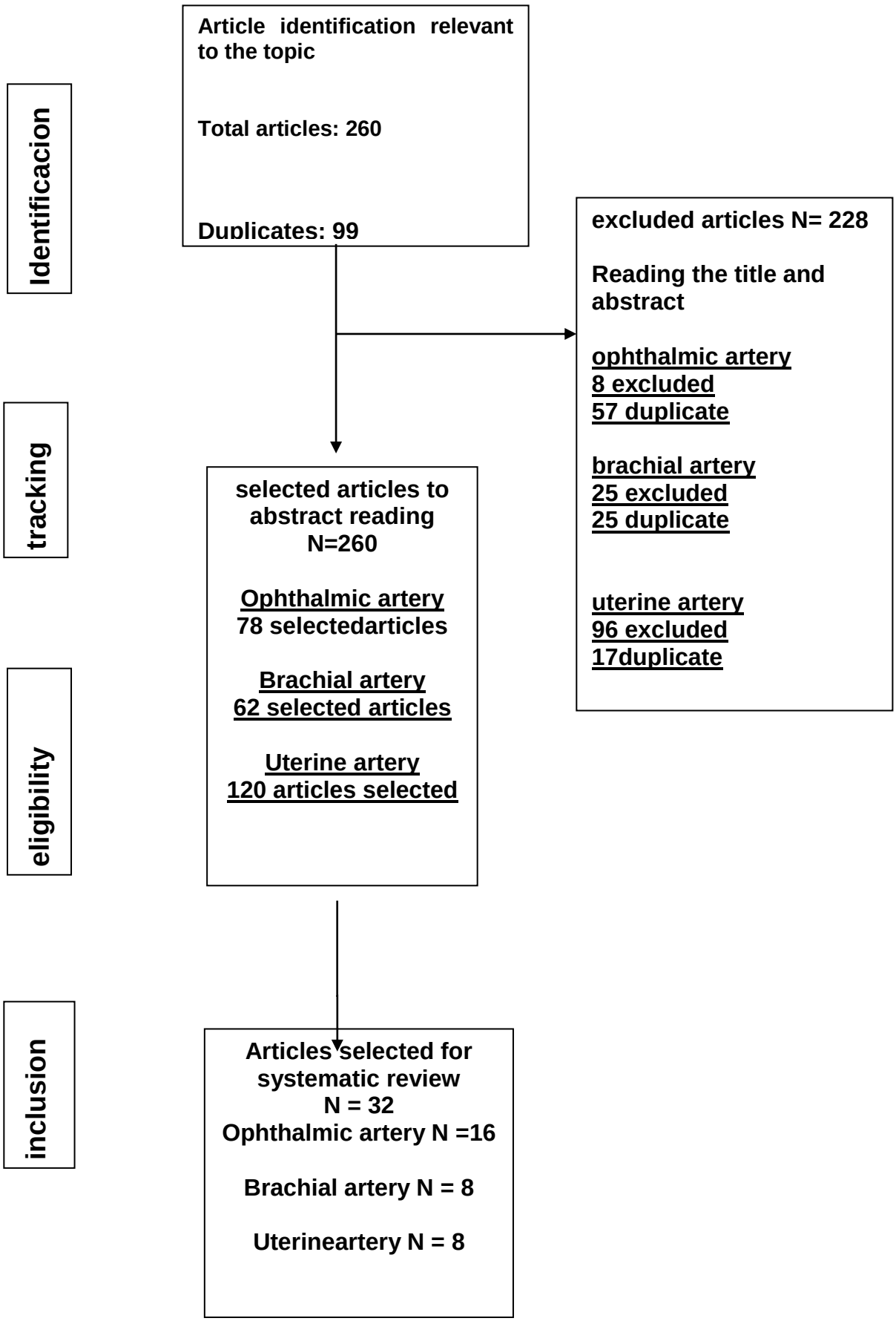

Table 1. Studies assessing use of Doppler ultrasound of ophthalmic artery in normal pregnant women and pregnant women with pre-eclampsia (PE)

Author / Year	Study Design	Sample	Degree of evidence	Variables	Results
Belfort *et al.*[11]	case-control	8PE		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.*[30]	case-control	1 PE puerperal	A		Prostaglandin E1 vasodilator effect
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.*[31]	cross-sectional study	27 PEL / M 3SP	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.[15]	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.*[16]	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*.[32]	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*.[33]	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
Gurgel *et al*.[18]	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	8PE	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.

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	Results
Savvidou *et al.* [19]	cross-sectional study	NP=19 NW= 157	B	6,4 ± 2,4%	8,84±3,18%		FMD significant increase until 32 weeks. Then there is a decrease
Savvidou *et al.* [20]	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	FMD decreased is a risk factor rather than a cause
Brodszki *et al.*[34]	cross-sectional study	P=57	B		13,7% UA without notches 6,3% UA with notches		FMD decreased in patients with GN uterine incisions. No mechanical differences.
Chambers *et al.* [35]	cross-sectional study	NW=48 PE=113	A		With PE in a previous pregnancy = 3,36 mm without PE in previous pregnancies = 3,29mm		FMD lower in the group that had PE in a previous pregnancy
Henriques *et al.* [36]	cross-sectional study	PE=60	B				PE in women with previous pregnancy have a higher frequency of FMD changed
Kamat *et al.* [37]	cross-sectional study	NW= 81	B				*Cut-off* =8,7%, S=88% E=93%
Filho *et al*[38]	cross-sectional study	PE= 14 SPE=13	B			SPE =6,0%(1,9-10,3) PE=13,6% (4,4-17,1)	Was not able to differentiate between PE and PES. However, data suggest that SPE is associated with a worse endothelial function.
Vieira *et al.*[21]	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)	Decreased FMD can be connected directly to morbidity of PE

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 a*l. [22]	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.* [23]	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.* [24]	50.490	PE<34sem=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 –Arriaga*et al.* [25]	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 s Flt-1/PlGF shows high specificity and low sensitivity to confirm PE
Scazzocchio *et al.*[26]	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.* [28]	382	PE *cut-off* = 1,79 EPE *cut-off* = 1,9		B	cross-sectional study	second trimester- Doppler das UA is not efficient in anticipating risk of PE in patients with low risk
Parra-Cordeiro *et a*l. [27]	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	Característicasmaternas, associadas a AU da Doppler e PlGF pode prever ½ das gestações que serão complicadas PELa PEP
Prajapati *et al.*[29]	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.

4.2 Artigo 2 – Maternal cerebral centralization of blood flow in pregnant women with Specific gestational hypertension

Short title: Maternal Cerebral Centralization

Submission Confirmation

Submission Confirmation

The American Journal of Obstetrics & Gynecology (ajog@rrohio.com)

Adicionar aos contatos

24/02/2015

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"MATERNAL CEREBRAL CENTRALIZATION OF BLOOD FLOW IN PREGNANT WOMEN WITH HYPERTENSIVE DISORDERS OF PREGNANCY"

Dear Prof. Glaucimeire Marquez Franco:

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Sincerely,

The Editors

Maternal cerebral centralization of blood flow in pregnant women with Specific gestational hypertension

Short title: Maternal Cerebral Centralization

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Abstract

Objectives: to evaluate the occurrence of maternal brain centralization in pregnant women with specific gestational hypertension; to establishing normal values of the ratio of the uterine artery with (mean and standard deviation) ophthalmic artery; to compare the ratio of uterine to the ophthalmic artery with normal and abnormal group; to establish the ROC curve for diagnosis of patients with specific hypertensive disease of pregnancy. **Methods** To achieve the proposed objectives a case-control study where. The sample consisted of 178 pregnant women patients divided into two groups. The control group included pregnant 83 normotensive pregnant women; a case group included 95 patients with clinical and laboratory diagnosis of specific gestational hypertension. **Results:** Patients with preeclampsia had lower values than the patients who had eclampsia. The Doppler parameters that were statistically significant were those of ratio of uterine artery with the ophthalmic artery (AU / AO) and vice versa. A normaly curve systole-diastole compared with the respective cutoff point was performed. A ROC curve is shown in the cut-off considering the systolic velocity, the diastolic velocity, the systole/diastole relation, and the index of resistance of the ophthalmic artery respectively. **Conclusion:** The maternal

centralization in high risk pregnancies was observed specific gestational hypertension is real. The normal curve has a mean and standard deviation of the relative Doppler of the uterine artery to the ophthalmic artery systolic / diastolic ratio was 0.43 ± 0.16 for normal pregnant patients. Comparing the group of patients with normal pathological group of patients there was a statistically significant difference between them considering the relation of Doppler uterine artery with ophthalmic artery. The cutoff point more sensitive, verified by ROC curve, wich defines maternal brian centralization in patients with specific gestational hypertension was 0.57 for the Doppler systolic / diastolic ratio of the uterine artery compared with the ophthalmic artery, with 78% sensivity and 13% false positive.

Key words: ophthalmic artery, brachial artery, uterine artery, Doppler sonography, preeclampsia, eclampsia

Introduction

Preeclampsia (PE) and eclampsia (E) are important causes of maternal and perinatal morbidity and mortality worldwide. They are complicated by other specific gestational hypertension in about 2% to 8% of pregnancies.[1-3]

According to the National Monitoring Report on the Millennium Development Goals by the World Health Organization, Brazil reported a drop of 43% in the proportion of deaths among women experiencing complications during pregnancy or childbirth from 1990 to 2013. This is in line with the reduction in maternal mortality worldwide. However, this rate will not achieve the proposed 35 maternal deaths per 100,000 births by 2015.[3,4]

PE is a disease of unknown cause. Various theories have been proposed to explain its pathophysiology, two of which greatly support the vascular theory and immune theory, respectively. The vascular theory is based on the presence of “ischemia-perfusion defects” that lead to oxidative stress and vascular disease. According to the immune theory, PE is caused by poor maternal and paternal immune adaptation i.e., a maternal alloimmune reaction triggered by rejection of the fetal graft.[5-7]

Effective prevention depends on the recognition of a latent and early stage of the disease that can be prevented or reversed and the availability of effective intervention methods. Clinical experience suggests that early detection and treatment of PE is beneficial to both the patient and fetus.[2,5,8-11]

Knowledge of vascular changes during the pregnancy-puerperal cycle is critical to ensuring a better prognosis for both pregnant women and their fetuses, and obstetric Doppler examination is the gold standard

technique for this analysis. Thus, the objective of this research was to evaluate the occurrence of maternal brain centralization in pregnant women with specific gestational hypertension, to establishing normal values of the ratio of the uterine artery with ophthalmic artery, to compare the ratio of uterine to the ophthalmic artery with normal and abnormal group. Setting the cutoff point by ROC curve, with specific gestational hypertension and to stablish de cutoff between normal and specific gestational hypertension

METHODS

A case-control study involving assessment of the OA, and UA was performed using Doppler ultrasound in pregnant women in the second and third quarter. Patients were recruited in 2013 from among pregnant women at low and high risk from the Department of Obstetrics and Gynecology, Hospital das Clinicas, Federal University of Goiás, Mother and Child Hospital, Clinical Diagnostics Femina Clinic Fertile services.

The sample size comprised 178 pregnant women. The patients were divided into a control group of 83 normal patients and a 95 pathological patients with clinical and laboratory diagnoses of PE and E. The pathological group was further divided into three subgroups: patients with mild preeclampsia (n = 31), severe preeclampsia (n = 60), and eclampsia (n = 4). The sample size was obtained through calculation for a finite population, assuming that the collection sites showed a flow of approximately 2,300 pregnant women from 1 month and with an error of 0.8%; a sample of 85.5 patients was required.

The inclusion criteria for both groups were women with spontaneous pregnancy and no comorbidities, no history of drug ingestion, normal blood pressure levels at the beginning of pregnancy, agreement to participate, and completion of written informed consent.

A further inclusion criterion in the PE and E groups was meeting the clinical and laboratory criteria for diagnosis of either PE or E, respectively. The criteria used for diagnosis of PE and E were those described in the National High Blood Pressure Education Program.[15] The criteria for PEL were one blood pressure measurement of ≥140/90 mmHg out of at least two measurements performed after the 20th week of pregnancy, without hypertension (except cases of trophoblastic disease which may be associated with PE before 20 weeks) associated with proteinuria of 0.3 to 2.0 g in 24 hours or 1+ on a random urine sample. PEG was considered to be present when a blood pressure of ≥160/110 mmHg was associated with any of the following signs, symptoms, or laboratory abnormalities: proteinuria of ≥2 g in 24 hours, serum creatinine above 1, 2 mg/dL proteinuria; persistent headache and/or abdominal pain and/or visual disturbances; changes in habitual behavior (mood swings); anasarca; signs of microangiopathic anemia and/or elevation of liver enzymes and/or a low platelet count (<100,000/mm^3); and eclampsia. Eclampsia is defined by the expression of one or more tonic-clonic seizures generalized and / or coma in a pregnant woman with gestational hypertension or preeclampsia, absence of neurological disorders [5, 6, 12-15]

Pregnant women who went into labor during Doppler ultrasound and those with other types of hypertension and comorbidities were excluded.

Imaging was performed with an ultrasound machine equipped with pulsed Doppler and color flow mapping and an electronic transducer (linear, 7.5 MHz; convex, 5.0 MHz) (Philips and Medison Accuvix). All examinations were performed by the own researcher who has experience in this type of examination, and was delivered to the patient a report with the results found

For Doppler examination of the OA, the patients were placed in the supine position and a drop of gel was administered onto the right upper eyelid with the patient's eyes closed. The transducer was then transversely positioned on the eyelid. The transducer was moved in the craniocaudal direction without pressure, thus avoiding possible changes in local flow. The evaluation technique described by Diniz et al.[16] was used.

After identifying the ophthalmic artery (OA), brachial artery (BA), uterine artery (UA) were recorded about six waves with a good standard, and the proposed index (velocidade sistólica, velocidade diastólica, índice de resistência e relação sístole-diástole) was then measured. The images were analyzed in real time. The insonation angle between the ultrasound beam and the blood flow was maintained to the greatest extent possible between 30 º and 60º-. The filter was 50 Hz, pulse repetition frequency was 125 KHz, and volume-adjusted sample was 2 to 3 mm.

The OA was displayed next to the optic nerve. Flow measurement of the OA was performed nasal and superior to the optic nerve 10 to 15 mm posterior scleral wall position, figura 1. A 7-MHz linear transducer was used.[16]

The UA was assessed near the iliac vessels in its portion proximally. A 3.5-MHz convex transducer was used.

The following Doppler parameters were analyzed in the three vessels: the systolic velocity (SV), diastolic velocity (DV), resistance index, and systole/diastole ratio. The resistance index was calculated as follows: (SV – DV) / SV. Additionally, epidemiological variables such as number of pregnancies, parity, abortion, weight, height, body mass index (BMI), maternal age, and gestational age were studied.

Comparison of the homogeneity of the groups was performed by calculating the mean, standard deviation for cutoff values, *p* normal course of epidemiological variables. The Kolmogorov–Smirnov test results showed that the data had a normal distribution. After removal of the variables, we used the Kruskal–Wallis test, Mann–Whitney test, Student's t test, and Fisher's exact test for validation of the associations found.

After determining the variables, a reference curve was plotted for the normal pregnancies to establish the cut-off point which determines maternal cerebral centralization. The ROC curve, with power of discrimination between normal pregnant women and women with specific gestational hypertension pregnant women was made.

The study protocol was approved by the Regional Ethics Committee of the Maternal and Child Hospital (HMI/SES).

RESULTS

A total of 178 patients took part in our study. The average age of patients in the group of normal pregnant patients was 29.8 ± 4.7 and patients with specific gestational hypertension was 26.14 ± 6.17. The mean gestational age of normal pregnant patients was 34.3 ± 3.5 weeks and

patients with specific gestational hypertension was 32.40 ± 3.37. The average body mass index (BMI) of normal pregnant women was 26.8 ± 5.6 and patients with specific gestational hypertension was 30.55 ± 5.12. Table 1.

Table 2 through logistic regression analysis the mean and standard deviation of the UD / AO in accordance with the normal group (control) and pathological (PEL, PEG, E) was performed. The Doppler parameters that were statistically significant were those of AU / AO and vice versa.

The curve of the systole-diastole normally compared with the respective cutoff point are shown in Figure 1.

Figure 2 shows the ROC curve with the cutoff point, considering the systolic velocity, diastolic velocity, systolic / diastolic ratio and resistance index of the ophthalmic artery respectively.

DISCUSSION

After an extensive literature review, we believe that the present study is the first to analyze the Doppler variables of two different vessel ratios (UA/OA) to screen for PE. This topic constitutes a growing interest in the academic population.

Table 1 shows the epidemiological characteristics of groups of normal pregnant women and patients with these specific hypertensive diseases of pregnancy. The patients with specific gestational hypertension presented index higher than that of normal pregnant patients body mass. Statistical significance for patients except abortion.

Making the analysis of the relationship of the AU / AO, all parameters were significant. Patients with specific gestational hypertension showed the mean values of systolic / diastolic ratio greater than normal patients. Table 2.

Because of limitations in the prevention of PE, focus has been placed on identifying women at high risk of PE along with monitoring clinical and laboratory parameters to recognize the disease in its early stages. Many clinical and laboratory variables have been used to assess the severity of the disease, including high blood pressure and proteinuria associated with symptoms such as headache, epigastric pain, and visual disturbances. New variables that can help to identify severe cases of PE would have great practical applications, allowing physicians to more intensively treat pregnant women at higher risk.

All parameters were significant in the analysis of the UA/OA ratio. Patients with PEG had lower ratios than did patients with E. These data suggest that an increase in the UA/OA ratio in patients with PEG indicate a worsening of symptoms and potential development of E.

The results were similar when we evaluated the right and left UA. When the Doppler variables were reversed (i.e., UA/OA to OA/UA), the normal pregnant women and women with specific gestational hypertension showed the greatest statistical significance.

Maternal centralization of blood flow is best documented when analyzing the UA/OA ratio. This may be explained by changes in the UA in accordance with placentation. There is a real possibility of maternal centralization of blood flow in pregnancies at high risk of PE is real. Tabel 2.

The normal curve has a mean and standard deviation of the relative Doppler of the uterine artery to the ophthalmic artery systolic / diastolic ratio was 0.43 ± 0.16 for normal pregnant women.

Comparing the group of patients with normal pathological group of patients there was a statistically significant difference between them considering the relation of Doppler uterine artery with ophthalmic artery.

The cutoff point by ROC curve, with power of discrimination between normal pregnant women and women with specific gestational hypertension pregnant women was 0.57 compared to the Doppler systolic / diastolic ratio of the uterine artery to the ophthalmic artery, with 78% sensitivity and 13% false positive.

Vascular endothelial injury, clinically characterized as endothelial dysfunction, has been widely demonstrated in patients with PE through Doppler flow meter measurement of the UA and OA.[17] There is evidence that vasodilation in healthy patients generally reflects an increase in production of endothelial-derived relaxing factor, especially those dependent on nitric oxide, decreased vascular reactivity, and vasoconstrictor peptides such as endothelin, thromboxane, and angiotensin II.[18] In patients with PE, placental ischemia leads to a release of soluble substances in the maternal bloodstream, resulting in hyperactivity of these vasoconstrictive factors. This change can be detected even before hypertension becomes apparent.[18]

Lower values of flow mediated dilation and high resistance indices of the uterine arteries have been demonstrated in patients who subsequently developed PE, indicating that the test can be used to predict the clinical

manifestations of PE.[19-22] Endothelial dysfunction apparently precedes the clinical manifestations of PE.[20]

The results of this study showed that the Doppler parameters of the relationship between the UA and OA in pregnant women with PE are significantly different from those of healthy pregnant women, indicating that the Doppler UA/OA ratio can be used to assess the severity of PE. However, confirmation of these findings in larger samples and more ethnically diverse populations is needed.

Conclusion

It is observed that the possibility of maternal centralization in high risk pregnancies such as specific gestational hypertension is real.

The normal curve has a mean and standard deviation of the relative Doppler of the uterine artery to the ophthalmic artery systolic / diastolic ratio was 0.43 ± 0.16 for GN.

Comparing the group of patients with normal pathological group of patients there was a statistically significant difference between them considering the relation of Doppler uterine artery with ophthalmic artery.

The cutoff point by ROC curve, with power of discrimination between normal pregnant women and women with specific gestational hypertension pregnant women was 0.57 compared to the Doppler systolic / diastolic ratio of the uterine artery to the ophthalmic artery, the sensitivity was 78% and the false positive of 13%.

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Conflict of interest: None

Table 1- Parameters of the variables in the epidemiological profile in accordance with the normal and abnormal group (pre-eclampsia, eclampsia and pregnant women), in Goiânia 2013-2014.

Variable	Norml (control)		Pathological (case)		p
	n	Mean ± SD	n	Mean ± SD	
Gestation	78	1,71±0,84	93	2,22±1,65	0,019*
Parturition	78	0,60±0,76	93	1,12±1,46	0,008*
Abortion	78	0,09±0,33	93	0,25±0,65	0,070
BMI	81	26,88±5,60	92	30,55±5,12	<0,001*
Age	82	29,87±4,71	94	26,14±6,17	<0,001*
IG	79	34,67±3,57	90	32,40±3,37	<0,001*

Teste: Teste Kruskal Wallis.
Body mass index (BMI), IG - Gestational Age

Table 2 - Analysis of Doppler parameters of the variables according to the normal group (control) and case (mild, severe and eclampsia), in Goiânia 2013-2014.

Variables	Normal (control)		Pathological (case)		p
	n	Mean ± SD	n	Mean ± SD	
UD/AO					
VS	83	2,35±1,14	95	1,56±1,20	<0,001*
VD	83	5,90±3,31	95	2,06±1,88	<0,001*
A/B	83	0,43±0,16	95	1,00±0,74	<0,001*
IR	83	0,57±0,16	95	0,84±0,37	<0,001*

Test: Logistic regression analysis.
VS-systolic velocity, VD- diastolic velocity, A/B – systole / diastole,
IR - Resistance index

Figure 1 – Normal Curve adjusted and with a cutting point of the systole/diastole relation of the relation uterine artery /ophthalmic artery in normal pregnant women, Goiânia, 2013-2014.

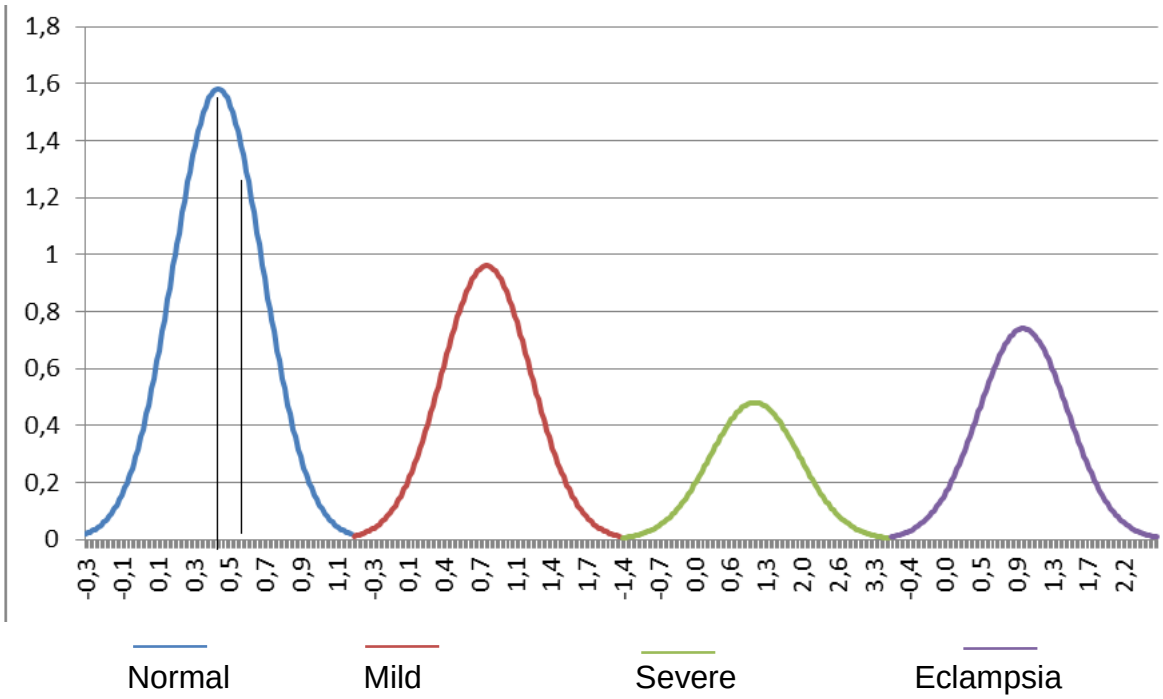
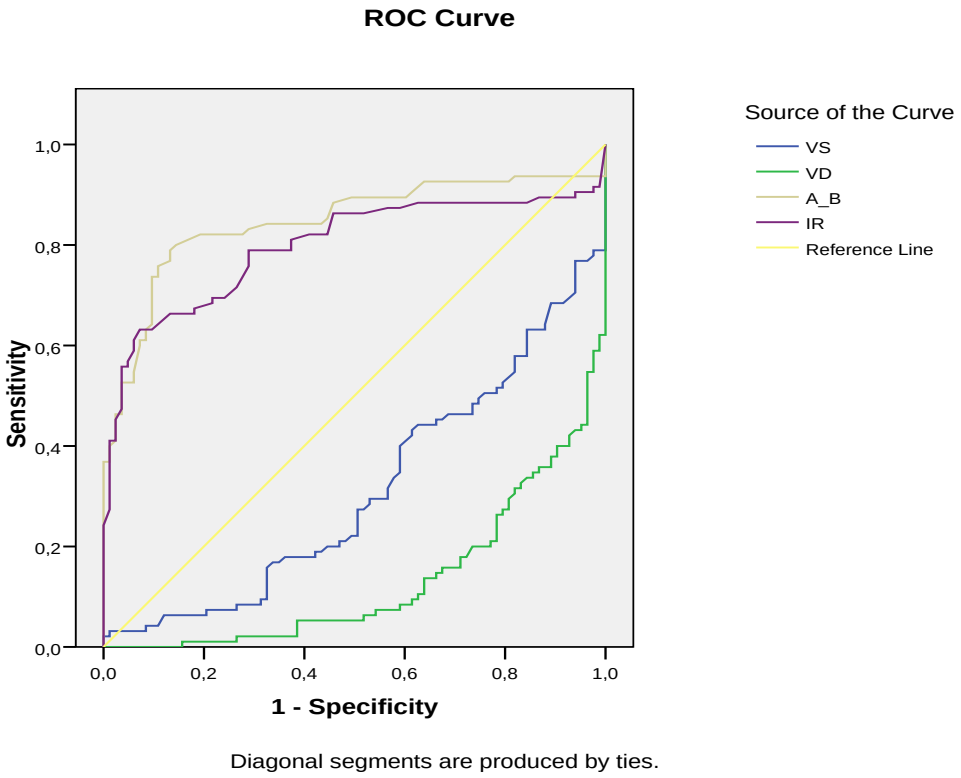


Figure 2- Receiver Operator Curve (ROC) for the systolic velocity, diastolic velocity, resistance index and systole/diastole relation, in pregnant women, Goiânia,2013-2014.



VS-systolic velocity, VD- diastolic velocity, A-B – systole / diastole, IR - Resistance index

CUTTING POINT

Variable	CONSIDERED VALUE		CUTTING POINT
	SENSITIVITY	1 - Specificity	
VS (UD/AO)	0,78	0,96	0,06
VD (UD/AO)	0,78	0,96	0,09
A/B (UD/AO)	0,78	0,13	0,57
IR (UD/AO)	0,81	0,51	0,56

VS-systolic velocity, VD- diastolic velocity, A-B – systole / diastole, IR - Resistance index
UD/AO- artery uterine / ophthalmic artery

5 CONSIDERAÇÕES FINAIS

Com base nos achados, sugere-se que o Doppler da artéria oftálmica, da artéria uterina, da relação sístole-diástole da artéria uterina com a artéria oftálmica, e a dilatação fluxo-mediada podem ser úteis para identificar pacientes em risco, acompanhar a progressão da doença e proporcionar intervenções eficazes.

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7 Apêndices

1. TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO
2. CONSENTIMENTO DA PARTICIPAÇÃO DA PESSOA COMO SUJEITO
3. LAUDO DE UTRASSONOGRAFIA

APÊNDICE A

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

NOME DA PESQUISA:

Centralização Cerebral Materna em Gestantes com Doença Hipertensiva Específica da Gestação

ORIENTADOR: Professor PhD. Waldemar Naves do Amaral

PESQUISADORA REPONSÁVEL: Dra. Glaucimeire Marquez Franco

Você está sendo convidada para participar, como voluntária, de uma pesquisa. Meu nome é Dra. Glaucimeire Marquez Franco. Sou a pesquisadora responsável. Atuo como Médica da Secretaria de Estado da Saúde, Preceptora do R4 de Ultrassonografia em Ginecologia Obstetrícia do Hospital Materno Infantil e Professora no curso de Medicina PUC GOIÁS. Esta pesquisa está sob a orientação do Professor PhD. Waldemar Naves do Amaral, da Faculdade de Medicina da Universidade Federal de Goiás, especialista em ginecologia e obstetrícia. Após ler com atenção este documento e ser esclarecida sobre as informações a seguir, no caso de aceitar fazer parte do estudo, assine ao final deste documento, que tem duas vias. Uma delas é sua e a outra é do pesquisador responsável.

Em caso de dúvidas sobre os seus direitos como participante nessa pesquisa, você poderá entrar em contato com o Comitê de Ética em Pesquisa do Hospital Materno Infantil, nos telefones: (62) 3201 3346, ou (62) 3201 3314.

Em caso de dúvida sobre a pesquisa, você poderá entrar em contato com os pesquisadores responsáveis: PhD. Waldemar Naves do Amaral, telefone (62) 9971 2943; Dra. Glaucimeire Marquez Franco, telefone (62) 9971 7278.

Essa pesquisa tem como objetivo verificar as alterações circulatórias em gestantes normais e com pré-eclâmpsia grave e com eclâmpsia. A sua participação é voluntária e envolve a realização de um exame de dopplerfluxometria da artéria braquial direita e oftálmica direita e das artérias uterinas, processo que tem a duração aproximada de dez minutos. O exame da artéria oftálmica direita consiste em se colocar uma gota de gel sobre a pálpebra do olho direito, para, em seguida, com o transdutor, fazer uma leve pressão, que não causa dor ou desconforto. O transdutor faz parte do aparelho de ultrassonografia, que tem uma forma retangular e mede aproximadamente 5 cm x 3 cm. O exame da artéria braquial consiste em se colocar uma gota de gel no terço médio da face 23 medial do braço direito, para, em seguida, com o transdutor, fazer uma leve pressão, que também não causa dor ou desconforto. O exame das artérias uterinas consiste em se colocar uma gota de gel nas laterais da parte inferior do abdome próximo à virilha e com um transdutor, que é semelhante ao descrito anteriormente, realiza-se o exame de dopplervelocimetria destes vasos.

A qualquer momento, você poderá desistir de participar, e retirar o seu consentimento. A sua recusa não trará nenhum prejuízo, seja na sua relação com a pesquisadora ou com a instituição, seja na continuidade do projeto e do pré-natal. Deixamos claro que o seu nome e a sua identificação não serão divulgados.

Basicamente, não há riscos, prejuízos, desconforto, lesões ou mesmo despesas que possam ser acarretados pela pesquisa. não haverá nenhum tipo de pagamento ou gratificação financeira pela sua participação.

A sua participação é muito importante para essa pesquisa, e você terá como benefício ter colaborado com o aprimoramento dos conhecimentos da medicina.

APÊNDICE B

CONSENTIMENTO DA PARTICIPAÇÃO DA PESSOA COMO SUJEITO

DA PESQUISA

Eu,

_____

_____, RG/CPF_____, abaixo-assinado, concordo em participar, como sujeito voluntário, do estudo: **Centralização Cerebral materna em Gestantes com Doença Hipertensiva Específica da Gestação**, sob a responsabilidade da Dra. Glaucimeire Marquez Franco e do PhD. Waldemar Naves do Amaral. Fui devidamente informada e esclarecida pela pesquisadora responsável sobre a pesquisa, dos procedimentos nela envolvidos, assim como dos possíveis riscos e benefícios decorrentes da minha participação. Foi-me garantido que posso retirar meu consentimento a qualquer momento, sem que isto leve a qualquer penalidade ou interrupção de meu acompanhamento/assistência/tratamento.

Local e data:

_____

Nome e assinatura do sujeito ou responsável

_____

Nome e assinatura do pesquisador responsável

_____

APÊNDICE C

LAUDO DE UTRASSONOGRAFIA

LAUDO DE UTRASSONOGRAFIA

Nome:

_____

DOPPLERVELOCIMETRIA DA ARTÉRIA OFTÁLMICA

DIREITA, DA ARTÉRIA BRAQUIAL DIREITA E DAS ARTÉRIAS UTERINAS

Artéria Oftálmica Direita,	Artéria Braquial Direita
V S:	V S:
V D:	V D:
A / B:	A / B:
I R:	I R:
Artéria Uterina Direita,	Artéria Uterina Esquerda
V S:	V S:
V D:	V D:
A / B:	A / B:
I R:	I R:
Incisura:	Incisura:

Média das uterinas:

Goiânia, ____ de _____ de 2013.

_____

Drª. Glaucimeire Marquez Franco

CRM 5927

8 ANEXOS

1. Parecer do Comitê de Ética
2. Certidão de Ata
3. Normas de publicação dos respectivos periódicos

ANEXO 1

Parecer do Comitê de Ética

Hospital Materno Infantil

igh Instituto de Gestão e Humanização

SUS Sistema Único de Saúde

SECRETARIA DE ESTADO DA SAÚDE

GOVERNO DE GOIÁS
NOSSO ESTADO CRESCE, VOCÊ CRESCE JUNTO

CA nº 01/13 – CEP/HMI

Goiânia, 04 de fevereiro de 2013.

CARTA DE APROVAÇÃO

Protocolo **Nº 37/12**
Título do Projeto: "Centralização Cerebral Materna em Gestantes com Pré-Eclâmpsia Grave e com Eclâmpsia".
Investigador(a) Responsável: Waldemar Naves do Amaral

Prezado(a) Senhor(a),

Informo que na reunião mensal do **Comitê de Ética em Pesquisa do Hospital Materno Infantil – CEP/HMI,** ocorrida no dia 1° de fevereiro do corrente, foi analisado e deliberado sobre o conteúdo do Projeto de Pesquisa em epígrafe, bem como o **Termo de Consentimento Livre e Esclarecido**, obtendo a aprovação segundo aos princípios éticos vigentes.

Informo, ainda, que a presente aprovação tem validade pelo período de tempo definido no projeto e caso hajam alterações no cronograma, ainda que alheias a vontade do pesquisador, estas deverão ser informadas a esse Comitê para fins de análise e deliberação.

Por oportuno, permito-me lembrar-lhe da necessidade de V.Sa. ter que elaborar e encaminhar à esse Comitê relatórios semestrais relativos ao andamento, encerramento, conclusão e publicação da pesquisa.

Atenciosamente,

Marco Aurélio Albernaz
Coordenador do CEP-HMI

Rua R 7, esquina com Av. Perimetral S/nº, Setor Oeste, Goiânia – Goiás, Cep: 74.530-020
Fone/Fax: 3956-2986
e-mail: cep.hmi@ig.org.br

ANEXO 2

Certidão de Ata

UFG

MINISTÉRIO DA EDUCAÇÃO
UNIVERSIDADE FEDERAL DE GOIÁS
FACULDADE DE MEDICINA
Departamento de Ginecologia e Obstetrícia

CERTIDÃO DE ATA

Certificamos para os devidos fins que, em reunião do Departamento de Ginecologia e Obstetrícia, realizada em 05 de dezembro de 2012, foi aprovado o Projeto de Pesquisa, "CENTRALIZAÇÃO CEREBRAL MATERNA MATERNA EM GESTANTES COM PRÉ-ECLÂMPSIA GRAVE E COM ECLÂMPSIA", tendo como orientador o Prof. Dr. Waldemar Naves do Amaral.

Departamento de Ginecologia e Obstetrícia da Faculdade de Medicina da Universidade Federal de Goiás aos 05 dias do mês de dezembro de 2012.

Prof. Dr. Waldemar Naves do Amaral
Chefe do Departamento de Ginecologia e Obstetrícia-FM-UFG

1ª Avenida, s/n - Setor Universitário – Goiânia – Goiás – CEP: 74605-050 – Fone: (62) 3209-6156

ANEXO 3

Normas de publicação dos respectivos periódicos

GUIDE FOR AUTHORS

AMERICAN JOURNAL OF OBSTETRICS & GYNECOLOGY

Article Types

Every submission must include a title page with a disclosure statement and a signed statement of authorship form. This requirement applies to ALL article types listed in the following section; including letters, replies, mixed media, etc. The editors encourage the supplementary use of multimedia components such as PowerPoint, additional images, or video clips. Color figures and images are free.

Original Research

Manuscripts are limited to 3000 words of main text (not counting the title page, abstract, condensation, acknowledgements, references, tables, figures, and legends). Longer submissions will

not be considered. All authors must meet authorship criteria (see Named Authors and Contributors). Research articles must be accompanied by a structured abstract (see “Abstract formats”) of no more than 350 words, accompanied by 3 to 5 alphabetized key words or short phrases for indexing. The type(s) of non-human animals or other species used in an investigation must be named in the Title, Abstract, and Materials and Methods sections of the manuscript. Each research article is published in 2 formats: 1) in the printed journal: in an abbreviated form, as a snapshot of the article, with 1 figure or table, and 2) in full on the Journal website (AJOG.org), where the article summary also appears. The full length article is the official version and is linked to search engines.

Authors of research articles are asked, upon initial acceptance, to highlight the most significant content of the article (up to 1000 words) for use in the preparation of an abbreviated version for the

print edition. To expedite publication, authors are encouraged to permit a Journal-affiliated medical writer to produce the article summary, which will be submitted to the authors for their review and approval prior to publication. Authors who prefer to produce the abbreviated version themselves will receive guidelines to follow. Author-produced article summaries are subject to editing for length, consistency, and conformity with Journal style.

The full-length article becomes available online for citation before the print issue containing the summary.

Impact Factors and other citation indices are based on the full-length online article.

Translational Science

Translational science is typically presented in the form of an original research manuscript; however, the only type of non-clinical research considered must be translational in nature and contain biological implications for obstetrics and gynecology. Basic science without direct clinical relevance will not be considered; please see Editorial Policies for examples.

Reports of Major Impact Authors who believe their original research article has the potential for affecting clinical practice in a major way or is otherwise of urgent importance may submit the manuscript under this category. The editors, in consultation with experts in the area addressed in the article, will assess the likely impact of the article and notify the authors whether it is being considered for this category or as a regular original research manuscript.

Articles accepted as Reports of Major Impact are reviewed and published as rapidly as possible. The authors are to follow the format for original research articles and submit the entire article. Once an article has been accepted in this category, the author, in conjunction with the Journal's science writer, will prepare a 1000-word summary, as for other research papers. Publication of the full manuscript will follow shortly thereafter in its entirety online. As with any article, concern about any potential conflict arising from the timing of publication relative to a presentation at a scientific meeting may be communicated to the editors, who will, at the authors' request, delay publication until the paper has been presented.

Reviews

The full-length article appears both in print and on the Journal website. No article summary is prepared.

Expert Review

These invited articles provide concise reviews on a topic in which the author has expertise. The manuscript should be comprehensive and balanced, but not exhaustive. Expert Reviews must be evidence based but may include some expert opinion and recommendations. The goal is to provide a concise update on the state of the art and guidelines for clinical care. Expert Reviews are limited to 3500 words of main text (not counting the title page, abstract, condensation, acknowledgments,

references, tables, legends, and figures). An unstructured abstract (1 paragraph, no categories) of no more than 350 words and 3 to 5 alphabetized key words or short phrases for indexing must be provided. Subheadings to separate and identify sections of text should be unique to the topic; the 4 prescribed subheadings required for research articles do not apply. To prevent such subheadings from occupying many lines on a page, they should be as short as possible, not exceeding approximately 6 words, and preferably 1 to 4 words.

Systematic Review

Each article in this category provides a comprehensive and exhaustive systematic review of the literature related to the topic.

Systematic reviews may not be combined with other manuscript types. Authors must adhere to the PRISMA and MOOSE guidelines (for guidance see Editorial Policies).
Systematic Reviews are limited to 5000 words of main text (not counting the title page, abstract, condensation, acknowledgements, references, tables, legends, and figures). Include an unstructured abstract (1 paragraph, no categories) containing no more than 350 words and 3 to 5 alphabetized key words or short phrases for indexing.
The abstract should summarize the elements of the review, including objectives, data sources, study eligibility criteria, study appraisal and synthesis methods, results, limitations, conclusions, and implications of key findings. Headings in the main text should include Introduction, Objective, Methods for Review, Results, and Comment.

Clinical Opinion
A Clinical Opinion paper presents a balanced, evidence-based discussion of a clinical issue pertinent to obstetricians and gynecologists.

The paper may address an emerging or controversial topic or bring attention to a topic of increasing clinical significance. Opinions rendered must be based on an interpretation of available evidence. Not appropriate for this category: 1) a review of an extensively researched subject. Submit as a Systematic Review. 2) an essay about issues for which minimal data exist, such as certain clinical, ethical, educational, practice, and research issues. Submit as a Viewpoint paper.

A Clinical Opinion paper is limited to 3000 words of main text (not counting the title page, abstract, condensation, acknowledgments, references, tables, legends, and figures). An unstructured abstract (1 paragraph; no headings) of no more than 350 words and 3 to 5 alphabetized key words or short phrases for indexing must be provided. Subheadings to separate and identify sections of the text should be unique to the topic; the 4 prescribed categories required for research articles do not apply. To prevent such subheadings from occupying many lines on a page, they should be as short as possible, not exceeding approximately 6 words and preferably 1 to 4 words. The full-length article appears both in print and on the Journal website. Article summaries are not created for Clinical Opinion papers.

Special Report

A Special Report is released by a consensus committee, working group, task force, or similar group, or summarizes the findings of an important meeting.

Include a condensation, an unstructured abstract (1 paragraph, no subheadings) of no more than 350 words, and 3 to 5 alphabetized key words or short phrases for indexing.
Subheadings to separate and identify sections of the text should be unique to the topic; the 4 prescribed categories required for research articles do not apply. To prevent such subheadings from occupying too many lines on a page, they should be as short as possible, not exceeding approximately 6 words and preferably 1 to 4 words.

The full-length article appears both in print and on the Journal website. Article summaries are not created for Special Reports.

Viewpoint

Viewpoint articles are well-founded, scholarly pieces that address a scientific, ethical, academic, or practice-related topic in women's health. The article should be balanced and based on a critical analysis of the literature.

Viewpoint articles are intended to stimulate discussion. Viewpoint articles are limited to 1500 words of main text (not counting the title page, condensation, abstract, acknowledgments, references, tables, legends, and figures). Include a

condensation, an unstructured abstract (1 paragraph, no subheadings) of no more than 350 words, and 3 to 5 alphabetized key words or short phrases for indexing.

The full-length article appears both in print and on the Journal website. Article summaries are not created for Viewpiont articles. Point/Counterpoint Point/Counterpoint presents 2 essays of differing views about a controversial issue of interest to AJOG's readers. These articles are generally solicited by the editors, but readers are encouraged to suggest topics for this section.

Each essay is limited to 1500 words of main text (not counting the title page, condensation, abstract, acknowledgments, references, tables, legends, and figures). Include a condensation, an unstructured abstract (1 paragraph, no subheadings) of no more than 350 words, and 3 to 5 alphabetized key words or short phrases for indexing.

Subheadings to separate and identify sections of the text should be unique to the topic; the 4 prescribed categories required for research articles do not apply. To prevent such subheadings from occupying too many lines on a page, they should be as short as possible, not exceeding approximately 6 words, and preferably 1 to 4 words.
The essays appear in full, both in print and on the Journal website. Article summaries are not created for Point/Counterpoint.

Call to Action
Call to Action is a topical piece highlighting a problem related to a clinical, research, social, ethical, political, or economic issue pertinent to obstetricians and gynecologists and a suggested solution to that problem.

Accordingly, the author must include a suggested corrective action; describing the problem alone is not sufficient.

Call to Action articles are limited to 2000 words of text (not counting the title page, condensation, abstract, acknowledgements, references, tables, legends, and figures).
Include a condensation, an unstructured abstract (1 paragraph, no subheadings) of no more than 350 words, and 3 to 5 alphabetized key words or short phrases for indexing.

The main text must include:

1) “The Problem:,” a one-sentence statement of the problem being presented;

2) “A Solution:,” a one-sentence summary of the proposed solution; and

3) the presentation. The full-length article appears both in print and on the Journal website. Article summaries are not created for Call to Action articles.

Case Report

The Journal no longer publishes Case Reports.

Editorials

Editorials are written or solicited by the editors. Spontaneous submissions are not considered for publication.

Images in Obstetrics;

Images in Gynecology An Interesting image of clinical significance, such as a clinical photograph or evidence of a diagnostic test (ultrasound scan, MRI film, slide, photomicrograph, DNA blot, or similar), is accompanied by a case description of no more than 350 words (not counting the title page, acknowledgements, references, tables, legends, and figures).

The manuscript must include:

Condensation: a 1-sentence condensation of the paper, consisting of no more than 25 words, to be placed in the Table of Contents.

Case Notes: a brief case presentation (under the heading "Case Notes") with introduction of relevant image(s) accompanied either in text or a figure legend by a short description of each Comment: a discussion of the clinical relevance of the figure (under the heading "Comment". (Together, the case notes and comment should not exceed 350 words.)

Figure and (if applicable) video legends. 7 or fewer references. The full text of the article appears both in print and online. The print version generally includes 1 image. Up to 5 images may be submitted for the online version. If the paper is accepted, the editors will work with the author to choose which image to display in the print. In addition to images, we encourage (for use online) the inclusion of multimedia components such as PowerPoint, additional images, or video clips.

Surgeon's Corner This content provides high-quality instruction or an application of a procedure or part of a procedure, designed to aid the practicing obstetrician or gynecologist in improving care. Surgeon's Corner is published in full online; the abstract, manuscript, and a photo or graphic are published in the print journal.

The manuscript must include all of the following:

Condensation: a 1-sentence condensation of the paper, consisting of no more than 25 words, to be placed in the Table of Contents. An unstructured abstract of no more than 300 words that summarizes the clinical situation and surgical solution, explains the figure used in the print edition (see item 4), and refers to the video.

A description of the clinical situation or problem (under the heading: "Problem") followed by your surgical solution (under the heading: "Our solution"), in 600 words or less (not counting the title page, acknowledgement, references, tables, legends, and figures). Lists and bullet points may be used as appropriate. The text should refer to the figures/photos and video (see items 4 and 5).

At least one high-quality photograph (300+ dpi; not taken from a website or cell phone), graphic, or figure, to be published in the print edition; this, plus up to 5 additional photos/ figures may be included for the online version. A video clip or computer graphic not longer than 5 minutes, or a maximum of 50MBs or less per clip, to be published in the online version. Figure and video legends. 7 or fewer references.

Sketches These articles describe interesting aspects of medical careers, work life, professional or personal development, or moments of insight, transformation, or inspiration related to professional experiences.

Sketches are limited to 1000 words of main text, 7 or fewer references, and require a condensation. The full-length article appears both in print and on the Journal website.

Article summaries are not created for Sketches. Mixed Media Mixed Media may include photos, graphic art, poems, animation, video, interviews, or other forms of creative expression that portray historical or contemporary topics of interest to obstetricians and gynecologists.

Typically, Mixed Media
articles are published online only; however, applicable portions may appear in the print edition of the Journal. Provide a title suitable for the table of contents.
Authors are encouraged to supply with their manuscripts, for publication, a professional “head shot” of the lead author. This must be a high-resolution digital photograph of at least 300 dpi and not taken from a website or cell phone. Photographs are optional.

Letters to the Editors, Replies and Replies

Every Letter to the Editors, Reply, and Research Letter must include a title page, conflict of interest disclosure, and a Statement of Authorship signed by all authors. These submissions are subject to minor editorial alterations, may be shortened without the authors' approval, and published both in print and on the Journal website.

Per ACOG/SMFM standard practice, letters related to these joint society guidelines are not published. As ACOG and SMFM are interested in feedback, AJOG will forward letters related to guideline articles to the committee and they will reply personally.

Please see Clinical Opinion as a venue for presenting a scholarly, evidence-based point of view about controversial issues in OB/GYN. Letters to the Editor and Replies Selected Letters to the Editors that cite at least 1 article published in the American Journal of Obstetrics & Gynecology within the previous 4 issues are considered for publication.

Letters to the Editors are limited to 3 authors, 400 words (not counting the title page or references), and 1 to 4 references. At least one of the references must cite the related Journal article(s). All data presented must be fully citable and cited in the supporting reference list. The editors routinely invite the author(s) of the related article to respond in writing.
Published letters are accompanied by either a reply from the original authors or the statement "Reply declined." Research Letters Research Letters, not linked to items published in AJOG, briefly summarize the results of original data.

Each Research Letter is considered a scientific publication; authors must meet all requirements regarding responsible conduct of research (eg, appropriate IRB approval, data integrity, data retention). Most undergo external peer review. Reviews, case reports, and opinion pieces are not considered for publication under this category. Research Letters are limited to 7 authors, 500 words (not counting the title page, references, or legend), 5 references and may include either 1 table or 1 figure.

Online supplementary materials are not permitted. Research Letters should be formatted similar to the structured abstract guidelines for original research and divided into 4 sections: Objective, Study Design, Results, and Conclusion.

Research Letters do not include an abstract or condensation. BEFORE YOU BEGIN Editorial Policies Queries about submission requirements may be addressed to either of the managing editors: Sandra Perrine • perrine@ajog.phxcoxmail.com Phone 480-812-9261 • Fax 480-812-9409 Donna L. Stroud • ajog@rrohio.com Phone 614-527-3820 • Fax 614-527-3821 Ethics of the editorial process A policy of the Journal entitled “Specific Inappropriate Acts in the Publication Process” (Am J Obstet Gynecol 2006;194:18A-23A) describes the Journal’s policies regarding ethical practices, which apply to all submitted articles, whether accepted for publication or not.

Authors must review this document prior to submission. Noncompliance with any of the provisions of this policy may lead to an investigation and an editorial judgment. Besides describing issues such as plagiarism and falsification of data, the document named above contains information regarding duplicate publication of which all prospective authors must be aware. If a report by any or all of the same author(s) has previously been published or is currently under preparation that deals with the same subjects, animals, or laboratory experiments, and deals with a similar subject as the submitted manuscript, the author(s) are to inform the editors in a cover letter about the similarities and differences of the reports. The editors may request that you upload such reports before further review. This requirement also applies to manuscripts in which subjects, animals, laboratory experiments, or data have been added to those reported previously. Please ensure that the final manuscript includes references for pertinent articles published prior to the publication of the AJOG paper.

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All submissions are subject to review with iThenticate Professional Plagiarism Prevention. http://www.ithenticate.com.

Human and nonhuman experimentation

Authors must follow the ethical standards for human experimentation established in the Declaration of Helsinki (World Medical Association Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997;277:925-6).

The editors assume that a manuscript emanating from an institution is submitted with the approval of the requisite authority. The authors of reports of human experimentation that require local institutional approval must have obtained this approval before the experiment was started; upon request of the Journal editors, the author(s) must provide copies of the appropriate documentation. Institutional approval must be indicated in the Materials and Methods section of the submitted manuscript. If the study is exempt from Institutional Review Board approval, an explanation must be provided under
Materials and Methods.

For reports of experiments on nonhuman animals or other species, authors must state under materials and methods that the guidelines for the care and use of the animals approved by the local institution were followed. The type(s) of nonhuman animals or other species used in an investigation must be named in the title, abstract, key words, and materials and methods sections of the manuscript.

For Images in Ob/Gyn, Surgeon's Corner, Viewpoint, or similar reports in which the identity of the patient is potentially identifiable, authors must have obtained written permission from the patient(s) on whom the report is based.

The author is is responsible for filing this in a secure location. The scope of the consent should allow the author to explicitly disclose the information to Elsevier and for Elsevier to republish the information in print and electronic format including journal web and social media sites.

Authors must attest to having obtained written consent in the manuscript and must be prepared to provide this documentation upon the editors' request. All research studies, including those involving patients, patient records, research participants or databases, require ethics committee approval (or documented exemption from the Human Subjects Committee) and informed consent (or documented waiver of consent), both of which must be documented in the paper.

Studies on patients, patient records, or volunteers require ethics committee approval and informed consent, both of which must be documented in the paper.

Trial and research guidelines

Authors must adhere to the following guidelines when formulating the study

Randomized controlled trial.

- All Randomized Clinical Trials require registration with clinicaltrials.gov (or other registered authority), prior to enrollment. Both the registration site and registration number must appear on the manuscript title page. –

Authors are to consult the updated CONsolidated Standards Of Reporting Trials (CONSORT Statement): Schulz KF, Altman DG, Moher D, CONSORT Group (2010). CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. PLoS Med 7(3): e1000251. doi:10.1371/journal.pmed.1000251

• Systematic review or metaanalysis.

Authors are to consult the PRISMA Statement: Moher D, Liberati A, Tetzlaff J, Altman DG, and the PRISMA Group. Preferred Reporting Items for Systematic reviews and Meta-Analyses: the PRISMA Statement. Ann Intern Med 2009;151:264-9. http://www.prisma-statement.org

• Metaanalysis or systematic review of observational studies. Authors are to consult the MOOSE Statement: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology [MOOSE] group. Metaanalysis Of Observational Studies in Epidemiology: a proposal for reporting. JAMA 2000;283:2008-12. http://www.consort-statement.org/resources/downloads/other-instruments

• Diagnostic test(s). Authors are to consult STAndards for the Reporting of Diagnostic accuracy studies (STARD Statement): Bossuyt PM, Reitsma JB, Bruns DE, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD Initiative. Clin Chem 2003;49:1-6. http://www.stard-statement.org

• Observational study in epidemiology. Authors are to consult the STROBE Statement: von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344-9. http://www.strobe-statement.org or PLoS Med. 2007 Oct 16;4(10):e296. PMID: 17941714

• Health economics. In addition to the general instructions for authors and other guidelines applicable to the study reported in a submitted manuscript (eg, CONSORT guidelines for a randomized controlled trial; see above), authors of health economics manuscripts should consider certain issues specific to such studies and address them in the manuscript and/or submission letter. The checklist specific to this topic must be completed and included with the general submission checklist. http://cdn.elsevier.com/promis_misc/ajoghealth.pdf

Translational Science The only type of non-clinical research considered must be translational in nature and contain biological implications for obstetrics and gynecology. Additionally, the direct clinical relevance of every submission is

considered when an editorial decision is made. Basic science without direct clinical relevance will not be considered. As many definitions of basic and translational science abound, please see the following translational science examples to assist you in differentiating study types. If uncertain, authors may email an abstract to either editorial office with an inquiry as to whether or not the submission is encouraged; however, this does not guarantee acceptance. Translational science examples Ectopic Pregnancy Clinical Study: an observational cohort study which shows that patients with a subnormal increase in hCG maternal serum concentration are at increased risk for ectopic pregnancy. [Encouraged submission] Translational Science (bench to bedside): proteomic analysis of maternal plasma shows differentially-expressed proteins in patients with ectopic vs. normal pregnancy. Or, an experiment in which the fallopian tubes are ligated in pregnant animals and hCG determinations are measured in maternal serum. [Encouraged submission] Translational Science (bedside to community): analysis of techniques to enhance the adoption of best practices in caring for women with ectopic pregnancy [Encouraged submission] Basic Science: a description of the glycosylation of protein structure of hCG (even if it is based on the purification of hCG from patients with ectopic pregnancies). [DISCOURAGED submission] Preterm birth Clinical Study: an observational study in which a particular biomarker measured in the mid-trimester increases or decreases the risk for spontaneous preterm labor and delivery. [Encouraged submission] Translational Science: the transcriptome, proteome, genome, or metabolome of patients who subsequently have spontaneous preterm labor and delivery. [Encouraged submission] Basic Science: protein sequence of a particular biomarker. [DISCOURAGED submission]

Conflict of interest statement Authors of all submissions must include a conflict of interest statement.

Disclosures must include any financial interest present within the past three years with commercial entities that are marketing or developing products (drugs, devices, diagnostic tools, etc.) related to the subject matter of the manuscript. Disclosures include, but are not limited to: stocks or shares, equity, employment, advisory or scientific board, grant funding, speaker's bureau, paid travel, consulting status, and honoraria. The monetary value of any such stock holdings should be named. No policy could cover every contingency that might be construed as a conflict of interest. Therefore, it is expected that should any potential conflict of interest exist, the authors have revealed this to the editors. All relevant conflicts of interest and

sources of funding should be included on the title page of the manuscript at the time of submission under the headings "Conflicts of Interest" and "Source of Funding" which will be published with the article. If the authors report no conflict, a statement of this will be published with the article. Failure to report disclosures may result in sanctions. Use as much or as little detail as appropriate.

Examples:

- The authors report no conflict of interest. - R.J.X, M.F., and L.Y.V.R. are employed by the Curette Company, Worthingham, MI. The remaining authors report no conflict of interest.

- R.H. received research funding from PharmaCo, San Antonio, TX, for participating in a multicenter drug trial in 2011-12 S.B. reports no conflict of interest. - This research was funded, in part, by a grant from the OxyContin Association (A.R.Z.)

- A.E.B. was on the Speaker's Bureau for PharmaCo in 2012.

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Changes to authorship

This policy concerns the addition, deletion, or rearrangement of author names in the authorship of accepted manuscripts: Before the accepted manuscript is published in an online issue: Requests to add or remove an author, or to rearrange the author names, must be sent to the Journal Manager from the corresponding author of the accepted manuscript and must include: (a) the reason the name should be added or removed, or the author names rearranged and (b) written confirmation (e-mail, fax, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed. Requests that are not sent by the corresponding author will be forwarded by the Journal Manager to the corresponding author, who must follow the procedure as described above. Note that: (1) Journal Managers will inform the Journal Editors of any such requests and (2) publication of the accepted manuscript in an online issue is suspended until authorship has been agreed.

After the accepted manuscript is published in an online issue: Any requests to add, delete, or rearrange author names will follow the same policies as noted above and require an erratum.

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An author may appeal an editorial decision within 30 days of receipt of the decision to decline a manuscript for publication. The editor's decision may be appealed only if the decision to decline involved a serious mistake, and not merely a judgment call that could have gone either way. Only one appeal is permitted per manuscript, and decisions on appeals are final. New submissions take precedence for the editors

over appeals. The basis for an appeal must be set forth clearly and fully in writing to the Editor by the corresponding author. Please contact one of the managing editors who will forward the written appeal to the Editor. In your appeal letter, state why you think the decision is mistaken and provide your specific responses to any of the reviewers' comments that seem to have contributed to the decision of ‘decline to publish’.

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