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Camila Zanella Benfica

Análise da Espessura da Coroide na Gestação Utilizando Tomografia de Coerência Óptica de Domínio Espectral

Porto Alegre, 2018

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Tese apresentada para obtenção de título de Doutor em Medicina à Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia

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Comissão Examinadora:

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Prof. Dr. Manuel Augusto Pereira Vilela (UFCSPA)

_____

Prof. Dr. Marcelo Krieger Maestri (UFRGS)

_____

Prof. Dra. Mirela Foresti Jiménez (UFCSPA)

LISTA DE ABREVIATURAS E SIGLAS

ACOG	Do inglês: *American College of Obstetricians and Gynecologists*
CSC	Coriorretinopatia serosa central
DCCT	Do inglês: *Diabetes Control Complications Trial*
DM	Diabetes melito
DMG	Diabetes melito gestacional
DM1	Diabetes melito tipo 1
DM2	Diabetes melito tipo 2
EDI	Do *inglês*: *Enhancement Depth Imaging*
EPR	Epitélio pigmentado da retina
ETDRS	Do inglês: *Early Treatment Diabetic Retinopathy Study*
FD-OCT	Do inglês: *Fourier-Domain Optical Coherence Tomography*
GDM	Do inglês: *Gestational diabetes mellitus*
HbA1c	Hemoglobina glicada
IADPSG	Do inglês: *International Association of the Diabetes and Pregnancy Study Group*
IRMA	Do inglês: *Intraretinal microvascular abnormality*
MODY	Do inglês: *Maturity-onset diabetes of the young*
OCT	Do inglês: *Optical Coherence Tomography*
OCTA	Do inglês: *Optical Coherence Tomography Angiography*
OMS	Organização Mundial da Saúde
PAD	Pressão arterial diastólica
PAS	Pressão arterial sistólica
PE	Pré-eclâmpsia
PEG	Pré-eclâmpsia grave
PIO	Pressão intra-ocular
PRES	Do inglês: *Posterior Reversible Encephalopathy Syndrome*
RD	Retinopatia diabética

RDNP	Retinopatia diabética não-proliferativa
RDP	Retinopatia diabética proliferativa
SD-OCT	Tomografia de Coerência Óptica de Domínio Espectral
SNC	Sistema nervoso central
SRD	Do inglês: *serous retinal detachment*
SS-OCT	Do inglês: *Swept-Source Optical Coherence Tomography*
TD-OCT	Do inglês: *Time-Domain Optical Coherence Tomography*
TOTG 75g-2h	Teste oral de tolerância à glicose com 75g em 2 horas
VEGF	Do inglês: *Vascular endothelial growth factor*
WHO	Do inglês: *World Health Organization*

SÍMBOLOS

%	porcentagem
<	menor
>	maior
≤	menor ou igual
≥	maior ou igual
=	igual
+	mais
-	menos
±	mais ou menos
β	beta
dL	decilitro
g	grama
h	hora
mg	miligrama
mm	milímetro
mmHg	milímetros de mercúrio
nm	nanômetro
µm	micrômetro

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SUMÁRIO

RESUMO

Objetivo: Avaliar a espessura da coroide no terceiro trimestre de gestação em pacientes sem comorbidades, com pré-eclâmpsia (PE) e com diabetes melito (DM) utilizando tomografia de coerência óptica de domínio espectral (SD-OCT).

Métodos: Estudo transversal que incluiu 306 olhos de 153 mulheres divididas em 6 grupos: 34 mulheres não grávidas saudáveis, 27 gestantes saudáveis, 47 gestantes com PE e 45 gestantes com DM, sendo 15 com diabetes melito gestacional (DMG), 16 com DM tipo 2 (DM2) e 14 com DM tipo 1 (DM1). Todas as gestantes estavam no terceiro trimestre de gestação. As medidas de espessura da coroide foram realizadas utilizando SD-OCT em 10 localizações: subfoveal e a cada 500μm até 2000μm nasal à fovea e 2500μm temporal à fóvea.

Resultados: Não houve diferença nas medidas de espessura da coroide entre o grupo de mulheres não grávidas e o grupo de gestantes saudáveis. Ao comparar a espessura da coroide entre gestantes saudáveis e gestantes com DMG, DM2, DM1, pacientes com DM1 apresentaram coroides mais finas em todas as localizações, com significância estatística nas medidas subfoveal e temporais. Gestantes com DMG e DM2 não apresentaram diferença nas medidas de espessura da coroide em comparação com gestantes saudáveis. Ao comparar o grupo de gestantes saudáveis com o grupo de gestantes com PE, as medidas de espessura da coroide foram maiores no grupo de gestantes com PE, com significância estatística nas medidas nasais. Ao dividir as gestantes com PE conforme critérios de gravidade, pacientes com PE grave apresentaram uma tendência a terem coroides mais espessas em comparação com pacientes com PE leve e gestantes saudáveis. Pacientes com PE e descolamento seroso de retina (SRD) apresentaram coroides significativamente mais espessas em todas as localizações em comparação com pacientes com PE sem SRD.

Conclusões: Por ser um exame rápido, seguro e não invasivo, a OCT é ideal para a análise da coroide durante o período gestacional. A gestação sem

intercorrências não modificou a espessura da coroide em pacientes no terceiro trimestre, em comparação com mulheres não grávidas. Gestantes com DM1, por outro lado, apresentaram coroides mais finas em comparação com gestantes saudáveis, provavelmente pelas alterações decorrentes da coroidopatia diabética. Gestantes com PE apresentaram coroides mais espessas em comparação com gestantes saudáveis, com significância estatística nas medidas nasais. Já pacientes com SRD apresentaram coroides marcadamente mais espessas em todas as localizações. Podemos concluir, a partir destes achados, que a PE cursa com um espessamento da coróide, que se inicia na região peripapilar. Com a progressão do desbalanço, toda a coróide torna-se espessada.

ABSTRACT

Objective: To analyze choroidal thickness of healthy pregnant women and pregnant women with preeclampsia (PE) and diabetes mellitus (DM) in the third trimester using spectral domain optical coherence tomography (SD-OCT).

Methods: This cross-sectional study included 306 eyes of 153 women divided into 6 groups: 34 healthy non-pregnant women, 27 healthy pregnant women, 47 pregnant women with PE and 45 pregnant women with DM, 15 of them with gestational diabetes mellitus (GDM), 16 with type 2 DM and 14 with type 1 DM. All pregnant women were in the third trimester of pregnancy. Choroidal thickness was measured using SD-OCT at ten different locations: at the fovea and every 500μm from the fovea up to 2500μm temporally and up to 2000μm nasally.

Results: There were no significant differences in choroidal thickness between healthy non-pregnant women and healthy pregnant women in the third trimester. Choroid tended to be thicker in subjects with preeclampsia in comparison with healthy pregnant women, with statistical significance in nasal measures. Dividing PE group accordingly disease severity, women with severe preeclampsia tended to have thicker choroids in comparison with mild preeclamptic and healthy pregnant women. Choroid was also significantly thicker in preeclamptic patients with serous retinal detachment (SRD) in comparison with preeclamptic patients without SRD. The choroidal thickness comparison between healthy pregnant women and pregnant women with GDM, type 2 DM and type 1 DM showed a thinner choroid in patients with type 1 DM in all locations, with statistical significance in subfoveal and temporal measurements. No differences were found in choroidal thickness between healthy pregnant women and pregnant women with GDM and type 2 DM.

Conclusions: EDI-OCT is a fast, noninvasive and safe method for choroid analysis during pregnancy. Pregnancy did not change choroidal thickness in third trimester patients compared to nonpregnant women. Pregnant women with type 1 DM had significantly thinner choroidal thickness measurements on subfoveal

and temporal locations, probably due to diabetic choroidopathy modifications. Choroid tends to be thicker in patients with preeclampsia, with statistical significance only in nasal measures. In patients with SRD, however, choroid is markedly thicker at all points analyzed. From these findings we can hypothesize that preeclampsia can cause a choroidal thickening, which begins in the peripapillary area. As the imbalance increases, the entire choroid becomes thickened.

1 INTRODUÇÃO

As adaptações anatômicas, fisiológicas e bioquímicas que ocorrem nas mulheres desde a fertilização até a lactação são significativas e essenciais para viabilizar a gestação[1]. Estas adaptações atingem todos os sistemas do organismo, e sua compreensão é essencial para otimizar o acompanhamento gestacional e definir critérios diagnósticos.

Algumas modificações fisiológicas oculares na gestação já estão bem estabelecidas. A sensibilidade corneana encontra-se diminuída na maioria das gestantes[2]. Reduções temporárias na capacidade acomodativa e aumento da curvatura e da espessura corneana também ocorrem, podendo acarretar modificações temporárias na refração e intolerância ao uso de lentes de contato[3,4,5]. A pressão intra-ocular (PIO) diminui durante a gestação, provavelmente em decorrência do aumento do escoamento do humor aquoso pela via uveoescleral e da redução da pressão venosa episcleral[3,6].

Aumentos no fluxo sanguíneo ocular também foram documentados[7], provavelmente em decorrência das modificações hormonais e circulatórias da gestação. Além da vasodilatação e da redução da resistência vascular, o aumento da volemia também pode ser um fator desencadeante do aumento do fluxo sanguíneo ocular. A expansão do volume plasmático se inicia entre a 10ª e a 20ª semana de gestação, atingindo um aumento de 40 a 45% após a 32ª semana. O débito cardíaco aumenta a partir da 5ª semana de gestação, refletindo uma redução da resistência vascular sistêmica e um aumento da frequência cardíaca[8].

Apesar dos conhecimentos já sedimentados, o efeito da gestação em leitos vasculares como a coroide ainda está sendo investigado. A coroide é um tecido pigmentado e ricamente vascularizado que se estende desde a ora serrata, anteriormente, até o nervo óptico, posteriormente. Histologicamente, a coroide se divide em cinco camadas: membrana de Bruch, coriocapilar, camada de Sattler, camada de Haller e supracoroide. De acordo com análises

histopatológicas, a coroide possui uma espessura média de 0,22mm posteriormente e de 0,10mm a 0,15mm anteriormente. A coroide é inervada pelas duas divisões do sistema nervoso autonômico, recebendo ainda fibras aferentes sensitivas primárias que se projetam para o gânglio trigeminal através do nervo oftálmico. A rede vascular da coróide é responsável por mais de 85% do fluxo sanguíneo do olho e é a única estrutura responsável pelo suprimento vascular do epitélio pigmentar da retina (EPR) e das camadas externas da retina. Também é a única fonte de nutrientes e oxigênio para toda região avascular da fóvea[9,10]. Anormalidades vasculares na coroide, por este motivo, podem ser responsáveis por disfunções dos fotorreceptores e comprometimento visual.

Acredita-se que a gestação por si só possa causar modificações na coroide, principalmente pela forte associação existente entre coriorretinopatia serosa central (CSC) e gestação[11,12]. A CSC é uma doença caracterizada por hiperpermeabilidade e aumento da pressão hidrostática na coroide, com quebra da barreira hematorretiniana externa e acúmulo de fluido subretiniano. Acredita-se que o aumento nos níveis de cortisol endógeno associado a uma possível disfunção nos vasos da coroide sejam responsáveis pelo aumento significativo do risco de CSC durante a gestação. Diversos autores já documentaram que pacientes com CSC apresentam coroides mais espessas em comparação com controles[13,14,15].

A COROIDE E A TOMOGRAFIA DE COERÊNCIA ÓPTICA

Um entendimento clínico preciso das alterações na coroide poderia proporcionar uma melhor avaliação de muitas doenças que acometem o segmento posterior do olho. Devido à sua localização entre o EPR superiormente e a esclera com sua estrutura rígida e opaca inferiormente, a coroide é difícil de ser visualizada por métodos convencionais de imagem. Até

recentemente, os métodos disponíveis para avaliação da coroide, como a angiografia com indocianina verde e a dopplerfluxometria a laser, eram úteis apenas para determinar anormalidades vasculares ou alterações no fluxo sanguíneo, mas incapazes de fornecer informações anatômicas precisas sobre a espessura e as camadas da coroide. Além disso, as angiografias com fluoresceína e indocianina verde devem ser evitadas durante o período gestacional, pelo perfil de segurança dos corantes endovenosos.

A Tomografia de Coerência Óptica (OCT) é um método de imagem não invasivo que utiliza reflectometria para obter cortes seccionais da retina em escala micrométrica[10]. A OCT baseia-se no princípio da reflectometria óptica, que envolve a medição do retroespelhamento da luz através de meios transparentes ou semitransparentes, como os tecidos oculares. Isto é conseguido medindo-se a intensidade e o tempo de atraso da luz que é dispersa a partir dos tecidos de interesse. A luz é dividida em dois braços, o braço de referência e o braço da amostra, o qual é refletido de volta a partir das estruturas do polo posterior do olho.

Durante a última década, a tecnologia empregada na OCT evoluiu drasticamente. A evolução da OCT por Domínio de Tempo (TD-OCT) para Domínio de Fourier (FD-OCT) permitiu velocidades de escaneamento muito mais rápidas, com grande ganho na resolução da imagem. Enquanto os aparelhos TD-OCT atingiam velocidades de digitalização de 400 scans/segundo, com uma resolução axial de 8 a 10μm, os FD-OCT apresentam velocidades entre 17.000 e 70.000 scans/segundo, com resolução axial entre 5-7μm[16].

Dentre os aparelhos que utilizam detecção por domínio de Fourier, o OCT por Domínio Espectral (SD-OCT) e o OCT Swept-Source (SS-OCT) inovaram as técnicas de análise do segmento posterior do olho. O SD-OCT utiliza um diodo superluminescente como fonte de luz, com um comprimento de onda central de aproximadamente 840nm[17]. Quanto maior o comprimento de onda da luz, menor é o reflexo de dispersão no EPR. Com o SD-OCT, muitas vezes este comprimento de onda da fonte de luz não é suficientemente longo para penetrar na coroide. Deste modo, a análise da coroide no SD-OCT é feita utilizando-se o

método de EDI - Enhancement Depth Imaging[18]. O EDI possibilita uma melhor visualização das camadas da coroide através da atenuação da luz emitida pelo aparelho, o que diminui a sua reflexão pelo EPR, com compensação pelo software para realce da imagem.

O surgimento do SD-OCT, através da modalidade EDI, possibilitou a realização de medidas precisas da espessura da coroide, com altas taxas de repetibilidade e elevado índice de concordância inter-observador e reprodutibilidade[19,20,21,22]. A medida pode ser realizada manualmente utilizando o software do OCT através de uma linha perpendicular que se estende da borda externa do EPR até o limite interno da esclera. Deve-se atentar, entretanto, que a espessura da coroide pode ser influenciada por fatores maiores como a idade, a refração e o comprimento axial do olho[10,23,24]. Deste modo, a espessura da coroide tende a ser maior em pacientes mais jovens e com menor comprimento axial. Wei et al.[24] também encontraram coroides mais espessas em pacientes do sexo masculino. Variações diurnas da espessura da coroide também já foram documentadas[25,26].

Com a progressão na padronização do método, diversos estudos passaram a analisar a espessura da coroide em olhos normais ou com diferentes patologias. As alterações fisiológicas da gravidez na coroide, por exemplo, está em investigação, mas os resultados ainda são controversos[6]. Como a gestação cursa com um aumento na volemia de aproximadamente 50%, associado a aumento do débito cardíaco e redução da resistência vascular periférica[1], algum reflexo em leitos vasculares com alto fluxo como a coroide pode ser esperado. Kara et al.[27], Sayin et al.[28] e Atas et al.[29] realizaram estudos analisando a espessura da coroide de mulheres grávidas e concluíram que a medida da espessura da coroide subfoveal é significativamente maior em mulheres grávidas em comparação com mulheres não grávidas. Outros autores, entretanto, encontraram resultados discordantes. Takahashi et al.[30] e Kim et al.[31] não encontraram diferenças estatisticamente significativas na espessura da coroide entre mulheres grávidas no terceiro trimestre e mulheres não-grávidas.

Goktas et al.[32] realizaram um estudo com 90 mulheres grávidas saudáveis, levando em consideração a idade gestacional. A coroide era significativamente mais espessa nas mulheres grávidas no segundo trimestre em comparação com as mulheres não grávidas. Dadaci et al.[33] compararam as medidas da espessura da coroide entre 27 mulheres grávidas e 25 mulheres não grávidas. As mulheres grávidas foram examinadas durante o primeiro e o terceiro trimestres. A espessura da coroide medida pelo OCT diminuiu significativamente em todos os pontos analisados no terceiro trimestre de gestação, em comparação com as medidas do primeiro trimestre. Não foi encontrada diferença estatisticamente significativa entre as pacientes grávidas e o grupo controle.

Ulusoy et al.[34] realizaram um estudo prospectivo para analisar a espessura da coroide em grávidas no terceiro trimestre e 3 meses após o parto. As medidas da coroide encontradas eram significativamente menores no pós-parto. Um grupo controle de mulheres não grávidas também foi analisado, apresentando coroides significativamente mais finas em comparação com mulheres grávidas. Rothwell et al.[35] usaram uma técnica diferente para analisar a estrutura da coroide, construindo mapas de volume macular para os 9 subcampos definidos pelo *Early Treatment Diabetic Retinopathy Study* (ETDRS), utilizando um SD-OCT. As medidas de espessura e volume no subcampo central foram significativamente maiores em pacientes grávidas no terceiro trimestre em comparação com pacientes não-grávidas.

Além destas modificações estruturais fisiológicas, devemos lembrar que a gestação também pode estar associada ao surgimento de patologias oftalmológicas novas ou à deterioração de uma condição pré-existente. Além da CSC, alterações retinianas e coroideas relacionadas ao diabetes melito (DM) e às doenças hipertensivas também podem ser encontradas, sendo a sua compreensão essencial para otimizar condutas e resultados.

DIABETES MELITO

O diabetes melito é um distúrbio metabólico de etiologia múltipla, caracterizado por hiperglicemia crônica, com alteração no metabolismo dos carboidratos, das gorduras e das proteínas, decorrente do comprometimento na secreção e/ou na ação da insulina[36]. No Brasil, em 2013, a Pesquisa Nacional de Saúde estimou que 6,2% da população com 18 anos ou mais referiram diagnóstico médico de diabetes[37]. De acordo com sua etiologia, o diabetes pode ser classificado em[38]:

- Diabetes Melito tipo 1 (DM1): causado pela destruição de células β-pancreáticas, geralmente acarretando deficiência absoluta de insulina.

- Diabetes Melito tipo 2 (DM2): causado por uma progressiva redução na secreção de insulina subjacente a um estado de resistência à insulina.

- Diabetes Melito Gestacional (DMG): diabetes diagnosticado no segundo ou terceiro trimestres da gestação, que não atinge os critérios para DM fora da gestação.

- Tipos específicos de DM secundários: síndromes monogênicas como DM neonatal e MODY (maturity-onset diabetes of the young), doenças do pâncreas exócrino como a fibrose cística e DM induzido por fármacos ou agentes químicos.

O DM fora da gestação pode ser diagnosticado por critérios de glicemia plasmática, como a glicemia de jejum, o teste oral de tolerância à glicose (TOTG) ou medida da hemoglobina glicada (HbA1c). Os critérios diagnósticos de DM em adultos fora da gestação incluem[38]:

- Glicemia de jejum $\geq$ 126 mg/dL ou

- Glicemia de 2 horas no Teste Oral de Tolerância à Glicose (TOTG) 75g $\geq$ 200mg/dL ou

- Hemoglobina glicada (HbA1c) $\geq$ 6,5% ou

- Glicemia ao acaso $\geq$ 200mg/dL em indivíduo com sintomas clássicos de hiperglicemia ou em crise hiperglicêmica.

A realização de um segundo teste de glicemia de jejum com nova amostra de sangue é recomendada para a confirmação diagnóstica, exceto em pacientes com claro diagnóstico clínico (crise hiperglicêmica, por exemplo) [38].

A hiperglicemia pode estar associada à gestação em duas situações distintas: no diabetes, diagnosticado ou não, que antecede a gestação e no diabetes gestacional propriamente dito. No diabetes pré-gestacional, em geral, a mulher já se sabe portadora da condição antes da concepção. Já o DMG ocorre, em geral, após 20 semanas de gestação, decorrente do aumento da resistência periférica à insulina associada à produção placentária de hormônios de ação antiinsulínica. É a alteração gestacional metabólica mais comum, com prevalência entre 3% e 25%[39].

Tanto o diabetes pré-gestacional como o DMG podem resultar em comprometimento materno e fetal. Possivelmente a hiperglicemia materna sustentada leva à hiperglicemia fetal e consequente hiperinsulinismo fetal[40]. A combinação diabetes e gestação está associada a aumento nas taxas de macrossomia fetal, cesariana primária, traumas de canal de parto, distúrbios hipertensivos e a outros desfechos neonatais adversos. As malformações congênitas estão associadas principalmente à presença de hiperglicemia materna no período periconcepcional, sendo mais prevalentes nos casos de diabetes pré-gestacional.

De acordo com consenso publicado em 2010 pela International Association of Diabetes and Pregnancy Study Groups (IADPSG)[41], endossado pela American Diabetes Association e pela Organização Mundial da Saúde[42], o DMG é diagnosticado quando:

- Em qualquer momento da gestação, a medida da glicemia de jejum for maior ou igual a 92mg/dL ou

- Se qualquer uma das três medidas de glicose plasmática no TOTG de 75g-2h for atingida ou ultrapassada: jejum 92mg/dl; 1ª hora após sobrecarga 180mg/dl e 2ª hora após sobrecarga 153mg/dl.

Apesar de ser uma doença oligossintomática ou até assintomática em estágios iniciais, o DM pode apresentar complicações agudas, como a

cetoacidose diabética e o coma hiperosmolar, e complicações crônicas, que ocorrem tanto em nível macrovascular quanto microvascular. Dentre as complicações microvasculares, a retinopatia diabética (RD) merece especial destaque pelo seu potencial risco de perda visual permanente.

No Brasil, ainda não há pesquisas que demonstrem com exatidão a prevalência da RD. Avaliando-se as estatísticas disponíveis com percentuais adaptados de outros países, estima-se que aproximadamente 2 milhões de brasileiros tenham algum grau de RD[43]. Sabe-se que o tempo de duração do diabetes e o controle glicêmico são, respectivamente, os dois fatores mais importantes relacionados com o desenvolvimento e a gravidade da RD[44,45,46,47]. Hipertensão arterial sistêmica[48], dislipidemia[49,50] e gravidez[51,52,53,54,55] também são fatores associados à severidade e progressão da RD. A patogênese da retinopatia diabética é multifatorial e envolve danos progressivos na unidade neurovascular da retina[56]. As alterações incluem a presença de dano endotelial severo, com perda de pericitos, espessamento da membrana basal dos capilares, formação de microaneurismas, quebra da barreira hemato-retiniana, oclusões microvasculares, isquemia tecidual retiniana crônica, edema neuronal e apoptose.

A RD pode ser classificada de acordo com os achados à fundoscopia em[57]:

- RD não-proliferativa (RDNP) leve: apenas microaneurismas;

- RD não-proliferativa moderada: achados mais abundantes do que a RD não-proliferativa leve, mas menos abundantes do que a RD não-proliferativa grave;

- RD não-proliferativa grave: presença de mais de 20 hemorragias intrarretinianas em cada um dos 4 quadrantes ou presença de ensalsichamento venoso em dois quadrantes ou presença de anormalidades microvasculares intrarretinianas (IRMAs) em um quadrante.

- RD proliferativa (RDP): presença de neovasos ou hemorragia vítrea ou pré-retiniana.

A presença de espessamento retiniano ou exsudatos duros no polo posterior configuram edema macular clinicamente significativo[57].

Além de alterações na morfologia retiniana, o DM também cursa com alterações morfológicas na coroide. A presença de microaneurismas, dilatações e obstruções vasculares na camada coriocapilar, remodelamento vascular com aumento da tortuosidade, áreas de não-perfusão e áreas de neovascularização já foram documentadas na coroide de pacientes diabéticos[58]. Esta coroidopatia diabética foi descrita pela primeira vez em 1985 por Hidayat e Fine[59], que já na época questionavam um possível papel da coroide na patogênese da retinopatia diabética. Mais recentemente, diversas anormalidades microvasculares também foram documentadas na coriocapilar de pacientes diabéticos utilizando angiografia por tomografia de coerência óptica (OCTA), inclusive em pacientes sem sinais clínicos de RD[60,61]. Estudos avaliando alterações hemodinâmicas na coroide usando a dopplerfluxometria a laser revelaram uma redução no volume e no fluxo de sangue nos vasos da coroide na região foveal em pacientes com RD proliferativa e com edema macular[62,63].

Como achados clínicos e experimentais prévios já sugeriram que a coroidopatia diabética pode estar envolvida na patogênese da RD, alguns autores avaliaram as alterações na espessura da coroide em pacientes com diabetes usando SD-OCT[64-75]. Esmaeelpour et al.[64] encontraram uma redução da espessura central da coroide em todos os olhos de pacientes com DM2, independentemente do grau da RD comparados com controles saudáveis. Regatieri et al.[65] examinaram pacientes com diabetes e indivíduos saudáveis pareados para idade e encontraram que a média da espessura foveal da coroide foi mais fina em pacientes com edema macular diabético e RD proliferativa tratada comparados com indivíduos saudáveis ou com aqueles com RD não-proliferativa. Querques et al.[66] avaliaram a espessura macular da coroide de pacientes com diabetes usando SD-OCT, demonstrando que existe um afinamento subfoveal da coroide nos grupos com diabetes comparados com o grupo controle, mas sem diferença significativa entre os vários graus de RD. Vujosevic et al.[67] demonstraram que a espessura central da coroide reduz

progressivamente com o aumento do nível da RD. Nenhuma diferença na espessura central da coroide foi encontrada entre os controles e pacientes com diabetes sem RD detectável. Em contraste com o estudo de Regatieri et al[65], a presença de edema macular diabético não influenciou a medida da espessura central da coroide**.** Lains et al.[68] utilizaram o SS-OCT para avaliar a relação entre retinopatia diabética e espessura da coroide. Os autores observaram que a espessura da coroide é significativamente menor em pacientes com RD, principalmente os com doença proliferativa. Shen[69] também relatou uma redução na espessura da coroide em pacientes com RD em comparação com pacientes controle. Yulek et al.[70] não encontraram relação entre a espessura da coroide subfoveal e o aumento na duração do DM.

No estudo de base populacional Beijing Eye Study[71], entretanto, Xu et al. examinaram 246 pacientes com diabetes, 23 deles com RD, tendo encontrado uma espessura subfoveal da coroide aumentada em associação ao DM. Kim et al.[72] concluiram que a espessura subfoveal da coroide aumenta significativamente com a gravidade da RD, sendo maior naqueles olhos com edema macular diabético. Estudos conduzidos por Yazici[73] e Tavares Ferreira[74] também demonstraram um aumento da espessura da coroide em pacientes com DM2 em comparação com pacientes controle.

RETINOPATIA E COROIDOPATIA DIABÉTICA NA GESTAÇÃO

A gravidez é um fator de risco independente para a progressão da RD, tanto em pacientes com DM1 como em pacientes com DM2[51,52,53,54,55]. Durante o Diabetes Control Complications Trial (DCCT), que randomizou participantes com DM1 para controle glicêmico intensivo ou convencional, 180 mulheres engravidaram. O risco de progressão da retinopatia diabética nessas pacientes foi 2,48 vezes maior em pacientes do grupo controle convencional e 1,63 vezes

maior em pacientes do grupo controle intensivo em comparação com as participantes não grávidas[52].

Os determinantes mais importantes para a progressão da retinopatia durante a gestação são a duração da doença e o grau de retinopatia no início na gestação. Diversos estudos já demonstraram consistentemente que, quanto maior o tempo de duração do diabetes, maior é o risco de progressão da RD durante a gestação[54,55,76,77,78,79,80]. No Diabetes in Early Pregnancy Study (DIEP)[55], 38% das pacientes com mais de 15 anos de diabetes progrediram para RDP, mas apenas 18% das pacientes com menos de 15 anos da doença apresentaram essa progressão. Também já foi demonstrado que, quanto mais grave a RD no início da gestação, maior a chance de progressão[55,77]. Ainda no DIEP[55], a progressão da RD foi proporcional à condição existente na gestação inicial: 10,3% das pacientes sem RD, 18,8% das pacientes com RDNP leve e 54,8% das pacientes com RDNP moderada ou grave.

O controle glicêmico tem aparentemente efeito paradoxal no desenvolvimento e progressão da RD em gestantes. O mau controle metabólico e a hiperglicemia são sabidamente fatores de risco para a evolução da RD durante a gestação, mas a compensação glicêmica abrupta também pode contribuir para essa piora[55,77,80]. O risco de progressão da RD é significativamente menor em pacientes com controle glicêmico intensivo antes da concepção[52]. A nefropatia e a hipertensão arterial também são consideradas fatores de risco adicionais para progressão da RD durante a gestação[81].

As razões pelas quais a gravidez causa, por si só, uma piora na progressão da retinopatia diabética ainda são desconhecidas. Já foi especulado que o aumento do débito cardíaco associado à redução da resistência vascular que ocorrem durante a gestação poderiam ser os fatores predisponentes[1,82]. Enquanto alguns autores sugeriram que uma hiperperfusão retiniana poderia agravar um dano microvascular pré-existente em pacientes gestantes com DM[83,84], outros sugeriram que uma redução no fluxo sanguíneo dos capilares retinianos poderia desencadear uma piora da isquemia nessas pacientes[85,86]. Além disso, há evidência que fatores de crescimento com concentrações

aumentadas durante a gestação poderiam contribuir para a piora da RD[87,88,89,90,91].

Embora essas hipóteses já tenham sido levantadas, uma possível relação entre a progressão da RD durante a gestação e alterações morfológicas da coroide deveria ser mais amplamente estudada. Embora diversos autores tenham estudado a espessura da coroide em pacientes diabéticas não gestantes e em gestações de risco habitual, encontramos apenas um estudo analisando a espessura da coroide em gestações complicadas por DMG até o momento. Acmaz et al.[92] concluiram que a espessura da coroide é maior em mulheres grávidas saudáveis e mulheres com DMG em comparação com mulheres não grávidas. No entanto, não foi encontrada diferença significativa de medidas entre o grupo DMG e o grupo das mulheres grávidas saudáveis. Até a presente data, não temos conhecimento de publicações analisando a espessura da coroide em mulheres com gestações complicadas por DM1 ou DM2.

PRÉ-ECLÂMPSIA

Os distúrbios hipertensivos da gestação estão entre as principais causas de morbidade e mortalidade materna e perinatal. Embora a prevalência varie entre as populações, acredita-se que cerca de 12 a 22% das gestantes apresentem alterações hipertensivas[93]. Entre as gestantes brasileiras com mais de 20 anos, 7,5% apresentam distúrbios hipertensivos[94].

Os distúrbios hipertensivos da gestação podem ser classificados em: pré-eclâmpsia (PE) / eclâmpsia, hipertensão crônica, hipertensão crônica com PE sobreposta e hipertensão gestacional[95]. A pré-eclâmpsia é uma síndrome que cursa com disfunção endotelial e vasoespasmo da circulação sistêmica periférica, podendo acarretar alterações em múltiplos órgãos e sistemas. Ocorre mais comumente na primeira gestação do casal e em gestantes com história prévia ou familiar da doença. A presença de hipertensão crônica, diabetes,

gestação múltipla, obesidade e trombofilias também configuram fatores de risco para a PE[96].

A literatura contemporânea sugere algumas hipóteses para o surgimento de PE: implantação placentária com invasão troflobástica anormal, má adaptação imunológica entre os tecidos maternos, paternos (placentários) e fetais, má-adaptação materna às alterações cardiovasculares e inflamatórias da gestação e fatores genéticos, como polimorfismos de genes e *imprint* epigenético[1]. Em uma gestação normal, ocorre uma adaptação circulatória materno-fetal para que se produza uma circulação placentária de baixa resistência, resultando em um sistema circulatório de alto fluxo, que parece estar comprometido na PE. A restrição no fornecimento de sangue para a placenta acaba causando uma disfunção na perfusão uteroplacentária, hipóxia e estresse oxidativo placentário. Como resultado, temos o desenvolvimento de uma resposta inflamatória sistêmica com disfunção endotelial materna e desequilíbrio entre fatores vasoconstritores e vasodilatadores. Estes fatores poderiam contribuir para o surgimento de um estado materno caracterizado por vasoespasmo da circulação periférica, vasodilatação do sistema nervoso central (SNC) e ativação endotelial e do sistema de coagulação, com alterações no controle da pressão arterial e do volume intravascular[1,96].

O diagnóstico de PE[95] é definido pelo surgimento de:

1. Hipertensão arterial:

- Pressão arterial sistólica (PAS) $\geq$140mmHg e/ou Pressão arterial diastólica (PAD) $\geq$90mmHg, em duas medidas com intervalo de pelo menos 4 horas, após a 20ª semana de gestação, em uma paciente previamente normotensa.

- PAS $\geq$160mmHg e/ou PAD$\geq$110mmHg, com confirmação em curto intervalo de tempo (minutos).

2. Proteinúria: $\geq$ 300mg/24 horas; ou relação proteinúria/creatinúria $\geq$ 0.3.

Na ausência de proteinúria, o diagnóstico de PE pode ser firmado pela presença de hipertensão arterial e, pelo menos, um dos achados:

- Trombocitopenia (plaquetas abaixo de 100.000/dL);

- Insuficiência renal (creatinina sérica >1,1mg/dL ou a duplicação da concentração prévia na ausência de doença renal prévia);

- Disfunção hepática: aumento das transaminases no mínimo duas vezes acima do limite superior da normalidade;

- Edema pulmonar;

- Sintomas neurológicos ou visuais.

Portanto, o surgimento de hipertensão após a 20ª semana de gestação, quando acompanhado por outras disfunções maternas, pode ser diagnosticado como pré-eclâmpsia mesmo na ausência de proteinúria significativa[95,97].

A presença de qualquer um dos seguintes critérios caracteriza a pré-eclâmpsia grave (PEG)[95]:

- PAS ≥160mmHg e/ou PAD≥110mmHg, em duas medidas com pelo menos 4 horas de intervalo, com a paciente em repouso no leito;

- Trombocitopenia (plaquetas abaixo de 100.000/dL);

- Insuficiência renal (creatinina sérica >1,1mg/dL ou a duplicação da concentração prévia na ausência de doenças renais);

- Disfunção hepática: aumento das transaminases no mínimo duas vezes acima do limite superior da normalidade ou dor persistente em epigástrio ou quadrante superior direito, não responsiva a analgésicos e sem outra causa aparente;

- Edema pulmonar;

- Sintomas neurológicos ou visuais.

Os níveis de proteinúria não são considerados critérios de gravidade. Gestantes com sinais ou sintomas de PEG apresentam uma enfermidade descompensada, que pode rapidamente evoluir com importante morbi-mortalidade materna e perinatal.

Eclâmpsia é a ocorrência de convulsões motoras generalizadas em gestantes com PE[96,98]. O envolvimento neurológico na síndrome de pré-eclâmpsia-eclâmpsia é conhecido como Síndrome de *PRES* (Posterior Reversible Encephalopathy Syndrome ou Síndrome de Encefalopatia Posterior Reversível), condição que se refere ao aparecimento súbito de cefaleia e

distúrbios visuais, muitas vezes associados a convulsões e ao coma, resultante de um edema vasogênico primário na substância branca subcortical dos lobos parieto-occipitais. A hipertensão arterial e o dano vascular subsequente à falha da autorregulação levariam à sobredistensão vascular e transudação para o interstício cerebral. A literatura evidencia que a diminuição do IR na artéria oftálmica (IR <0,56) é o mais relevante preditor da evidência de PRES na pré-eclâmpsia grave[99].

A partir da década de 90, estudos sobre a análise dopplervelocimétrica das artérias oftálmicas em pacientes com PE começaram a ser realizados[100-105]. A artéria oftálmica possui similaridade embriológica, anatômica e funcional às artérias do sistema nervoso central. Ela dá origem à artéria central da retina e às artérias ciliares posteriores, sendo estas últimas as grandes responsáveis pela formação do leito vascular da coroide. A artéria central da retina é um vaso terminal, sem anastomoses significativas, com mecanismo próprio de autorregulação. A circulação da coroide, por outro lado, sofre influência do sistema nervoso autônomo[9].

Hata et al.[100], em 1995, relataram achados de redução na resistência vascular da artéria oftálmica em mulheres com pré-eclâmpsia, contrastando com a teoria mais aceita até então de vasoconstrição generalizada. Estudos posteriores confirmaram a presença de quedas nos índices de pulsatilidade e de resistência das artérias oftálmicas em gestantes portadoras de PE[101-105]. Atualmente, a dopplervelocimetria das artérias oftálmicas é utilizada como auxílio no diagnóstico diferencial entre PE e hipertensão arterial crônica. Os achados compatíveis com hiperperfusão e vasodilatação da artéria oftálmica em pacientes com PE, devem ser analisados em conjunto com os achados de vasoconstrição dos vasos mais periféricos do globo ocular encontrados nestas pacientes.

ALTERAÇÕES OFTALMOLÓGICAS ASSOCIADAS À PRÉ-ECLÂMPSIA

A pré-eclâmpsia é caracterizada por um estado inflamatório com disfunção endotelial sistêmica, podendo cursar inclusive com comprometimento do sistema visual. A PE pode estar associada a diversas alterações coroidianas e retinianas, algumas muito similares às da retinopatia hipertensiva, bem como a sintomas oculares como diplopia, escotomas, fotopsias e queda da acuidade visual. A presença de sintomas oftalmológicos configura critério de gravidade para pacientes com PE.

Estreitamento arteriolar focal ou difuso é uma das alterações retinianas mais prevalentes em pacientes com PE, embora também encontrado em pacientes com hipertensão crônica. Outras alterações típicas da retinopatia hipertensiva como exsudatos algodonosos, hemorragias em chama de vela e edema de disco óptico geralmente não estão presentes em pacientes com pré-eclâmpsia, indicando necessidade de investigação sistêmica adicional[106].

A presença de alterações na circulação coroidiana e isquemia coroidiana já estão bem documentados na literatura[107,108,109,110]. Estudos anteriores de angiografia com indocianina verde em pacientes com pré-eclâmpsia demonstraram áreas de não-perfusão nas fases iniciais do angiograma e impregnação dos vasos com extravasamento sub-retiniano nas fases tardias do angiograma, sugerindo dano vascular grave na coroide[107]. Sathish[111] também relatou perfusão tardia nos vasos da coriocapilar, com áreas de não perfusão e vazamento gradual da fluoresceína em paciente com pré-eclâmpsia e descolamento seroso de retina. Os achados de manchas de Elschnig em pacientes com pré-eclâmpsia também corroboram a presença de infartos isquêmicos do EPR e da coroide. Um EPR isquêmico pode causar quebra da barreira hemato-retiniana, permitindo o vazamento de fluido da coroide para o espaço sub-retiniano[112]. Os achados tendem a ser bilaterais e simétricos, com resolução espontânea no pós-parto.

Embora as angiografias com fluoresceína ou indocianina verde possam fornecer informações sobre os vasos da coroide, seu uso durante a gestação deve ser evitado, principalmente durante o primeiro trimestre. A mensuração da

espessura da coroide com o SD-OCT surgiu como uma nova ferramenta para a análise dessa estrutura em gestantes com PE. Atas et al.[29], Duru et al.[113] e Sayin et al.[28] relataram coroides mais finas em gestantes com pré-eclâmpsia em comparação a gestantes saudáveis. Kim et al.[31], no entanto, demonstraram que a coroide de pacientes com PE era significativamente mais espessa que a de gestantes saudáveis e adultas não gestantes. Garg et al.[114] também relataram espessamento coroideo no cenário de pré-eclâmpsia grave. Tanto Duru et al.[113] como Kim et al.[31] encontraram uma diminuição significativa na espessura da coroide após o parto em gestantes com PE.

1.1 JUSTIFICATIVA

Um melhor entendimento das modificações que ocorrem na coroide durante a gestação é essencial para compreender a evolução e otimizar o tratamento de algumas doenças durante este período. Inicialmente, deve-se entender as modificações fisiológicas que ocorrem em gestações não-complicadas. Até hoje não está esclarecido se a circulação hiperdinâmica da gestação, com aumento da volemia e redução da resistência vascular periférica, acarreta repercussões no leito vascular da coroide.

Embora o motivo ainda seja desconhecido, sabe-se que a gestação é um fator de risco independente para a progressão da retinopatia diabética. A evolução mais agressiva da retinopatia e a impossibilidade de tratamento com anti-angiogênicos tornam o manejo da retinopatia diabética durante a gestação um desafio, com possíveis consequências desastrosas para a função visual.

As alterações na retina e coroide associadas à pré-eclâmpsia também podem apresentar repercussões visuais importantes, além de serem um indicativo da gravidade da doença de base. Sabe-se que as alterações vasculares da coroide em pacientes com pré-eclâmpsia são significativas e provavelmente associadas aos descolamentos de retina encontrados nestas pacientes. Os mecanismos envolvidos nesta coroidopatia, entretanto, ainda são desconhecidos.

Devido ao provável envolvimento da coroide na patogênese e progressão da RD, bem como nas alterações oftalmológicas associadas à pré-eclâmpsia, o presente estudo se propõe a analisar possíveis alterações na espessura da coroide em gestantes saudáveis, com DM e com pré-eclâmpsia utilizando o SD-OCT. O desconhecimento do comportamento da coroide durante o período gestacional, bem como a escassez de trabalhos na literatura sobre o assunto e a presença de resultados contraditórios apontam para a necessidade de mais pesquisas na área.

1.2 OBJETIVOS

1. Medir a espessura da coroide de gestantes saudáveis no terceiro trimestre utilizando SD-OCT.

2. Medir a espessura da coroide de gestantes no terceiro trimestre com diagnóstico de DMG, DM2 e DM1 utilizando SD-OCT.

3. Medir a espessura da coroide de gestantes no terceiro trimestre com diagnóstico de pré-eclâmpsia utilizando SD-OCT.

2 PUBLICAÇÕES

2.1 CAPÍTULO 1

COMPARATIVE ANALYSIS OF CHOROIDAL THICKNESS IN THIRD TRIMESTER PREGNANT WOMEN.

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Comparative analysis of choroidal thickness in third trimester pregnant women

Camila Zanella Benfica[1,2*], Teresinha Zanella[3], Lucas Brandolt Farias[1,2], Maria Lúcia Rocha Oppermann[1,3], Luis Henrique Santos Canani[1,4] and Daniel Lavinsky[1,2]

Abstract

Background: The impact of pregnancy on the choroid is still under investigation. The aim of this study is to compare choroidal thickness measurements of healthy pregnant women in the third trimester and healthy non-pregnant women using spectral-domain optical coherence tomography (OCT).

Methods: This cross-sectional study included 122 eyes of 61 women, divided into two groups: 27 healthy pregnant women in the third trimester and 34 age-matched healthy non-pregnant women. Choroidal thickness was measured using Enhanced Depth Imaging OCT at ten different locations: at the fovea and every 500 µm from the fovea up to 2500 µm temporally and up to 2000 µm nasally.

Results: There were no significant differences in the ten measurements of choroidal thickness comparing both groups. Mean subfoveal choroidal thickness was 304.1 + 9.6 µm in the control group and 318.1 + 15.6 µm in the pregnant women group ($p = 0.446$). There was also no statistically significant association between gestational age and choroidal thickness measurements in the healthy pregnant women group.

Conclusions: Our study showed no statistically difference in choroidal thickness between healthy non-pregnant women and healthy pregnant women in the third trimester.

Keywords: Choroidal thickness, Enhanced depth imaging optical coherence tomography, Pregnancy, Choroid

Background

Physiological changes during pregnancy are significant and their knowledge is essential to optimize outcomes. Volemia augmentation in pregnancy averages 40–45% above the nonpregnant blood volume after 32–34 weeks. Cardiac output is increased as early as the 5th week and reflects a reduced systemic vascular resistance and an increased heart rate [1–3].

Ocular changes during pregnancy like an increased central corneal thickness and curvature and decreased corneal sensitivity and intraocular pressure (IOP) were already described [4, 5]. Changes in ocular blood flow may also occur, as an increased pulsatile ocular blood flow [6].

The impact of pregnancy on the choroid, however, is still under investigation, with mixed results. A strong association of central serous chorioretinopathy and pregnancy is well documented [7, 8]. Choroidal dysfunction and ischemia are also a common ocular complication of preeclampsia [9].

The development of the enhanced depth imaging (EDI) technique of spectral-domain optical coherence tomography (SD-OCT) systems allowed analysis of choroidal morphologic features in normal and pathological eyes [10]. EDI-OCT promotes better documentation of the choroid and choroidal–scleral interface by decreasing signal strength posterior to the retinal pigment epithellium. Since it is a noninvasive diagnostic method, EDI-OCT would be ideal for the study of choroid changes during an uncomplicated pregnancy.

The aim of this study was to compare choroidal thickness measurements of healthy women, pregnant and non-pregnant, using EDI-OCT.

*Correspondence: camilazbenfica@gmail.com
[1] Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil
Full list of author information is available at the end of the article

Methods

This cross-sectional study included 122 eyes of 61 women, divided into two groups: 27 healthy pregnant women in the third trimester and 34 age-matched healthy non-pregnant women. The participants were recruited between March and September of 2016 at Hospital de Clinicas de Porto Alegre (HCPA), Brazil. All participants received in person full explanation about the study and provided written informed consent. This study was approved by HCPA research ethics committee and was conducted in accordance with the Declaration of Helsinki guidelines.

Participants underwent an interview with demographic and background history and complete ophthalmic examination. Subjects with any previous ocular surgery or ocular pathology including refractive disorders with spherical equivalent greater than ± 1.0 diopters were excluded. All pregnant women enrolled in the study were attending prenatal care and were having uneventful singleton pregnancy. Participants with history of smoking or diagnosed with any systemic disease, such as diabetes mellitus, hypertension, preeclampsia, renal, rheumatologic or cardiovascular diseases, were also excluded.

All OCT scans were performed in the morning (8:00 am to 12:00 pm) to avoid diurnal variations of choroidal thickness [11, 12]. The same experienced ophthalmologist (CB) performed all OCT scans, using Heidelberg Spectralis OCT (Heidelberg Engineering Co, Heidelberg, Germany). Choroid was imaged with a 6-line radial scan (30°, 9.2 mm) using EDI setting, with 100 images averaged per section. All scans were reviewed before their inclusion in the study; those with image artefacts or inaccurate choroidal limits were excluded. Only one single horizontal scan through the fovea was used for analysis.

Choroidal thickness was determined as the vertical distance from the outer surface of the line formed by the retinal pigment epithelium to the chorioscleral interface using the Spectralis OCT measurement software. The measurements were made by an experienced ophthalmologist (DL) masked to the participant group. Previous studies have already demonstrated the reproducibility of choroidal thickness measurements, even across different OCT systems [13–15]. Choroidal thickness was measured at ten different locations: at the fovea and every 500 µm from the fovea up to 2500 µm temporally and up to 2000 µm nasally (Fig. 1). We used the following abbreviations for the macular points: T5: choroidal thickness at 2500 µm temporally to the fovea; T4: choroidal thickness at 2000 µm temporally to the fovea; T3: choroidal thickness at 1500 µm temporally to the fovea; T2: choroidal thickness at 1000 µm temporally to the fovea; T1: choroidal thickness at 500 µm temporally to the fovea; SF: choroidal thickness at the fovea; N1: choroidal thickness at 500 µm nasally to the fovea; N2: choroidal thickness at 1000 µm nasally to the fovea; N3: choroidal thickness at 1500 µm nasally to the fovea; N4: choroidal thickness at 2000 µm nasally to the fovea.

Statistical analysis

Statistical analyses were performed using SPSS V.15.0 (SPSS Science, Chicago, Illinois, USA). Quantitative variables from sample demographics were presented as mean ± SD. To compare variables between groups a t test was used for quantitative data and a Fisher's exact test for qualitative data. Choroidal thickness measures were presented as mean ± SE. Differences in choroidal thickness were analysed using generalized estimating equations (GEE) with Bonferroni adjustment. Pearson's correlation was used to analyze the relationship between choroidal thickness and gestational age. A p value ≤ 0.05 was considered statistically significant.

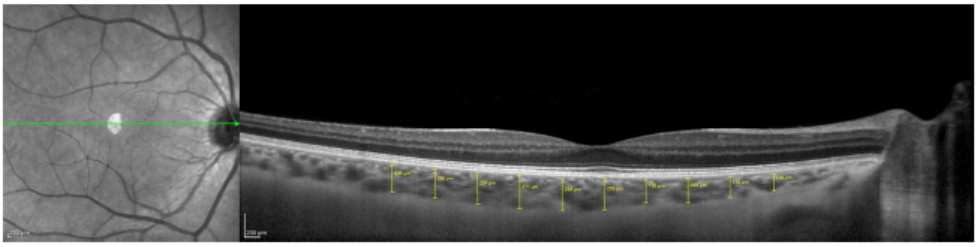

Fig. 1 Measurements of choroidal thickness. Choroidal thickness measured at ten different locations: at the fovea and every 500 µm from the fovea up to 2500 µm temporally and up to 2000 µm nasally

Results

This study included 68 eyes of 34 healthy non-pregnant women (Control Group) and 54 eyes of 27 healthy pregnant women in the third trimester (Pregnant Group). Mean age of non-pregnant and pregnant women was 26.8 ± 5.0 and 28.1 ± 7.0 years, respectively (p = 0.439; t test). Racial distribution included 31 (91.2%) caucasians and 3 (8.8%) african-american in control group and 25 (92.6%) caucasians and 2 (7.4%) african-american in pregnant group (p = 1.000; Fisher's exact test). The mean gestational age in the pregnant group was 33.3 ± 2.6 weeks.

The OCT scans were performed in all 54 eyes of the 27 healthy pregnant women and in all 68 eyes of the 34 healthy non-pregnant women. There were no significant differences in the ten measurements of choroidal thickness across the groups. (Table 1) Mean subfoveal choroidal thickness was 304.1 + 9.6 µm in the control group and 318.1 + 15.6 µm in the pregnant group (p = 0.446).

We also analyzed if there was any correlation between the choroidal thickness measurements of both eyes and the gestational week in the third trimester of gestation using Pearson's correlation. There was no statistically significant association between the gestational week and choroidal thickness measurements of both eyes in healthy pregnant women in the third trimester (Table 2).

Discussion

The choroid is a complex vascular network which provides vascular supply for the retinal pigment epithelium and outer retina layers. It also provides thermal stability for the ocular tissues, removes ocular waste and acts in the uveoscleral aqueous drainage and regulation of intraocular pressure [4, 16]. Choroidal circulation is characterized by a high blood flow controlled by autonomic innervation, while retinal blood flow is mainly determined by autoregulatory mechanisms and local factors [17]. This vascular network is responsible for more than 85% of the blood flow in the eye and it can be influenced by hemodynamic factors such as blood flow and perfusion pressure [18].

Table 1 Choroidal thickness measurements of healthy pregnant women in the third trimester and control group

	Control group Mean + SE (µm)	Pregnant group Mean + SE (µm)	p value
T5	277.4 + 9.6	278.5 + 13.9	0.949
T4	284.8 + 10.1	291.5 + 15.2	0.716
T3	292.1 + 9.8	300.9 + 14.3	0.611
T2	301.7 + 8.9	308.2 + 14.8	0.708
T1	299.1 + 8.6	311.2 + 14.8	0.478
SF	304.1 + 9.6	318.1 + 15.6	0.446
N1	285.1 + 9.6	291.3 + 14.9	0.730
N2	270.3 + 10.6	267.1 + 14.7	0.860
N3	245.6 + 10.9	239.4 + 13.9	0.725
N4	213.5 + 11.5	210.2 + 12.2	0.843

GEE with Bonferroni adjustment

T5: choroidal thickness at 2500 µm temporally to the fovea; T4: choroidal thickness at 2000 µm temporally to the fovea; T3: choroidal thickness at 1500 µm temporally to the fovea; T2: choroidal thickness at 1000 µm temporally to the fovea; T1: choroidal thickness at 500 µm temporally to the fovea; SF: choroidal thickness at the fovea; N1: choroidal thickness at 500 µm nasally to the fovea; N2: choroidal thickness at 1000 µm nasally to the fovea; N3: choroidal thickness at 1500 µm nasally to the fovea; N4: choroidal thickness at 2000 µm nasally to the fovea

Pregnancy itself promotes metabolic, hormonal and hemodynamic changes which could lead to changes in choroidal blood flow. During pregnancy there is an expansion of blood volume up to 45%, an increase in cardiac output and renin and angiotensin levels, and a decrease in colloid osmotic pressure, vascular resistance and arterial blood pressure [1, 3]. There are also some conditions such as central serous chorioretinopathy (CSC) which has an increased prevalence during pregnancy, especially in the third trimester [7, 19]. Previous studies have shown that patients with CSC have thickening of choroid when compared to controls [20, 21]. Choroidal vasodilation and vascular hyperpermeability can cause subsequent vascular leakage and increased hydrostatic pressure in the choroid. The high plasma cortisol concentration may also be a contributor for CSC development in pregnancy. All considered, it is essential to ask whether pregnancy itself can change choroidal structure and thickness.

Traditional imaging modalities such as indocyanine green angiography and Doppler ultrasonography were used in the past to assess choroidal function during pregnancy [9, 22]. The development of EDI-OCT, however, provided a fast, noninvasive and safe method to analyze choroidal thickness. Choroidal thickness can be influenced by major factors such as age, refractive error and axial length (AL), with increasing age, AL and decreasing refractive diopter being associated with a reduction of choroidal thickness [23]. Previous authors have measured choroidal thickness during pregnancy, with conflicting results [16, 24–32]. Different methodology may justify these different results. Table 3 summarizes results of different studies comparing choroidal thickness measurements of healthy pregnant and non-pregnant women using EDI-OCT.

Kara et al. [24], Sayin et al. [25] and Atas et al. [26] conducted studies comparing choroidal thickness of healthy pregnant women in different gestational ages with healthy non-pregnant women. The authors concluded that subfoveal choroid was significantly thicker in pregnant women. However, other studies did not find this difference in choroid thickness. Takahashi et al. [27] and Kim et al. [28] demonstrated that choroidal thickness was not significantly different when comparing pregnant

Table 2 Correlation of gestational week and choroidal thickness measurements of both eyes in third trimester healthy pregnancies

	Pearson correlation coeficiente (r)	p value
T5		
OD	− 0.345	0.085
OS	− 0.202	0.322
T4		
OD	− 0.228	0.263
OS	− 0.167	0.414
T3		
OD	− 0.234	0.250
OS	− 0.093	0.650
T2		
OD	− 0.223	0.274
OS	− 0.073	0.723
T1		
OD	− 0.200	0.327
OS	− 0.141	0.492
SF		
OD	− 0.193	0.345
OS	− 0.213	0.295
N1		
OD	− 0.237	0.243
OS	− 0.216	0.289
N2		
OD	− 0.199	0.330
OS	− 0.180	0.378
N3		
OD	− 0.144	0.482
OS	− 0.149	0.468
N4		
OD	− 0.089	0.665
OS	− 0.143	0.487

T5: choroidal thickness at 2500 µm temporally to the fovea; T4: choroidal thickness at 2000 µm temporally to the fovea; T3: choroidal thickness at 1500 µm temporally to the fovea; T2: choroidal thickness at 1000 µm temporally to the fovea; T1: choroidal thickness at 500 µm temporally to the fovea; SF: choroidal thickness at the fovea; N1: choroidal thickness at 500 µm nasally to the fovea; N2: choroidal thickness at 1000 µm nasally to the fovea; N3: choroidal thickness at 1500 µm nasally to the fovea; N4: choroidal thickness at 2000 µm nasally to the fovea

women in their third trimester and healthy non-pregnant women.

Other authors attempted to evaluate choroidal thickness considering gestational age. Goktas et al. [29] conducted a study with 90 healthy pregnant women, 30 at each pregnancy trimester, and 30 non-pregnant healthy women. Choroidal was significantly thicker in second trimester pregnant women in comparison with non-pregnant women. Dadaci et al. [30] compared choroidal thickness measurements of 54 eyes of 27 healthy pregnant women with 50 eyes of 25 non-pregnant women. The pregnant women underwent two OCT scans, one in the first trimester and the other in the third trimester. Choroidal thickness was significantly decreased at all measured points during the third trimester compared to the first trimester. The measurements of the control group were not statistically different.

Ulusoy et al. [16] conducted a prospective study to analyze choroidal thickness in third trimester pregnant women and 3 months after delivery. The subfoveal choroidal thickness was significantly reduced after delivery. A different control group of non-pregnant women was also analyzed and showed significantly thinner choroid measurements in comparison with pregnant women. Rothwell et al. [31] used a different technique to analyze choroid structure by constructing volume macular maps for the 9 subfields defined by the Early Treatment Diabetic Retinopathy Study. The measurements of thickness and volume in the central subfield were significantly greater in third trimester pregnant patients than in non-pregnant patients.

In this study, there were no significant differences in choroidal thickness among the two groups in ten macular points. We also found no significant correlation between choroid thickness and gestational age. These findings did not confirm our initial hypothesis that choroid could be thicker at pregnancy by an overall increase in choroidal blood flow and a decrease in intraocular pressure. However, the results of other studies about choroidal thickness during uncomplicated pregnancy are conflicting, and our findings are similar to those of Takahashi [27] and Kim [28].

Our study has some limitations, such as the small number of subjects. In addition, the cross-sectional design allow us to analyze choroid characteristics only in the third trimester of pregnancy, which could explain our lack of difference, since some authors described thicker choroids specifically at first or second trimesters. More consistent results could be achieved with a longitudinal study of choroidal thickness during the three trimesters of pregnancy and postpartum period with a large number of subjects.

In conclusion, our study reinforces absence of statistical difference in choroidal thickness between healthy third trimester pregnant women and healthy non-pregnant women. Further prospective studies with a larger number of subjects should be performed during different gestational ages and also after delivery.

Table 3 Summarized results of different studies comparing choroidal thickness measurements of healthy pregnant and non-pregnant women using EDI-OCT

References	Subjects	Gestational age at exam	Mean subfoveal choroidal thickness (SFCT)	Conclusion
Takahashi et al. [27]	30 pregnant women 30 non-pregnant women	Third trimester	275 ± 84 µm 273 ± 92 µm	No significant difference in choroidal thickness between groups ($p = 0.925$)
Sayin et al. [25]	46 pregnant women 40 non-pregnant women	Variable 28.0 ± 5.8 weeks (range: 17–37 weeks)	368.6 ± 67.6 µm 334.8 ± 59.9 µm	SFCT in normal pregnant women was significantly thicker than in non-pregnant healthy women ($p = 0.038$)
Kara et al. [24]	100 pregnant women 100 non-pregnant women	Variable 27.3 ± 6.6 weeks (range: 15–38 weeks)	371.1 ± 61.8 µm 337.2 ± 62.4 µm	SFCT in normal pregnant women was significantly thicker than in non-pregnant healthy women ($p < 0.01$)
Atas et al. [26]	25 pregnant women 26 non-pregnant women	Over 28 weeks	387.2 ± 60.76 µm 322.35 ± 63.89 µm	SFCT in normal pregnant women was significantly thicker than in non-pregnant healthy women ($p < 0.001$)
Goktas et al. [29]	30 pregnant women in the first trimester 30 pregnant women in the second trimester 30 pregnant women in the third trimester 30 non-pregnant women	First trimester Second trimester Third trimester	362 ± 81 µm 395 ± 80 µm 368 ± 70 µm 335 ± 86 µm	SFCT was significantly thicker in pregnant women in the second trimester ($p = 0.007$)
Ulusoy et al. [16]	29 pregnant women 36 non-pregnant women	Third trimester 3 months after delivery	387.97 ± 59.91 µm 332.40 ± 26.02 µm 320.86 ± 59.18 µm	SFCT significantly increases during pregnancy and returns to normal range 3 months after delivery
Kim et al. [21]	14 pregnant women 21 non-pregnant women	Third trimester	274.23 ± 29.30 µm 264.95 ± 21.03 µm	No significant difference in choroidal thickness between groups ($p = 0.325$)
Dadaci et al. [30]	27 pregnant women 25 non-pregnant women	First trimester Third trimester	OD: 349.22 ± 82.11 µm OE: 341.30 ± 85.22 µm OD: 333.56 ± 76.61 µm OE: 326.93 ± 75.84 µm OD: 318.88 ± 53.13 µm OE: 310.60 ± 51.09 µm	Choroidal thickness measurements in the third trimester were significantly decreased in both eyes compared to first trimester measurements
Rothwell et al. [31]	12 pregnant women 12 non-pregnant women	Third trimester	319.58 ± 6.11 µm 287.58 ± 43.44 µm	Choroidal thickness in normal pregnant women was significantly thicker than in non-pregnant healthy women ($p = 0.034$)
Acmaz et al. [32]	24 pregnant women 38 non-pregnant women	After 24 weeks	393.77 ± 61.83 µm 322.49 ± 65.58 µm	Choroidal thickness in normal pregnant women was significantly thicker than in non-pregnant healthy women ($p < 0.001$)

Authors' contributions
CZB participated of the conception, acquisition and analysis of data and drafting of the manuscript. TZ contributed selecting subjects from prenatal care. LBF assisted in the ophthalmological exams. MLRO, LHC and DL analyzed and interpreted the patient data and contributed in writing the manuscript. All authors read and approved the final manuscript.

Author details
[1] Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil. [2] Department of Ophthalmology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. [3] Department of Gynecology and Obstetrics, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. [4] Department of Endocrinology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil.

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Not applicable.

Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors report no conflicts of interests.

Consent for publication
Consent for publication was obtained from the participant whose OCT image was used for Fig. 1.

Ethics approval and consent to participate
All participants received in person full explanation about the study and provided written informed consent. This study was approved by Hospital de Clinicas de Porto Alegre research ethics committee (CAAE 33897314.1.0000.5327) and was conducted in accordance with the Declaration of Helsinki guidelines.

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2.2 CAPÍTULO 2

MACULAR CHOROIDAL THICKNESS IN PREGNANT WOMEN WITH TYPE 1, TYPE 2 AND GESTATIONAL DIABETES MELLITUS MEASURED BY SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY.

Clinical Ophthalmology

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ORIGINAL RESEARCH

Macular choroidal thickness in pregnant women with type 1, type 2 and gestational diabetes mellitus measured by spectral-domain optical coherence tomography

This article was published in the following Dove Press journal:
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Camila Zanella Benfica[1,2]
Teresinha Zanella[3]
Lucas Brandolt Farias[1,2]
Maria Lúcia Rocha Oppermann[1,3]
Luis Henrique Santos Canani[1,4]
Daniel Lavinsky[1,2]

[1]Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil; [2]Department of Ophthalmology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [3]Department of Gynecology and Obstetrics, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [4]Department of Endocrinology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Purpose: To analyze choroidal thickness (CT) of pregnant women with type 1 diabetes mellitus (DM), type 2 DM and gestational diabetes mellitus (GDM) using spectral-domain optical coherence tomography.

Patients and methods: This cross-sectional study included 144 eyes of 72 pregnant women in the third trimester divided into four groups: 27 non-diabetic pregnant women; 15 pregnant women with GDM; 16 with type 2 DM and 14 with type 1 DM. CT was measured using optical coherence tomography at ten different locations. We also analyzed possible confounding factors, such as gestational age, glycosylated hemoglobin, time from DM diagnosis, hypertension and severity of diabetic retinopathy.

Results: The comparison between the four groups showed a thinner choroid in patients with type 1 DM in all locations, with statistical significance in subfoveal and temporal measurements. When comparing only patients with type 1 and type 2 DM, adjusting for confounding factors, the choroid of patients with type 1 DM remained thinner at all macular points, also with statistical significance in subfoveal and temporal measurements.

Conclusion: Pregnant women with type 1 DM had significantly thinner CT measurements on subfoveal and temporal locations. No differences were found in CT between the control group and pregnant women with GDM and type 2 DM.

Keywords: choroid, enhanced depth imaging optical coherence tomography, pregnancy, gestational diabetes mellitus, diabetes mellitus

Introduction

Diabetic retinopathy (DR) is a major cause of visual impairment in women during their childbearing years. It is known that pregnancy is an independent risk factor for DR progression,[1–3] and its implications can persist for the first year after delivery. Other risk factors include glycemic control, duration of diabetes, baseline level of DR, hypertension and preeclampsia.[4,5] Previous reports, however, suggest that rapid optimization in glucose control may result in an increased risk for the progression of DR during pregnancy.[3,4]

The reasons why pregnancy itself causes a worsening in DR are still being questioned. A possible relation with morphological changes of the choroid should be studied. Diabetic choroidopathy, first reported by Hidayat and Fine in 1985,[6] might be present before the onset of DR.[7] Several choroidal changes have been described

Correspondence: Camila Zanella Benfica
Universidade Federal do Rio Grande do Sul, Ramiro Barcelos, 2400 Porto Alegre, Brazil
Tel +55 51 9 9712 6309
Email camilazbenfica@gmail.com

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in diabetic patients, including microaneurysms, dilatation and obstruction of the choriocapillaris, increased vascular tortuosity, vascular dropouts, areas of vascular non-perfusion and choroidal neovascularization.[8]

The development of the enhanced depth imaging (EDI) technique of spectral-domain optical coherence tomography (SD-OCT) systems have allowed adequate analysis of choroidal morphologic features in normal and pathological eyes.[9] EDI-OCT dramatically increases image resolution of the choroid by decreasing signal strength posterior to the retinal pigment epithelium. Although many authors have reported a decrease in choroidal thickness (CT) among diabetic patients,[10–15] there are some discordant studies.[7,16,17]

The presence of choroidal changes related to pregnancy is also being investigated. The strong correlation between central serous chorioretinopathy (CSC) and pregnancy is well documented.[18,19] Choroidal dysfunction and ischemia are also a common ocular complication of preeclampsia.[20–22] Since it is a noninvasive diagnostic method, OCT is ideal for the study of choroidal changes in pregnant women. Some studies have already analyzed CT in healthy pregnant women using OCT,[23–28] but the results are still inconclusive.

The aim of this study was to analyze CT measurements of non-diabetic pregnant women and of pregnant women with type 1, type 2 and gestational diabetes mellitus (GDM) using SD-OCT.

Patients and methods

This cross-sectional study included 144 eyes of 72 pregnant women in the third trimester divided into four groups: Group 1 consisted of 27 non-diabetic pregnant women (control group); Group 2 consisted of 15 pregnant women with GDM; Group 3 consisted of 16 pregnant women with type 2 diabetes mellitus (type 2 DM) and Group 4 consisted of 14 pregnant women with type 1 diabetes mellitus (type 1 DM). The participants were recruited between March and September 2016 at the Hospital de Clinicas de Porto Alegre (HCPA), Brazil. All participants received in person a full explanation about the study and provided written informed consent. This study was approved by the HCPA research ethics committee and was conducted in accordance with the Declaration of Helsinki guidelines.

All participants were receiving prenatal care at HCPA and were in their third trimester of singleton pregnancy. Subjects with a history of laser photocoagulation, anti-vascular endothelial growth factor (VEGF) treatment, ocular surgery or any ocular pathology except for DR were excluded. Refractive disorders with spherical equivalent greater than ±1.0 diopters, intraocular pressure higher than 21 mmHg or best-corrected visual acuity worse than 0,1 logMAR were also exclusion criteria. Participants with preeclampsia, multiple pregnancies, renal or rheumatological diseases or history of smoking were also excluded.

The criteria used for GDM diagnosis followed the International Association of Diabetes in Pregnancy Study Groups (IADPSG) recommendations.[29] We analyzed the glycosylated hemoglobin A1c (HbA1c) of all diabetic patients; the blood samples for HbA1c were collected within 30 days of the ophthalmic exam. DR grading was performed according to the international severity scale:[30] mild nonproliferative DR (microaneurysms only); moderate nonproliferative DR (more than just microaneurysms but less than severe nonproliferative DR); severe nonproliferative DR (more than 20 intraretinal hemorrhages in each of four quadrants or venous beading in two quadrants or prominent intraretinal microvascular abnormalities in 1 quadrant) and proliferative DR (neovascularization or vitreous/preretinal hemorrhage). The diagnosis for each individual was based on the grading of the worse eye per subject. Only treatment-naive patients were included.

All study participants underwent an interview with demographic and background history. The ophthalmic examination included uncorrected visual acuity, best-corrected visual acuity, Goldmann applanation tonometry, slit-lamp assisted biomicroscopy, indirect ophthalmoscopy and SD-OCT. All OCT scans were performed in the morning (8:00 am to 12:00 pm) to avoid diurnal variations of CT. The same experienced ophthalmologist (CB) performed all ophthalmic examinations and OCT scans, using Heidelberg Spectralis OCT (Heidelberg Engineering Co, Heidelberg, Germany). Choroid was imaged with a 6-line radial scan (30°, 9.2 mm) using the EDI setting, with 100 images averaged per section. All scans were reviewed before being included in the study. Those with image artefacts or inaccurate choroidal limits were excluded.

CT was determined as the vertical distance from the outer surface of the line formed by the retinal pigment epithelium to the chorioscleral interface using the Spectralis OCT measurement software. The measurements were made by an experienced ophthalmologist (DL) masked to the participant group. Previous studies have already demonstrated the reproducibility of this technique, even across different OCT systems.[31–33] CT was measured at ten different locations: at the fovea and every 500 µm from the fovea up to 2,500 µm temporally and up to 2,000 µm nasally (Figure 1). We used the following abbreviations

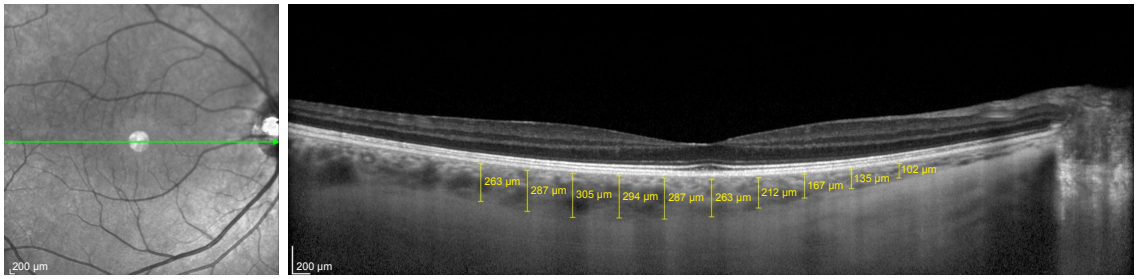

Figure 1 Measurements of choroidal thickness at 10 locations.

for the macular points: T5: CT at 2,500 µm temporally to the fovea; T4: CT at 2,000 µm temporally to the fovea; T3: CT at 1,500 µm temporally to the fovea; T2: CT at 1,000 µm temporally to the fovea; T1: CT at 500 µm temporally to the fovea; SF: CT at the fovea; N1: CT at 500 µm nasally to the fovea; N2: CT at 1,000 µm nasally to the fovea; N3: CT at 1,500 µm nasally to the fovea and N4: CT at 2,000 µm nasally to the fovea.

Statistical analysis

Statistical analyses were performed using SPSS V.15.0 (SPSS Science, Chicago, IL, USA). Quantitative variables were presented as mean (±SD) or median and interquartile range. Categorical variables were described by absolute and relative frequencies. To compare means between groups, analysis of variance (ANOVA) complemented by Tukey was applied. In case of asymmetry, Mann–Whitney and Kruskal–Wallis tests were used. For qualitative data, a chi-squared test was used. Differences in CT were analyzed using generalized estimating equations (GEE) with Bonferroni adjustment. A p-value ≤ 0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of the subjects are summarized in Table 1. The OCT scans were performed in 54 eyes of 27 healthy pregnant women, 30 eyes of 15 pregnant women with GDM, 32 eyes of 16 pregnant women with type 2 DM and 28 eyes of 14 pregnant women with type 1 DM. There was no significant difference in age, ethnicity and gestational age between groups. As expected, time from DM diagnosis was significantly higher in subjects with type 1 DM in comparison with subjects with type 2 DM. HbA1c values were significantly higher

Table 1 Demographic and clinical characteristics of the study and control groups

Clinical features	Nondiabetic group (n=27)	GDM group (n=15)	Type 2 DM group (n=16)	Type 1 DM group (n=14)	*p*-value
Age (years) Mean ± SD	28.1 ± 7.0	31.9 ± 5.8	31.4 ± 6.0	28.1 ± 6.6	0.177[a]
Ethnicity, n (%)					
Caucasian	25 (92.6)	10 (66.7)	13 (81.3)	13 (92.9)	0.209[b]
African-American	2 (7.4)	5 (33.3)	3 (18.8)	1 (7.1)	
Gestational age (weeks) Mean ± SD	33.3 ± 2.6	33.7 ± 3.19	32.0 ± 3.6	31.7 ± 3.0	0.183[a]
Time from DM diagnosis (years) Median (P25–P75)			1.5 (0.9–4.5)	13.5 (5–20)	<0.001[c]
HbA1c (%) Mean ± SD		5.7 ± 0.8[a]	6.6 ± 1.7[a,b]	7.4 ± 1.2[b]	0.006[a]
Hypertension, n (%)	0 (0)	2 (13.3)	6 (37.5)	0 (0)	0.001[b]
Diabetic retinopathy, n (%)			1 (6.3%)	6 (42.9%)	0.031[d]

Notes: [a]Analysis of variance (ANOVA); [b]Chi-squared test; [c]Mann–Whitney test; a,b same letter does not differ from each other at a 5% of significance by Tukey test; [d]Fisher's exact test.

Abbreviations: DM, diabetes mellitus; GDM, gestational diabetes mellitus.

Table 2 Comparison of CT measurements of all groups; adjusted for the presence of hypertension

Location	Nondiabetic group (n=27), mean ± SE (μm)	GDM group (n=15), mean ± SE (μm)	Type 2 DM group (n=16), mean ± SE (μm)	Type 1 DM group (n=14), mean ± SE (μm)	*p*-value (adjusted for hypertension)
T5	250.9 ± 16.3[a,b]	260.2 ± 12.7[b]	242.4 ± 11.2[a,b]	212.7 ± 15.1[a]	0.049
T4	269.4 ± 18.0[a,b]	273.4 ± 15.4[b]	252.9 ± 12.1[a,b]	226.6 ± 14.1[a]	0.026
T3	277.8 ± 16.4[b]	283.5 ± 15.7[b]	274.9 ± 10.2[a,b]	232.2 ± 12.2[a]	0.007
T2	283.9 ± 17.7[a,b]	294.5 ± 16.7[b]	288.8 ± 12.2[a,b]	240.6 ± 14.7[a]	0.015
T1	287.1 ± 18.4[a,b]	304.8 ± 17.4[b]	304.3 ± 14.3[a,b]	248.2 ± 15.6[a]	0.014
SF	293.9 ± 19.0[a,b]	311.3 ± 19.6[a,b]	318.4 ± 14.0[b]	255.1 ± 15.5[a]	0.014
N1	267.2 ± 20.2	294.3 ± 23.4	291.7 ± 16.2	242.7 ± 16.3	0.067
N2	243.4 ± 19.0	274.3 ± 20.9	282.8 ± 14.9	231.7 ± 15.1	0.106
N3	217.6 ± 17.6	242.1 ± 18.7	257.2 ± 14.4	218.6 ± 14.7	0.338
N4	190.0 ± 15.6	222.9 ± 18.2	227.0 ± 12.6	191.5 ± 13.5	0.190

Note: [a,b]Same letter does not differ from each other at a 5% of significance by GEE with Bonferroni adjustment.

Abbreviations: CT, choroidal thickness; DM, diabetes mellitus; GDM, gestational diabetes mellitus; N1, choroidal thickness at 500 μm nasal to the fovea; GEE, generalized estimating equations; N2, choroidal thickness at 1,000 μm nasal to the fovea; N3, choroidal thickness at 1,500 μm nasal to the fovea; N4, choroidal thickness at 2,000 μm nasal to the fovea; SF, choroidal thickness at the fovea; T1, choroidal thickness at 500 μm temporal to the fovea; T2, choroidal thickness at 1,000 μm temporal to the fovea; T3, choroidal thickness at 1,500 μm temporal to the fovea; T4, choroidal thickness at 2,000 μm temporal to the fovea; T5, choroidal thickness at 2,500 μm temporal to the fovea.

in patients with type 1 DM (7.4% ± 1.2%) compared with GDM patients (5.7% ± 0.8%) (p=0.06). Two patients from group 2 and six patients from group 3 had chronic hypertension diagnosis (p=0.001), requiring adjustment in CT analysis.

Of the 14 subjects with type 1 DM, 6 (42.9%) were diagnosed with DR (1 mild nonproliferative, 4 moderate nonproliferative and 1 proliferative DR). In comparison, only one patient (6.3%) with type 2 DM was diagnosed with moderate nonproliferative retinopathy (p=0.031). None of the subjects with DR had macular edema on OCT and all of them were treatment-naive at the time of the exam.

Comparing the 10 CT measurements of the four groups, adjusted for the presence of hypertension, the choroid always tended to be thinner in patients with type 1 DM. There was no significant differences between nondiabetic, GDM and type 2 DM groups. From macular points T5 to T1, macular thickness was significantly higher in pregnant women with GDM in comparison with pregnant women with type 1 DM. In the subfoveal measurement, however, macular thickness was significantly higher in pregnant women with type 2 DM in comparison with pregnant women with type 1 DM. No measures nasal to the fovea were statistically different between the groups. All measurements and p-values are shown in Table 2.

When we analyzed only the groups with diabetic patients, adjusting also for HbA1c levels, the choroid was thinner in patients with type 1 DM in comparison with patients with GDM or type 2 DM (Table 3). CT measurements in T5, T3, T2, T1 and SF macular points were significantly thinner in patients with type 1 DM in comparison with patients with GDM and type 2 DM. The choroid in T4 and N1 macular points, however, was significantly thinner in patients with type 1 DM only in comparison with patients with DMG. No statistically significant difference between groups was found at the N2, N3 and N4 macular points.

In order to analyze CT adjusting also for time of DM diagnosis and presence of DR, we also performed an analysis only between the type 1 DM and type 2 DM groups (Table 4). CT of patients with type 1 DM remained thinner than in patients with type 2 DM at all macular points, but with statistical significance only in T4, T3, T2, T1 and SF points.

Discussion

The choroid is a complex vascular network which provides vascular supply for the retinal pigment epithelium and outer retina layers, representing the sole provider of oxygen and nutrients to the avascular fovea. This vascular network is responsible for more than 85% of the blood flow in the eye. Unlike the retina, autoregulation of choroidal blood flow is limited and it has intense autonomic innervation. Abnormal choroidal blood flow can result in photoreceptor dysfunction and death.[34,35]

CT is influenced by major factors such as age, refractive error and axial length (AL), with increasing age, AL and decreasing refractive diopter being associated with a reduction of CT.[36] Diurnal variations in CT have also been reported.[37,38] Although choroidal thickness has more precise characteristics in some diseases such as CSC and age-related macular degeneration (AMD), choroidal changes in diabetic patients have been studied and controversial results have been published.

Table 3 Comparison of CT measurements of pregnant patients with GDM, type 1 DM and type 2 DM, adjusted for HbA1c values and for the presence of hypertension

Location	GDM group (n=15), mean ± SE (μm)	Type 2 DM group (n=16), mean ± SE (μm)	Type 1 DM group (n=14), mean ± SE (μm)	*p*-value (adjusted for HbA1c and hypertension)
T5	271.5 ± 43.3[b]	243.5 ± 35.7[b]	209.4 ± 39.2[a]	0.002
T4	287.9 ± 47.7[b]	254.2 ± 38.6[a,b]	222.4 ± 42.5[a]	0.001
T3	397.6 ± 59.4[b]	276.4 ± 56.1[b]	227.9 ± 51.6[a]	<0.001
T2	311.7 ± 75.3[b]	290.4 ± 74.0[b]	235.5 ± 64.0[a]	0.001
T1	221.1 ± 77.3[b]	305.8 ± 76.7[b]	243.4 ± 66.0[a]	0.002
SF	327.1 ± 85.9[b]	319.9 ± 88.9[b]	250.4 ± 72.6[a]	0.005
N1	310.5 ± 104.6[b]	293.2 ± 106.1[a,b]	237.8 ± 86.1[a]	0.037
N2	284.1 ± 105.4	284.1 ± 107.4	228.5 ± 86.7	0.081
N3	248.7 ± 100.6	258.4 ± 100.5	216.4 ± 83.3	0.244
N4	223.8 ± 80.5	227.8 ± 77.4	190.8 ± 66.6	0.188

Note: [a,b]Same letter does not differ from each other at a 5% of significance by GEE with Bonferroni adjustment.
Abbreviations: CT, choroidal thickness; DM, diabetes mellitus; GDM, gestational diabetes mellitus; GEE, generalized estimating equations; HbA1c, glycosylated hemoglobin A1c; N1, choroidal thickness at 500 μm nasal to the fovea; N2, choroidal thickness at 1,000 μm nasal to the fovea; N3, choroidal thickness at 1,500 μm nasal to the fovea; N4, choroidal thickness at 2,000 μm nasal to the fovea; SF, choroidal thickness at the fovea; T1, choroidal thickness at 500 μm temporal to the fovea; T2, choroidal thickness at 1,000 μm temporal to the fovea; T3, choroidal thickness at 1,500 μm temporal to the fovea; T4, choroidal thickness at 2,000 μm temporal to the fovea; T5, choroidal thickness at 2,500 μm temporal to the fovea.

Recent studies conducted by Yazici et al[7] and Tavares Ferreira et al[16] found that the choroid is thicker in diabetic patients. The population-based Beijing Eye study[17] also found that DM can lead to a slight thickening of the choroid, although not related to the severity of DR. Yulek et al concluded that subfoveal CT was not significantly correlated with increased duration of diabetes.[39] Regatieri et al,[10] however, reported a thinner CT in patients with diabetic macular edema or treated proliferative DR compared with normal subjects. Vujosevic et al,[11] Esmaeelpour et al,[12,13] Querques et al[14] and Shen et al[15] also demonstrated that CT decreases in diabetic eyes with clinical signs of DR compared with controls.

Table 4 Comparison of CT measurements of pregnant patients with type 1 DM and type 2 DM; adjusted for HbA1c values and the presence of hypertension

Location	Type 2 DM group (n=16), mean ± SE (μm)	Type 1 DM group (n=14), mean ± SE (μm)	*p*-value (adjusted for HbA1c, time of DM diagnosis and presence of diabetic retinopathy and hypertension)
T5	244.7 ± 86.5	211.2 ± 83.3	0.051
T4	255.6 ± 78.9	221.9 ± 76.2	0.026
T3	274.6 ± 87.8	234.8 ± 75.4	0.034
T2	287.8 ± 112.9	242.6 ± 95.8	0.047
T1	303.5 ± 117.6	248.0 ± 100.9	0.022
SF	320.8 ± 132.1	249.6 ± 110.2	0.007
N1	295.9 ± 155.4	240.3 ± 127.6	0.079
N2	285.2 ± 153.4	225.3 ± 126.9	0.053
N3	260.2 ± 153.9	206.1 ± 129.5	0.083
N4	220.8 ± 122.7	186.6 ± 101.9	0.199

Note: GEE with Bonferroni adjustment.
Abbreviations: CT, choroidal thickness; DM, diabetes mellitus; GEE, generalized estimating equations; HbA1c, glycosylated hemoglobin A1c; N1, choroidal thickness at 500 μm nasal to the fovea; N2, choroidal thickness at 1,000 μm nasal to the fovea; N3, choroidal thickness at 1,500 μm nasal to the fovea; N4, choroidal thickness at 2,000 μm nasal to the fovea; SF, choroidal thickness at the fovea; T1, choroidal thickness at 500 μm temporal to the fovea; T2, choroidal thickness at 1,000 μm temporal to the fovea; T3, choroidal thickness at 1,500 μm temporal to the fovea; T4, choroidal thickness at 2,000 μm temporal to the fovea; T5, choroidal thickness at 2,500 μm temporal to the fovea.

The aim of this study was to analyze these possible changes in CT in diabetic patients during pregnancy. Since pregnancy is an independent risk factor for the progression of DR, we questioned if possible changes in the choroid may contribute to this progression. There is limited data on this issue and to the best of our knowledge this is the first study to compare CT in pregnant women with type 1 and type 2 DM. Acmaz et al[40] reported that CT was significantly thicker in healthy pregnant women and women with GDM in comparison with non-pregnant women. However, there was no significant difference between the GDM group and the healthy pregnant women group.

As pregnancy itself could lead to physiological changes in the choroid, our control group consisted of nondiabetic pregnant women. In this study, we found no difference in CT between non-diabetic pregnant women, women with GDM and pregnant women with type 2 DM. Pregnant women with type 1 DM, however, had smaller CT measurements at all points analyzed.

This choroid thinning in patients with type 1 DM was more significant in the measurements located temporally to the fovea. Measurements of CT nasally to the fovea were not statistically different.

We also performed this analysis only among diabetic patients to enable adjustment for HbA1c, with similar results. When we compared only pregnant women with type 1 and type 2 diabetes, adjusting also for time of diabetes and presence of retinopathy, CT remained significantly thinner in subjects with type 1 DM between T4 and SF points.

Despite being a controversial subject, most of the available evidence seems to indicate that choroid thins in diabetic eyes.[41] According to our findings, pregnant subjects with type 1 DM also followed this thinning pattern. The significantly higher prevalence of DR found in these patients may have contributed to this finding. It is possible to hypothesize that choroidal thinning in type 1 pregnant diabetic patients occurs as part of diabetic choroidopathy modifications. The decreased choroidal blood flow found in diabetic patients,[42–44] along with changes such as atrophy and dropout of the choriocapillaris,[6,45] could contribute to this thinning. It remains to be understood how these ocular blood flow abnormalities seen in diabetic patients are influenced by pregnancy hyperflow and whether these modifications could contribute to the DR progression seen in pregnancy.

Since CT measurements may be susceptible to several confounding factors, we tried to minimize possible biases. The examinations were performed only in the morning shift to avoid diurnal variations, and patients with refractive disorders with spherical equivalent greater than ±1.0 diopters were excluded. Exams without clear identification of the choroid-scleral junction were also excluded from the analysis. Since laser photocoagulation and anti-VEGF treatments may change CT,[10,41,46] only treatment-naive patients were included. None of the subjects with DR had macular edema on OCT.

Our study also has some limitations, such as the small number of subjects. Its cross-sectional design allow us to analyze choroid characteristics only from the third trimester of pregnancy. Further prospective studies with a larger number of subjects should be performed to confirm these findings.

Conclusion

Our study showed no statistically significant difference in CT between non-diabetic pregnant women, pregnant women with GDM and pregnant women with type 2 DM during the third trimester. Pregnant women with type 1 DM had significantly thinner CT measurements on subfoveal and temporal to the fovea analysis.

Disclosure

The authors report no conflicts of interest in this work.

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2.3 CAPÍTULO 3

CHOROIDAL THICKNESS IN PREECLAMPSIA MEASURED BY SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY.

Original Article:

CHOROIDAL THICKNESS IN PREECLAMPSIA MEASURED BY SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY

Camila Zanella Benfica[a,b]; Teresinha Zanella[c]; Lucas Brandolt Farias[a,b]; Maria Lúcia Rocha Oppermann[a,c]; Luis Henrique Santos Canani[a,d]; Daniel Lavinsky[a,b]

[a] Universidade Federal do Rio Grande do Sul (UFRGS)

[b] Department of Ophthalmology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

[c] Department of Gynecology and Obstetrics, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

[d] Departament of Endocrinology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Corresponding author at:
Camila Zanella Benfica (camilazbenfica@gmail.com)
Cabral 732/1204 Porto Alegre, RS, Brazil
90420-121
Phone: +55 51 997126309
ORCID: 000-0001-9390-9958

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ABSTRACT

Purpose: To compare choroidal thickness (CT) measurements in preeclamptic and healthy women in the third trimester of pregnancy using optical coherence tomography (OCT).

Methods: This cross-sectional study included 148 eyes of 74 women, divided into two groups: 27 healthy pregnant women in the third trimester (control group) and 47 age matched pregnant women in the third trimester with preeclampsia (PE group). Of the 47 subjects in preeclampsia group, 26 were classified as having mild PE and 21 as having severe PE. Choroidal thickness was measured at ten different locations: at the fovea and every 500μm from the fovea up to 2500μm temporally and up to 2000μm nasally.

Results: Comparing CT of both groups, choroid always tended to be thicker in subjects with preeclampsia in comparison with healthy pregnant women, with statistical significance in nasal measures. Dividing PE group accordingly disease severity, women with severe preeclampsia tended to have tchicker choroids in comparison with mild preeclamptic and healthy pregnant women. Choroid was also significantly thicker in preeclamptic patients with serous retinal detachment (SRD) in comparison with preeclamptic patients without SRD ($p<0,01$ in all macular points).

Conclusion: Our study showed that choroid tends to be thicker in patients with preeclampsia, with statistical significance only in nasal measures. In patients with SRD, however, choroid is markedly thicker at all points analyzed. From these findings we can hypothesize that preeclampsia can cause a choroidal thickening, which begins in the peripapillary area. As the imbalance increases, the entire choroid became thickened.

Keywords: Preeclampsia; Pregnancy; Choroidal Thickness; Optical Coherence Tomography; Serous Retinal Detachment.

INTRODUCTION

Preeclampsia (PE) is a pregnancy specific multisystem hypertensive disorder and a leading cause of maternal, neonatal morbidity and mortality. PE is associated with new onset hypertension in the second half of pregnancy, often associated with proteinuria. Although the unknown exact pathophysiology, preeclampsia is associated with an inadequate maternal vascular response to placentation, with increased systemic vascular resistance and dysfunctional condition of the endothelium [1].

Some physiological ocular changes of pregnancy are well known, as an increased central corneal thickness and curvature, and a decreased corneal sensitivity and intraocular pressure [2]. Preeclampsia can also lead to numerous ocular changes, including optic neuropathy, retinal edema, central serous chorioretinopathy, retinal hemorrhages, Elsching's spots, cotton wool spots, segmental or generalized constriction of the retinal arterioles and retinal detachment. Visual symptoms as decreased vision, photopsia and visual field defects may also occur [3].

Changes in choroidal circulation and choroidal ischaemia in patients with pre-eclampsia have also been reported [4-6]. Choroidal ischaemia involves the retinal pigment epithelium, causing breakdown of the blood-retinal barrier, resulting in leakage of proteins and fluid through the retinal pigment epithelium. This abnormal choroidal vascular pattern seen in preeclamptic patients could be the leading cause of the serous retinal detachment rarely seen in these patients [7,8].

Traditional imaging modalities such as indocyanine green [6] and fluorescein [4] angiography and Doppler ultrasonography [9] were used in the past to assess choroidal function during pregnancy. The development of the enhanced depth imaging (EDI) technique of spectral-domain optical coherence tomography (SD-OCT) systems have allowed a better analysis of choroidal morphologic features [10]. EDI-OCT dramatically increased image resolution of choroid by decreasing

signal strength posterior to the retinal pigment epithelium. As a noninvasive diagnostic method, EDI-OCT is an important tool for studying the choroidal changes in preeclampsia [11,12].

The aim of this study was to compare choroidal thickness measurements in preeclamptic and healthy women in the third trimester of pregnancy using the EDI-OCT.

MATERIALS AND METHODS

This cross-sectional study included 148 eyes of 74 women, divided in two groups: 27 healthy pregnant women in the third trimester (control group) and 47 age matched third trimester pregnant women with preeclampsia or eclampsia (PE group). Participants were recruited between March and September 2016 at Hospital de Clinicas de Porto Alegre (HCPA), Brazil. All participants were interviwed in-person and given full explanation about the study procedures and objectives and provided a written informed consent. This study was approved by HCPA research ethics committee and was conducted in accordance with the Declaration of Helsinki guidelines.

All women receiving prenatal care at HCPA at the third trimester of a singleton pregnancy were eligible. Preeclampsia was defined according to the American College of Obstetricians and Gynecologists (ACOG) criteria [13], as was the distinction between mild and severe preeclampsia. Exclusion criteria were any previous ocular surgery or pathology, refractive disorders with a spherical equivalent greater than ±1.0 diopters or intraocular pressure higher than 21mmHg. In addition, pregnant women with chronic hypertension, pre-gestational or gestational diabetes were also excluded.

All study participants underwent an interview with demographic and background history. The ophthalmic examination included uncorrected visual acuity, best-corrected visual acuity, Goldmann applanation tonometry, slit-lamp assisted

biomicroscopy, indirect ophthalmoscopy and SD-OCT. All OCT scans were performed in the morning (8:00am to 12:00pm) to avoid diurnal variations of choroidal thickness [14,15]. The same experienced ophthalmologist (CB) performed all ophthalmic examinations and OCT scans, using Heidelberg Spectralis OCT (Heidelberg Engineering Co, Heidelberg, Germany). Choroid was imaged with a 6-line radial scan (30 degrees, 9.2 mm) using the EDI setting, with 100 images averaged per section. All scans were reviewed before being included in the study. Those with image artefacts or inaccurate choroidal limits were excluded.

Choroidal thickness was determined as the vertical distance from the outer surface of the line formed by the retinal pigment epithelium to the choroidal-scleral interface using the Spectralis OCT measurement software. The measurements were made by an experienced ophthalmologist (DL) blinded to the participant group. Previous studies have already demonstrated the reproducibility of this technique, even across different OCT systems [16-18]. Choroidal thickness was measured at ten different locations: at the fovea and every 500μm from the fovea up to 2500μm temporally and up to 2000μm nasally. We used the following abbreviations for the macular points: T5: choroidal thickness at 2500μm temporally to the fovea; T4: choroidal thickness at 2000μm temporally to the fovea; T3: choroidal thickness at 1500μm temporally to the fovea; T2: choroidal thickness at 1000μm temporally to the fovea; T1: choroidal thickness at 500μm temporally to the fovea; SF: choroidal thickness at the fovea; N1: choroidal thickness at 500μm nasally to the fovea; N2: choroidal thickness at 1000μm nasally to the fovea; N3: choroidal thickness at 1500μm nasally to the fovea; N4: choroidal thickness at 2000μm nasally to the fovea.

Statistical analysis

Statistical analyses were performed using SPSS V.15.0 (SPSS Science, Chicago, Illinois, USA). Quantitative variables were presented as mean (±SD). Categorical variables were described by their absolute and relative frequencies. Quantitative data were compared by Student's t-test and a chi-squared test was used for qualitative data. Differences in choroidal thickness were analysed using generalized estimating equations (GEE) with Bonferroni adjustment. GEE eliminates the effect of laterality and identifies possible discrepancies between eyes. A P value ≤ 0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics by group are summarized in Table 1. The OCT scans were performed in 148 eyes of 74 women: 27 healthy third trimester pregnant women and 47 age matched third trimester pregnant women with preeclampsia. Of the 47 subjects in preeclampsia group, 26 were classified as having mild preeclampsia and 21 as severe preeclampsia, none progressed to eclampsia. Five women with severe preeclampsia had serous retinal detachment at the ophthalmologic exam and OCT.

Comparing the 10 choroidal thicknesses measurements of both groups, choroid always tended to be thicker in subjects with preeclampsia, especially in nasal measurements. This difference was statistically significant in the N4, N3 and N2 macular points (Table 2).

We also performed a subgroup analysis, stratifying preeclampsia group into mild and severe form. Pregnant women with severe preeclampsia tended to have thicker choroids in comparison with the other groups (Table 3). In N3 macular point, macular thickness was significantly higher in mild preeclampsia group in comparison with healthy pregnant group. In N4 macular point, macular thickness was significantly higher in mild and severe preeclampsia groups as compared to the healthy pregnant group.

As an expressive number of women with severe pre-eclampsia were diagnosed with serous retinal detachment, we also analyzed the choroidal thickness of these patients (Table 4) (Figure 1). Choroid was significantly thicker in preeclamptic patients with serous retinal detachment in comparison with preeclamptic patients without serous retinal detachment ($p<0,01$ at all macular points).

DISCUSSION

Preeclampsia affects 2% to 8% of pregnancies worldwide and is associated with significant morbidity and mortality to both mother and fetus/neonate [19,20]. Changes in choroidal circulation and choroidal ischaemia in preeclampsia have already been reported [5]. The choroid is a complex vascular network which provides vascular supply for the retinal pigment epithelium and outer retina layers, representing the sole provider of oxygen and nutrients to the avascular fovea. Previous studies with indocyanine green angiography in patients with preeclampsia have demonstrated non-perfusion in the early phases of the angiogram and staining of the choroidal vasculature with subretinal leakage in the late phases of the angiogram, suggesting severe damage to choroidal vascular walls [6]. Sathish [21] also reported a delayed perfusion of the choriocapillaris, with areas of non-perfusion and gradual fluorescein leakage in a patient with preeclampsia and serous retinal detachment. The presence of Elschnig's spots in preeclamptic patients also demonstrates the presence of ischemic infarcts of RPE and choroid. An ischemic RPE may cause breakdown of the blood-retinal barrier, allowing leakage of fluid from the choroid into the subretinal space [22].

Although indocyanine green or fluorescein angiography can provide important information about choroid vessels, its unknown but possible deleterious effects on the developing fetus should be highlighted. Recent studies have analyzed

possible changes in choroidal thickness in patients with preeclampsia using OCT, with controversial results [23-27]. Choroidal thickness can be influenced by major factors such as age, refractive error and axial length (AL). Aging, AL and decreasing refractive diopter had been associated with a reduction of choroidal thickness [28]. Atas et al., Duru et al. and Sayin et al. found that the choroid is thinner in women with preeclampsia in comparison with healthy pregnant women. Kim et al., however, reported that the choroid in preeclamptic subjects was significantly thicker than in non pregnant and healthy pregnant women. Garg et al. also reported choroidal thickening in the setting of severe preeclampsia. Both Duru et al. and Kim et al. found a significant decrease in choroidal thickness after delivery in preeclamptic subjects.

In this study, subjects with preeclampsia had thicker choroids in comparison with healthy pregnants. However, this difference was statistically significant only in nasal measurements, where the difference was more expressive. These findings may lead to the hypothesis that choroidal thickening during preeclampsia begins by the peripapillary area. When we classified patients with preeclampsia by severity criteria, patients with severe preeclampsia had the highest choroid thickness measurements. Again, significant differences were found only at the points closest to the optic disk.

From 21 patients with severe preeclampsia, 5 had serous retinal detachment. The apparent high prevalence of SRD among subjects with preeclampsia may be due to the hospital tertiary level of care. Patients with significant visual complaints are referred from hospitals which do not provide ophthalmologic care. Choroidal thickness of patients with SRD was significantly higher at all macular points in comparison with other preeclamptic patients. Choroid thickening in these subjects is very significant, with much larger measures compared to the other subjects. Subretinal fluid in preeclamptic patients is probably secondary to a complex imbalance of the choroid, possibly caused by endothelial cell dysfunction, choroidal and RPE ischaemia, hyperpermeability and increased hydrostatic pressure.

Our study has some limitations, such as the small number of subjects. In addtion, the cross-sectional design allows us to analyze choroidal characteristics only for the third trimester of pregnancy.

However, we attempted to minimize possible confounding factors by excluding subjects with pre-gestational or gestational diabetes or with chronic hypertension from the analysis. We also performed all the OCT exams during the morning to avoid diurnal variations, and excluded subjects with refractive disorders with spherical equivalent greater than ±1.0 diopters.

In conclusion, our study showed that choroid tends to be thicker in patients with preeclampsia, with statistical significance only in the measurements nasal to the fovea. In patients with SRD, however, choroid is markedly thicker at all points analyzed. From these, we are tempted to hypothesize that preeclampsia may cause a choroidal thickening, which begins in the peripapillary area. As the imbalance increases, the entire choroid became thicker. Further prospective studies with a larger number of subjects should be performed to confirm these findings and to analyze if perhaps choroidal thickness could be a predictive marker for preeclampsia severity.

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Figure 1: Measurements of choroidal thickness in preeclamptic patients with serous retinal detachment.

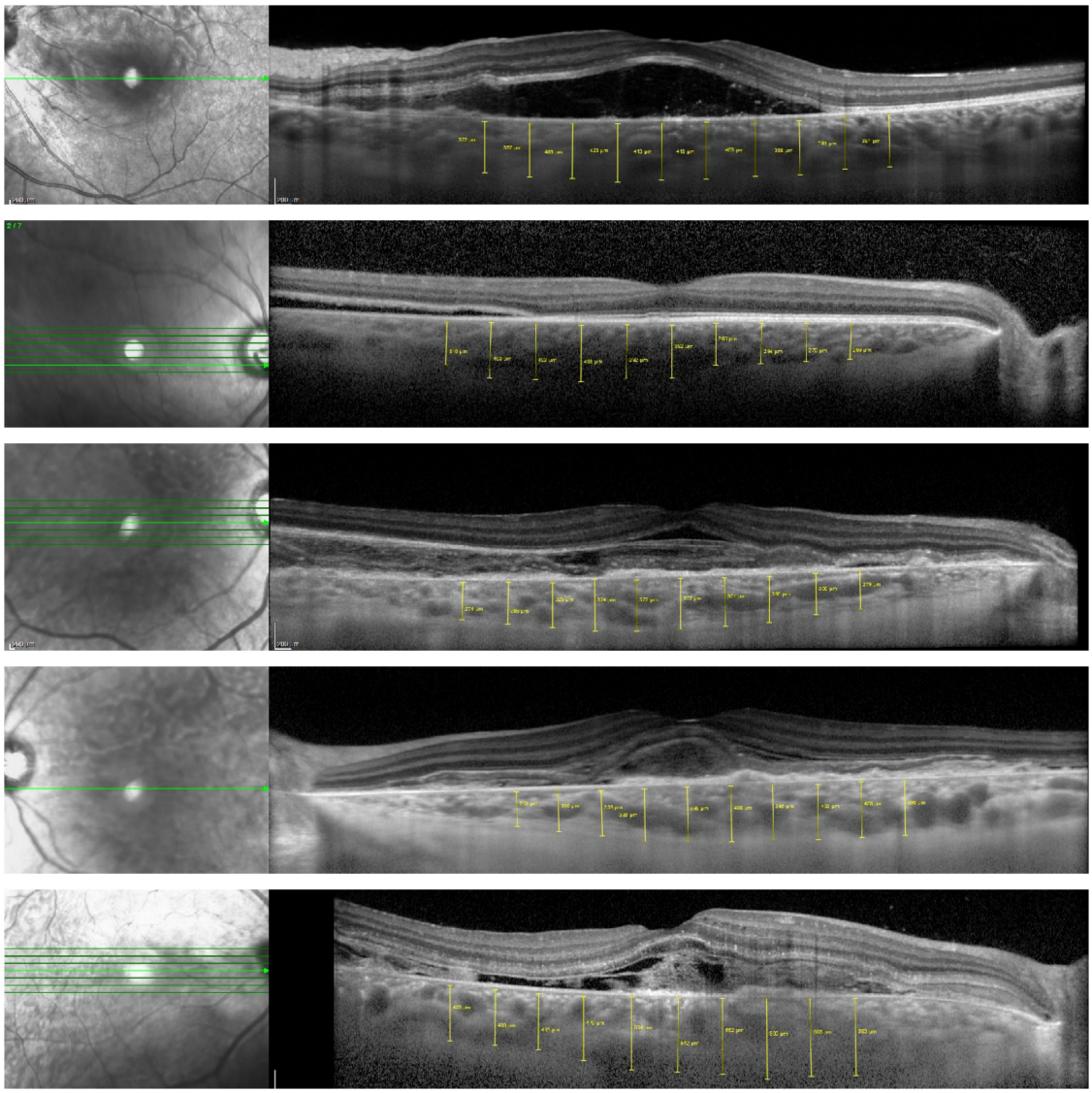

Table 1: Demographic and clinical characteristics of the study and control groups.

	Healthy Pregnancy Group (n=27)	Preeclampsia Group (n=47)	P- Value
Age (years) Mean + SD	28,1 ± 7,0	28,3 ±6,7	0,902*
Ethnicity – n(%) Caucasian African-american	25 (92,6) 2 (7,4)	33 (73,3) 12 (26,7)	0,091**
Gestational age (weeks) Mean + SD	33,3 ± 2,6	32,6±3,4	0,369*

* t-test

** chi-squared test

Table 2: Comparison of choroidal thickness measurements between healthy pregnant women and women with preeclampsia.

	Healthy Pregnancy Group (n=27) Mean + SE (µm)	Preeclampsia Group (n=47) Mean + SE (µm)	P-value
T5	278,5 + 13,9	285,5 + 12,4	0,708
T4	291,5 + 15,2	301,8 + 12,4	0,600
T3	300,9 + 14,3	312,4 + 13,2	0,557
T2	308,2 + 14,8	324,8 + 13,9	0,413
T1	311,2 + 14,8	340,0 + 13,9	0,155
SF	318,1 + 15,6	346,7 + 14,9	0,184
N1	291,3 + 14,9	332,0 + 14,8	0,052
N2	**267,1 + 14,7**	**315,2 + 14,3**	**0,019**
N3	**239,4 + 13,9**	**294,4 + 13,8**	**0,005**
N4	**210,2 + 12,2**	**269,8 + 13,8**	**0,001**

GEE with Bonferroni adjustment.

N1: choroidal thickness at 500µm nasal to the fovea; N2: choroidal thickness at 1000µm nasal to the fovea; N3: choroidal thickness at 1500µm nasal to the fovea; N4: choroidal thickness at 2000µm nasal to the fovea; SF: choroidal thickness at the fovea; T1: choroidal thickness at 500µm temporal to the fovea; T2: choroidal thickness at 1000µm temporal to the fovea; T3: choroidal thickness at 1500µm temporal to the fovea; T4: choroidal thickness at 2000µm temporal to the fovea; T5: choroidal thickness at 2500µm temporal to the fovea.

Table 3: Comparison of choroidal thickness measurements between healthy pregnant women, women with mild preeclampsia and women with severe preeclampsia.

	Healthy Pregnancy Group (n=27) Mean + SE (µm)	Mild Preeclampsia Group (n=26) Mean + SE (µm)	Severe Preeclampsia Group (n=21) Mean + SE (µm)	P-value
T5	278,5 + 13,9	262,8 + 11,0	312,9 + 22,5	0,129
T4	291,5 + 15,2	282,8 + 12,4	324,9 + 21,9	0,247
T3	300,9 + 14,3	295,4 + 13,6	332,8 + 23,5	0,380
T2	308,2 + 14,8	309,1 + 14,8	344,3 + 24,6	0,409
T1	311,2 + 14,8	328,2 + 13,4	354,4 + 25,7	0,328
SF	318,1 + 15,6	337,9 + 15,2	357,6 + 27,3	0,401
N1	291,3 + 14,9	324,4 + 15,2	341,5 + 27,1	0,150
N2	267,1 + 14,7	308,6 + 14,3	323,5 + 26,4	0,060
N3	**239,4 + 13,9a**	**287,1 + 13,0b**	**303,4 + 26,2ab**	**0,017**
N4	**210,2 + 12,2a**	**260,3 + 12,3b**	**281,4 + 26,5b**	**0,004**

a,b same letter don't differ from each other at a 5% of significance by GEE with Bonferroni adjustment.
N1: choroidal thickness at 500µm nasal to the fovea; N2: choroidal thickness at 1000µm nasal to the fovea; N3: choroidal thickness at 1500µm nasal to the fovea; N4: choroidal thickness at 2000µm nasal to the fovea; SF: choroidal thickness at the fovea; T1: choroidal thickness at 500µm temporal to the fovea; T2: choroidal thickness at 1000µm temporal to the fovea; T3: choroidal thickness at 1500µm temporal to the fovea; T4: choroidal thickness at 2000µm temporal to the fovea; T5: choroidal thickness at 2500µm temporal to the fovea.

Table 4: Comparison of choroidal thickness measurements between women with preeclampsia without serous retinal detachment and those with serous retinal detachment.

	Preeclampsia without RD (n=42) Mean + SE (µm)	Preeclampsia with RD (n=5) Mean + SE (µm)	P-value
T5	**266,7 + 10,2**	**441,1 + 27,0**	**<0,001**
T4	**284,3 + 10,7**	**447,0 + 26,6**	**<0,001**
T3	**294,9 + 12,0**	**456,9 + 25,2**	**<0,001**
T2	**307,4 + 12,9**	**470,8 + 24,6**	**<0,001**
T1	**321,9 + 12,6**	**489,7 + 25,7**	**<0,001**
SF	**328,4 + 13,9**	**500,7 + 25,2**	**<0,001**
N1	**313,7 + 13,7**	**486,0 + 28,6**	**<0,001**
N2	**296,9 + 12,9**	**469,5 + 29,9**	**<0,001**
N3	**276,6 + 12,3**	**443,4 + 35,1**	**<0,001**
N4	**252,4 + 12,1**	**415,9 + 40,2**	**<0,001**

GEE with Bonferroni adjustment.

N1: choroidal thickness at 500µm nasal to the fovea; N2: choroidal thickness at 1000µm nasal to the fovea; N3: choroidal thickness at 1500µm nasal to the fovea; N4: choroidal thickness at 2000µm nasal to the fovea; SF: choroidal thickness at the fovea; T1: choroidal thickness at 500µm temporal to the fovea; T2: choroidal thickness at 1000µm temporal to the fovea; T3: choroidal thickness at 1500µm temporal to the fovea; T4: choroidal thickness at 2000µm temporal to the fovea; T5: choroidal thickness at 2500µm temporal to the fovea.

3 DISCUSSÃO

Neste projeto, foram avaliadas as alterações que ocorrem na espessura da coroide durante o período gestacional, tanto em gestantes saudáveis como em mulheres com DMG, diabetes pré-gestacional e pré-eclâmpsia. O objetivo geral era avaliar o comportamento da coroide no terceiro trimestre de gestação, incluindo pacientes com intercorrências prevalentes e relevantes.

Ao analisar a espessura da coroide em gestantes de risco habitual àquela de mulheres não grávidas, não encontramos diferença significativa. Nossos resultados contrariaram nossa hipótese inicial de aumento da espessura da coroide, que teoricamente poderia ser esperada em virtude do aumento do fluxo sanguíneo na coroide associado à redução da pressão intra-ocular. A maior prevalência de CSC durante o período gestacional também contribuiu para a formulação da hipótese inicial, visto ser uma doença que cursa primariamente com alterações e espessamento da coroide. Também não encontramos associação entre a espessura da coroide e a idade gestacional.

Foi possível postular, a partir desses achados, que as modificações circulatórias fisiológicas da gestação não acarretam modificações estruturais na espessura da coroide em gestantes durante o terceiro trimestre. As publicações em gestações sem intercorrências têm resultados confiltantes, alguns autores demontrando a presença de espessamento da coroide e outros não. Ao analisar estes resultados divergentes, deve-se salientar que o presente estudo avaliou apenas gestantes durante o terceiro trimestre. Goktas et al.[32] e Dadaci et al.[33], por exemplo, encontraram coroides mais espessas respectivamente no segundo e no primeiro trimestre de gestação. Os resultados encontrados, portanto, não podem ser extrapolados para outros períodos gestacionais.

Ao comparar a espessura da coroide de gestantes saudáveis, com DMG, DM2 e DM1, foram encontradas coroides mais afinadas em gestantes com DM1 nas topografias subfoveal e temporal à fóvea. A diferença se manteve mesmo quando comparadas somente gestantes com DM2 e DM1, corrigindo para a

presença de hipertensão, níveis de HbA1c, duração do DM e presença de retinopatia diabética. Não foi encontrada diferença estatisticamente significativa na espessura da coroide entre gestantes saudáveis, gestantes com DMG e gestantes com DM2.

É possível hipotetizar que o achado de afinamento da coroide possa ser causado primariamente por alterações da coroidopatia diabética, que seriam mais marcantes em pacientes com DM1, pela duração e gravidade da doença. O fluxo sanguíneo diminuído encontrado na coroide de pacientes com diabetes[62,115], juntamente com alterações como atrofia e *dropout* dos vasos da coriocapilar[59], poderiam contribuir para esse afinamento. Ainda permanece a dúvida se a gestação por si só pode contribiur para este afinamento, já que não encontramos achados similares nas nossas gestantes com DMG e DM2.

Até o momento não foram publicados estudos que tenham analisado a espessura da coroide em gestantes com DM1 e DM2. Estudos prospectivos são necessários para avaliar se as anormalidades do fluxo sangüíneo ocular observadas em pacientes diabéticas são influenciadas ou não pelo hiperfluxo e alterações hormonais da gravidez, e se essas modificações podem contribuir para a progressão da RD observada na gestação.

Comparando a espessura da coroide de gestantes saudáveis com gestantes com pré-eclâmpsia, entretanto, observou-se uma tendência ao aumento da espessura no segundo grupo. Embora a coroide seja mais espessa em todas as localizações analisadas nas pacientes com PE, apenas nas medidas nasais, marcantemente diferentes, foi atingida significância.

Ao categorizar a PE por parâmetros de gravidade, não encontramos diferença significativa na espessura da coroide entre os dois grupos, embora as medidas fossem maiores em todas as localizações nas mulheres com PE grave. Diferença significativa foi encontrada apenas na comparação destes grupos com o grupo das gestantes saudáveis, novamente nas medidas nasais à fóvea, nos levando a pensar que a pré-eclâmpsia poderia acarretar espessamento da coroide, iniciando na região peripapilar.

Das 47 pacientes com PE, 5 apresentavam descolamento seroso de retina ao exame, o que por si só já pode configurar critério de gravidade da doença. Ao analisar a espessura da coroide das pacientes com descolamento seroso de retina, em comparação às demais pacientes com PE, foram observadas coroides com espessura muito aumentada nestas pacientes em todas as localizações.

Atualmente ainda não se compreende totalmente como a disfunção endotelial e as alterações circulatórias que caracterizam a PE podem afetar a circulação da órbita, globo ocular, coroide e retina. Pode-se postular que as alterações isquêmicas encontradas consistentemente na retina e na coroide de pacientes com PE sejam o resultado de um vasoespasmo causado pelo estado hipertensivo. O vasoespasmo exacerbado, neste caso, seria responsável pelo desenvolvimento de um processo isquêmico, com edema citotóxico e infarto tecidual. Recentemente, entretanto, análises dopplervelocimétricas da artéria oftálmica destas pacientes vêm demonstrando consistentemente uma diminuição da resistência vascular e aumento do fluxo sanguíneo neste leito arterial, possivelmente por um mecanismo de centralização. Deste modo, é possível postular também que o aumento da pressão hidrostática, associado à disfunção endotelial, possa acarretar extravasamento de plasma e edema vasogênico. Embora alguns autores possam defender essas teorias separadamente, parece razoável concluir que o mecanismo mais provável para a disfunção da coroide na PE seja uma combinação das duas. Hipóteses muito similares também são utilizadas para justificar o surgimento das complicações neurológicas da pré-eclâmpsia e sua progressão para eclâmpsia e *PRES*.

Deste modo, o aumento do fluxo sanguíneo na artéria oftálmica, associado ao aumento da pressão hidrostática, a disfunção endotelial e a formação de edema vasogênico poderiam justificar o aumento da espessura da coroide encontrado em pacientes com PE. De acordo com os resultados encontrados, esse espessamento seria mais pronunciado na região peridiscal. Com a progressão do desequilíbrio, toda a coroide aumentaria consideravelmente de volume, culminando com o acúmulo de fluido

subretiniano. O descolamento seroso de retina que ocorre em pacientes com PE grave e que acarreta considerável redução visual ocorreria, deste modo, como consequência final de um complexo mecanismo de disfunção endotelial, isquemia do EPR, hiperpermeabilidade e aumento da pressão hidrostática da coroide.

Outros autores já estudaram possíveis alterações na espessura da coroide em pacientes com pré-eclâmpsia. Atas et al.[29], Duru et al.[113] e Sayin et al.[28], por exemplo, observaram coroides mais finas em pacientes com pré-eclâmpsia, tendo atribuído esse achado ao quadro sistêmico de aumento da resistência vascular e vasoespasmo descrito em pacientes com pré-eclâmpsia. Outros autores documentaram um significativo espessamento da coroide em pacientes com PE. Garg[114] atribuiu esse espessamento ao aumento nos níveis séricos do Fator de Crescimento do Endotélio Vascular (VEGF) em mulheres com PE, tendo em vista o seu efeito de aumento da permeabilidade vascular na coriocapilar. Este fator pode ser considerado como outra variável presente no complexo desbalanço circulatório que ocorre na coroide destas pacientes.

A variabilidade de resultados encontrados na literatura pode ser justificada em parte pelo não controle de diferentes fatores que podem influenciar a espessura da coroide. Para minimizar esses vieses, apenas pacientes com equivalente esférico de mais ou menos uma dioptria foram incluídas neste trabalho. Apesar desta margem restrita reduzir consideravelmente as pacientes elegíveis, julgamos ser este um importante fator a ser controlado. Pacientes com cirurgias oftalmológicas prévias e glaucoma também foram excluídas. Por motivos intrínsecos ao estado gestacional, apenas mulheres em idade fértil foram incluídas. Nos grupos de DM, foram excluídas pacientes que já haviam sido submetidas a tratamento com fotocoagulação a laser ou anti-VEGF, pelo possível efeito já documentado desses tratamentos na espessura da coroide[65,68]. Todos os exames de OCT foram realizados no período da manhã, para reduzir os efeitos das variações diurnas nas medidas da coroide[25,26].

A multiplicidade de protocolos de localização utilizados para as medidas da coroide e o uso de diferentes aparelhos de OCT são outras possíveis causas para essa diversidade de resultados. Neste trabalho, todos os exames foram realizados pelo mesmo examinador, utilizando o aparelho Heidelberg Spectralis. As medidas de espessura da coroide foram realizadas por um examinador diferente, cegado para os grupos. A comparação entre medidas realizadas em diferentes pontos da região macular limita a extrapolação dos resultados entre diferentes autores. Por este motivo, optou-se pela utiização de um protocolo mais abrangente, que inclui 10 medidas da espessura da coroide através de um corte em alta resolução que passa pela fóvea. Outro protocolo bastante utilizado analisa apenas a espessura da coroide subfoveal, desconsiderando outras medidas nasais ou temporais.

Este estudo apresenta potenciais limitações que merecem ser comentadas. O desenho transversal do estudo apenas permite fazer associações, sem considerar relação de causa e efeito. Análises longitudinais são necessárias para confirmar o comportamento da coroide durante o período gestacional. A amostra estudada foi relativamente pequena considerando os grupos individualmente. Apesar disso, foram estabelecidos critérios de inclusão rígidos para minimizar possíveis vieses e garantir a similaridade entre os grupos. Outra limitação é a possibilidade de ocorrência de erros nas medidas da coroide, já que as medidas são realizadas manualmente, embora estudos recentes tenham encontrado alta reprodutibilidade e elevada correlação interobservador nas medidas da espessura da coroide[19-22].

Neste trabalho, portanto, objetivou-se realizar uma análise abrangente do comportamento da coroide na gestação durante o terceiro trimestre, incluindo um grupo controle de não grávidas, gestantes de baixo risco e gestantes com comorbidades prevalentes do período. De acordo com os achados obtidos, apenas gestantes com DM1 e com pré-eclâmpsia apresentaram modificações significativas na espessura da coroide.

Como há potenciais riscos ao feto em desenvolvimento, o uso de corantes endovenosos como a fluoresceína e a indocianina verde ficam

limitados neste período. A OCT, deste modo, desponta como o principal exame para a análise estrutural da coroide nestas pacientes, principalmente por se tratar de um exame rápido, seguro e não invasivo, que possibilita a visualização direta da coroide com detalhes anatômicos precisos. Para análises futuras, estudos longitudinais devem ser conduzidos para a confirmação dos achados. Atualmente, novos aparelhos de OCT com tecnologias mais avançadas já incorporaram softwares de medida automatizada da estrutura da coroide, reduzindo os vieses das medidas manuais. O SS-OCT, por utilizar um comprimento de onda maior, consegue melhorar a qualidade das imagens de camadas mais profundas, como a coroide, permitindo imagens em alta resolução até a superfície escleral[17,116]. A utilizaçao da angiografia por tomografia de coerência óptica, que permite a visualização da microvasculatura da retina e da coriocapilar sem o uso de corantes exógenos[117] também poderia fornecer informações importantes para a compreensão do comportamento da coroide no período gestacional.

4 CONCLUSÕES

1. Não foi encontrada diferença significativa nas medidas da espessura da coroide utilizando SD-OCT entre mulheres não grávidas e mulheres com gestação de risco habitual no terceiro trimestre.

2. Não foi encontrada diferença significativa nas medidas da espessura da coroide utilizando SD-OCT entre gestantes não-diabéticas, gestantes com DMG e gestantes com DM2 no terceiro trimestre de gestação. Gestantes com DM1 no terceiro trimestre apresentaram afinamento significativo da coroide em algumas localizações em comparação aos demais grupos.

3. Pacientes com PE no terceiro trimestre apresentaram coroides mais espessas em todas as localizações em comparação às gestantes de risco habitual no terceiro trimestre, embora com diferença significativa apenas nas medidas nasais à fóvea. Dentre as pacientes com PE no terceiro trimestre, aquelas com descolamento seroso de retina apresentaram coroides significativamente mais espessas em todas as localizações quando comparadas àquelas sem descolamento seroso de retina.

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